Molnupiravir for treating COVID-19 (ID6340)

For screen – CON information redacted

Technology appraisal committee C [5 November 2024]

Chair: Stephen O'Brien

Lead team: Stella O'Brien, John Hampson, Mark Corbett

External assessment group: Southampton Health Technology Assessments Centre

Technical team: Zain Hussain, Adam Brooke, Ross Dent

Company: Merck Sharp & Dohme

Molnupiravir for treating COVID-19 (ID6340)

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on COVID-19

Causes

- COVID-19 is an acute respiratory illness caused by SARS-CoV-2

Epidemiology

- In England, between 6 October 2023 and 4 October 2024, 10,281[1] deaths occurred involving COVID-19

Symptoms and prognosis

- May start with a cough, fever or breathlessness (viral replication phase with peak of infectiousness and viral shedding). Infection can spread before any symptoms observed
- Infections range from mild and self-limiting to severe
    - If infection is uncontrolled, the body's excess immune response to the virus may result in severe complications (inflammatory phase) accompanied by a high risk of hospitalisation and death
- In the community, people with severe infections are often hospitalised and may need support with high-flow / low-flow oxygen and treatment in intensive care units.
    - In England, 120,852[1] COVID-19 patients were admitted to hospital between 1 October 2023 and 28 September 2024
- COVID-19 can progress to post-COVID-19 syndrome / Long-COVID
    - May manifest as debilitating symptoms like fatigue and pain, common long term multisystem effects include dyspnoea, variations in heart rate, dysautonomia

1. UKHSA Data dashboard – COVID-19 https://ukhsa-dashboard.data.gov.uk/ Accessed 23/10/2024

Patient perspectives

There is an unmet need for COVID-19 treatment, particularly for high-risk patients

Patient expert submissions from Clinically Vulnerable Families, Cardiothoracic Transplant Patient Group and Long Covid SOS

- Many patients remain at high risk of severe COVID-19 infections
- There is an unmet need for treatments options for COVID-19, particularly in high-risk patients
    - Currently very few treatment options available, some of which are extremely difficult to access
    - Patients with no anti-bodies or who are ineligible for nirmatrelvir/ritonavir might benefit from access to other effective treatments if they are available
- If Molnupiravir is inferior to sotrovimab, the CTPG believe that molnupiravir approval will disadvantage some patients who have had either a heart and / or lung transplant

"Since "freedom day" we have felt abandoned…while the rest of the world behaves as if the pandemic is over"

"We live very restricted lives in our attempts to avoid infection"

"…Knowledge that we could access other effective treatments would reduce our fears of becoming infected and help open up our lives"

"overwhelming majority of transplant patients make lifestyle adjustments to avoid COVID-19, over half reporting behaviours closer to full COVID-19 lockdown"

"I'd love the opportunity to be given an antiviral to prevent worsening of my symptoms. . . it's very likely each time I get worse I don't recover to the point I was at previously"

Abbreviations: CTPG, Cardiothoracic transplant patient group

Clinical perspectives

Molnupiravir can address unmet need for alternative oral treatment option for COVID-19

Submissions from RCPath, UKCPA and 1 clinical expert

- Aim of COVID-19 treatment is to prevent severe illness, resulting in hospitalisation or long-term disability
- Current management is variable depending on severity and risk factors and includes nirmatrelvir/ritonavir or sotrovimab
    - Nirmatrelvir/ritonavir is the only oral treatment option and is associated with significant risk of interactions, particularly due to ritonavir in chemotherapy patients
- Molnupiravir addresses the unmet need for an oral treatment option where nirmatrelvir plus ritonavir is contraindicated
    - Associated with minimal side effects
    - Only alternative to pharmacokinetically boosted antiviral
- There is evidence of reduction in hospitalisations and death related to COVID-19 in unvaccinated individuals and faster time to recovery from COVID-19 with molnupiravir
- Molnupiravir appears to confer modest improvements in time to recovery and long-term symptoms

"Sotrovimab has uncertain efficacy due to genomic mutation, both sotrovimab and remdesivir require intravenous treatment making them unavailable in the timespan required"

"The impact of COVID-19 on medium to long-term disability e.g. from long covid needs to be considered as part of the QALY calculation"

"Eligibility should be restricted to those with proven SARS-CoV-2 infection, high risk of poor outcome and where other treatments are contraindicated"

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Abbreviations: QALY: Quality-adjusted life year; RCPath; Royal College of Pathologists; UKCPA; UK Clinical Pharmacy Association

Equality considerations

Patient organisation (Clinically Vulnerable Families)**:**

- Most eligible patients are disabled in some way by their pre-existing condition or by society's current response to us

Clinical expert

- Molnupiravir is contraindicated in pregnant women and a pregnancy test is required to be taken before having it

Company:

- Supports the need for an easy to administer oral treatment for mild to moderate disease to provide options for people, particularly those with protected characteristics, and clinicians to eliminate any residual and unobserved aspects of access inequality.
    - People with protected characteristics may have additional burden of travel to hospitals to have IV treatment
    - A number of people are contraindicated to or likely to have drug-drug interactions to the currently recommended first-line treatment, nirmatrelvir plus ritonavir
    - Treating people with multiple comorbidities and medications is complicated due to risk of drug-drug interactions or requiring dose adjustments
    - Patients with renal impairment contraindicated to nirmatrelvir plus ritonavir, thus only option with current recommendations is sotrovimab. The prevalence of renal impairment is higher in black, Asian and other ethnic minority backgrounds, and the risk of death and hospitalisation from COVID-19 is also higher in these groups
- Molnupiravir is an oral home treatment that reduces risk of transmission within a hospital setting, where there are substantial numbers of vulnerable individuals, as well as health care professionals

Are there any equality issues which can be addressed in this appraisal?

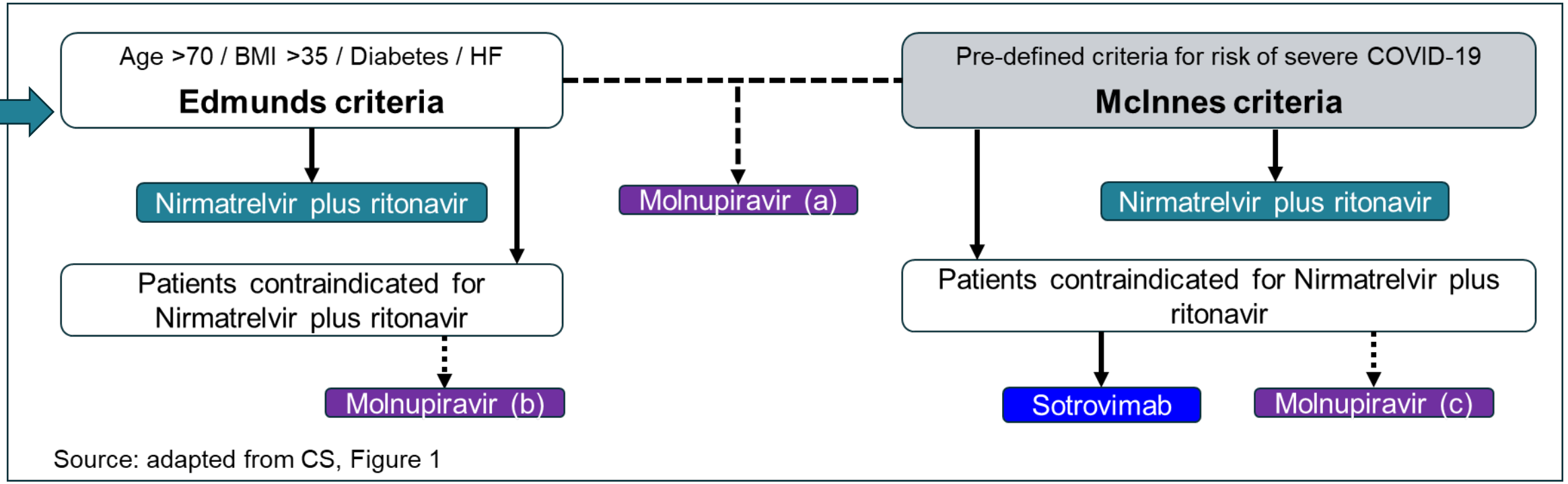
Molnupiravir (Lagevrio, Merck Sharp & Dohme)

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. • The prodrug, molnupiravir, is metabolised to NHC, which is then phosphorylated in cells to the pharmacologically-active NHC-TP. • Viral RNA polymerase incorporates NHC-TP into the viral RNA resulting in accumulation of errors in the viral genome and inhibition of replication.
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: DHSC: Department of Health and Social Care; MHRA: Medicines and Healthcare products Regulatory Agency; NHC = N-hydroxycytidine; NHC-TP = NHC triphosphate

Treatment pathway

Proposed positioning for molnupiravir – restructured by NICE technical team



Source: adapted from CS, Figure 1

•n.b. until June 2025, there is a funding variation meaning that access is limited to: age 85+; end-stage heart failure who have LVAD; people on the organ transplant waiting list; people aged 70+, or who have a BMI of 35 kg/m^2 or more, diabetes or heart failure, AND are resident in a care home, or are already hospitalised.

a) Alternative to nirm/rit for people at risk of severe disease as per McInnes+Edmunds criteria
b) When nirm/rit contraindicated for people at risk of severe disease as per Edmunds criteria→ currently no treatment option
c) When nirm/rit contraindicated for people at risk of severe disease as per McInnes criteria, as an alternative to sotrovimab

NICE BMI: Body mass index; HF: Heart failure

See appendix: Company's proposed positioning for molnupiravir, McInnes definition and Edmunds report and Decision problem

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

Schwartz, Apr-Aug 22

Cowman, Apr-Dec 22

Manciulli, Jan-Mar 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

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

Key issues

Key issues	Resolved?	ICER impact
Uncertainty around the clinical effectiveness of molnupiravir in the endemic setting of COVID-19	No – for discussion	Large 
Uncertain viral clearance profile of molnupiravir in relation to its mechanism of action	No – for discussion	Not applicable
Hospitalisation rates for untreated patients	No – for discussion	Large 
Treatment effect on hospitalisation	No – for discussion	Large 
Proportion of patients with long-term sequelae	No – for discussion	Large 
Health state utilities	No – for discussion	Large 
Other issues		
Restriction of the decision problem population to non-hospitalised patients	No	Unknown 

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Clinical effectiveness evidence: Overview

Table: MOVe-OUT and PANORAMIC study design and outcomes

	MOVe-OUT (N=1,433)	PANORAMIC (N=26,411)
Design	Phase 2/3 multicentre, randomised, double-blinded, parallel assignment, interventional, placebo-controlled trial	Multicentre, primary care, open-label, multigroup, prospective, platform adaptive trial
Population	Non-hospitalised people ≥ 18 years of age with laboratory-confirmed SARS-CoV-2 infection and signs/symptoms attributable to COVID-19 and at least 1 risk factor for development of severe illness from COVID-19	People in the community ≥ 50 years of age or ≥18 years of age with comorbidities who had COVID-19 symptoms with a positive SARS-CoV-2 test
Intervention	Molnupiravir	• Molnupiravir plus usual care • Nirmatrelvir plus ritonavir plus usual care
Comparator	Placebo	Usual care
Follow-up	29 days and 7 months	28 days
Primary outcome	All-cause hospitalisation or death, AEs (including those leading to treatment discontinuation	All-cause hospitalisation or death
Locations	Multicentre with 6 UK sites	65 PANORAMIC General Practice Hubs encompassing 4,509 practices across the UK

Source: CS, Doc B, Table 5 and 6

See appendix: MOVe-OUT study design and MOVe-OUT – baseline characteristics

MOVe-OUT – Results

Table: MOVe-OUT study results

Outcome	Comparison: molnupiravir versus placebo	
Primary outcome: All-cause hospitalisation or death at Day 29	**Interim analysis:** • Molnupiravir 7.3% vs placebo 14.1% • Adjusted difference (95% CI); -6.8 (-11.3 to -2.4); p=0.0012	**Final analysis:** • Molnupiravir 6.8% vs placebo 9.7% • Adjusted difference (95% CI); -3.0 (-5.9 to -0.1); p=0.0218
All-cause hospitalisation or death Day 30 - Month 7	• All cause death lower for molnupiravir (3 patients; 0.4%) versus placebo (6 patients; 0.6%) • All cause hospitalisation (2 patients; 0.3%) versus placebo (3 patients; 0.4%)	
No statistically significant difference was observed for sustained resolution or improvement of COVID-19 symptoms, progression of each targeted self-reported sign/symptom of COVID-19 and WHO 11-point ordinal scale		

EAG comments

- MOVe-OUT was a well-conducted randomised controlled trial (RCT) at low risk of bias ➔ Reasonable certainty in the interim analysis that molnupiravir is more effective than placebo in reducing all-cause hospitalisation or death in the pandemic phase of COVID-19.
  - However, the treatment effect appears marginal at the final analysis
- Trial population unlikely to be generalisable to UK population due to differences in vaccination status
- There is limited evidence available for some of the specified at-risk subgroups in the economic model
- Also limited evidence to support the usefulness of molnupiravir in reducing the requirement for respiratory support or reducing the viral load compared to placebo.

See appendix: MOVe-OUT study design and MOVe-OUT – baseline characteristics

CI: Confidence interval

PANORAMIC – Results

Table: PANORAMIC study primary outcome results

Primary outcome	Molnupiravir	Usual care
All-cause hospitalisation or death at Day 29	105/12,529 (1%)	98/12,525 (1%)
Treatment effect (Odds ratio)	1.06 (0.81-1.41)	
* Bayesian logistic regression model adjusted for age, vaccination status, and comorbidity at baseline. An odds ratio <1 favoured molnupiravir plus usual care over usual care only.		

Company critique of PANORAMIC trial:

The cohort enrolled in PANORAMIC is not as representative of the population in this appraisal and the results from PANORAMIC may be biased against molnupiravir

- Definition of high risk for severe COVID-19 in PANORAMIC broader than the McInnes definition and the inclusion criteria for the MOVe-OUT trial (e.g includes age 50+ without comorbidity) ➔ Baseline probability of events is lower in PANORAMIC than in the target population for this appraisal
- PANORAMIC would not have included patients at highest risk who were eligible for treatment through UK interim clinical commissioning policies
- Patients enrolled in PANORAMIC were less likely to be hospitalised and do not reflect the patient population who would most likely benefit from treatment with molnupiravir
- Access to treatments outside of the trial is likely to confound the usual care treatment arm and limit any possible treatment effects in the study

Abbreviations: CI: Confidence interval

Key issue: Uncertainty around the clinical effectiveness of molnupiravir in the endemic setting of COVID-19

Company

- Conducted two sets of network meta-analyses (NMAs), for 11 RCT studies and 22 real world evidence (RWE) studies
  - The RCT NMAs had major limitations (unaccounted for heterogeneity, risks of bias, and lack of generalisability) and do not provide convincing evidence of the clinical effectiveness of molnupiravir and they do not inform the economic analysis
  - Only the RWE NMAs, considered more generalisable to current endemic COVID-19, inform the economic analysis
  - One RCT, MOVe-OUT informs a scenario analysis

See appendix: NMAs of RWE – relevant studies and comparisons

RCT: Randomised controlled trial

NMAs of RCTs – Results for hospitalisation or death

Table: Results of the NMAs of RCTs – hospitalisation or death

Outcome	Results for molnupiravir versus each comparator unless stated otherwise the statistic is an odds ratio (95% credible interval)			
	Nirmatrelvir plus ritonavir	Sotrovimab	Remdesivir	Placebo
All-cause hospitalisation or death	8.95 (0.58 to 321.34) No significant difference	3.47 (1.38 to 10.02) Favours sotrovimab	2.48 (0.88 to 8.24) No significant difference	0.63 (0.43 to 0.92) Favours molnupiravir
COVID-19 related hospitalisation or death	5.05 (2.23 to 12.71) Favours nirmatrelvir plus ritonavir	2.02 (0.06 to 31.05) No significant difference	6.09 (1.48 to 45.29) Favours remdesivir	0.67 (0.45 to 1.0) Favours molnupiravir (just)
All-cause hospitalisation	8.52 (0.55 to 328.59) No significant difference	3.33 (1.33 to 9.74) Favours sotrovimab	2.49 (0.88 to 8.30) No significant difference	0.63 (0.43 to 0.92) Favours molnupiravir
COVID-19 related hospitalisation	6.82 (2.64 to 21.75) Favours nirmatrelvir plus ritonavir	2.72 (0.08 to 44.26) No significant difference	6.11 (1.47 to 46.40) Favours remdesivir	0.67 (0.45 to 1.00) Favours molnupiravir (just)
All-cause death	Odds ratio not reported. Risk difference: 0.05 (0.01 to 0.14) Favours nirmatrelvir plus ritonavir	Odds ratio not reported. Risk difference: 0.05 (0.01 to 0.14) Favours sotrovimab	No data for this comparison	0.27 (0.07 to 0.76) Risk difference: -0.12 (-0.20 to -0.04) Favours molnupiravir

Source: EAR appendix 5

NMAs: Network meta-analyses; RCTs: Randomised controlled trials

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- ≥65
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 64)

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

Key issue: Uncertainty around the clinical effectiveness of molnupiravir in the endemic setting of COVID-19

EAG comments

- Agrees that RWE NMAs are more generalisable than RCT NMAs to the current endemic COVID-19
- RWE NMAs show molnupiravir was statistically more effective at reducing hospitalisation than no treatment
- Uncertainty exists around the appropriate time cut-off to ensure current relevance of studies, and generalisability of RWE NMA results, given the lack of UK studies
    - Only 1 UK study was included in the RWE NMAs. Another UK study using OpenSAFELY platform (Tazare et al. 2023) showed lack of molnupiravir effectiveness compared to no treatment. Study was not identified in company search.
- Evidence provided does not include outcomes for COVID-19 symptom progression or resolution, virological outcomes, or the requirement for respiratory support ➔ Clinical effectiveness evidence limited
- Clinical significance of statistically significant reductions in hospitalisation rate is uncertain
- Used different evidence sources from the NMAs and individual studies in scenario analyses

- What is an appropriate time cut-off to distinguish studies that are relevant or not relevant to populations and clinical practices in the current endemic phase of COVID-19?
- Is evidence from RWE NMAs or individual studies more appropriate to inform the clinical effectiveness evidence for molnupiravir versus relevant comparators?
- Are statistically significant changes in hospitalisation considered clinically important?

Abbreviations: NMAs: Network meta-analyses; RCT: Randomised controlled trial; RWE: Real world evidence

Key issue: Uncertain viral clearance profile of molnupiravir in relation to its mechanism of action

Background

- Molnupiravir has a mechanism of action which alters the RNA of the virus, causing novel mutations of SARS-CoV-2 that may potentially be transmitted if the virus is not fully cleared
- The scientific literature highlights viral clearance is necessary to avoid transmitting the virus, as well as any viral mutations generated by the mechanism of action of molnupiravir ➔ could have implications for genotoxicity in humans, risk of development of new SARS-CoV-2 variants, and/or potential drug efficacy

EAG comments

- Limited results for the virological outcomes of MOVe-OUT trial were reported in clarification response, compared to the expected virological endpoints, and the company virological report was not provided
- Virological outcomes could only be analysed in the NMAs of RCTs, which are subject to limitations, whereas the NMAs of RWE studies are more generalisable to the current endemic phase of COVID-19
- Concerns around viral clearance are an issue of potential future risk ➔ Resource implications for the NHS if additional patient information, monitoring or data collection is needed

Are there any potential risks associated with viral clearance outcomes profile of molnupiravir?

NMAs: Network meta-analyses; RCTs: Randomised controlled trials; RNA: Ribonucleic Acid; RWE: Real world evidence

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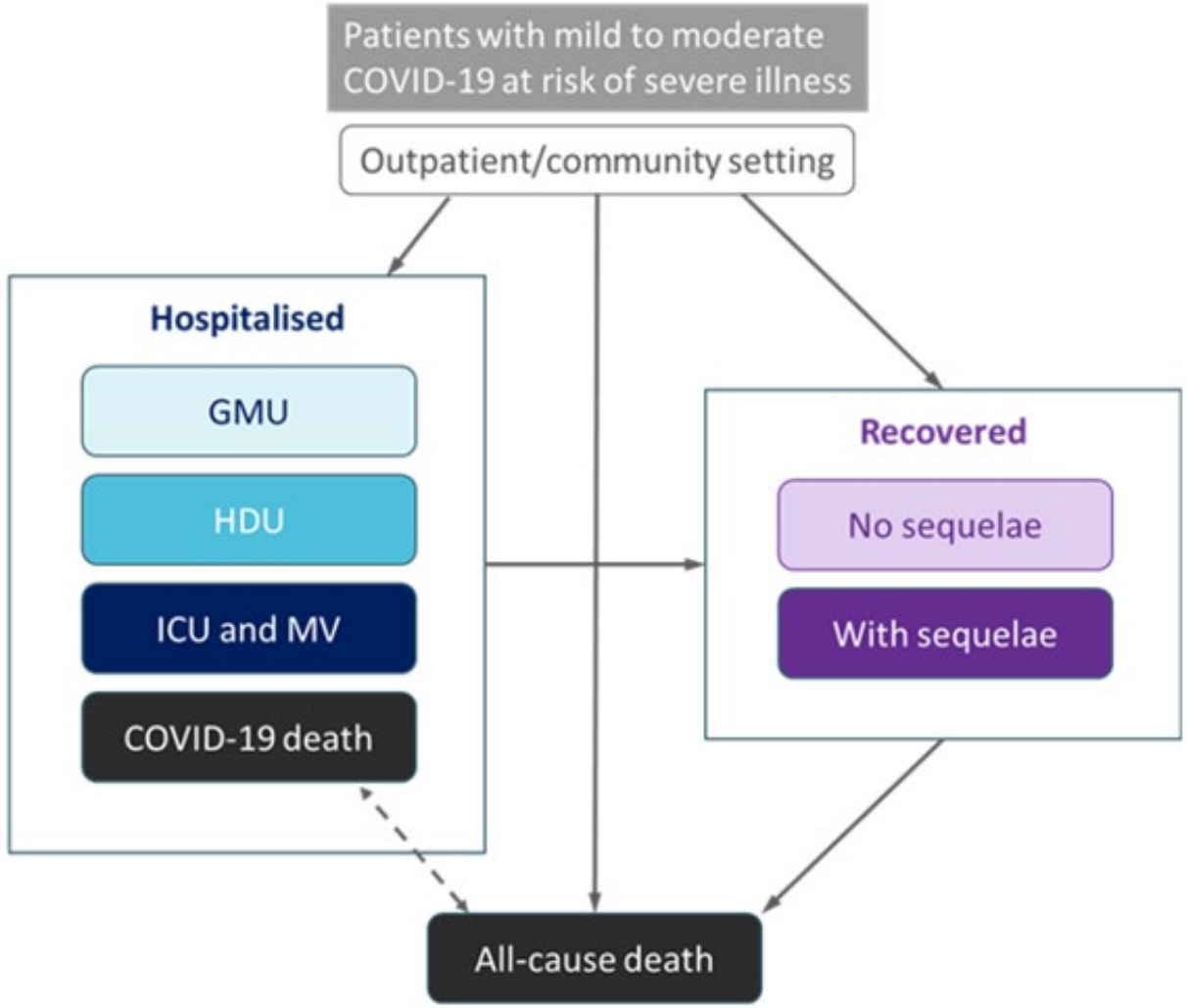
Company's model overview

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

Key issue: Hospitalisation rates for untreated patients

Company uses hospitalisation rates for untreated patients from RWE NMA, EAG uses values from previous NICE appraisals (TA878 and TA971)

EAG comments

- For all cause hospitalisation rate, there were no UK studies in the RWE NMAs.
- Previous appraisals of antivirals for COVID-19 (TA878 and TA971) considered that hospitalisation rates for untreated patients should be between 2.41% and 2.82% based on estimates from OpenSAFELY and DISCOVER-NOW
- The hospitalisation rates for patients aged ≥70 years and for immunocompromised patients are very similar to the MOVe-OUT trial values ➔ It is uncertain whether this is reflective of the current clinical practice as MOVe-OUT was conducted during the pandemic period of COVID-19

Table: Hospitalisation rates for untreated patients – Overall population

Parameter	RWE NMA	MOVe-OUT trial (company's scenario)	OpenSAFELY (TA878 and TA971)	DISCOVER-NOW (TA878 and TA971)
All-cause hospitalisation rate %	3.79 (company's base case)	[redacted]	-	-
COVID-19 related, %	2.93	[redacted]	2.41 (EAG base case)	2.82

Which are the most appropriate sources for the hospitalisation rates to be used in the economic model?

See appendix: Hospitalisation rates for untreated patients

NMAs: Network meta-analyses; RWE: Real world evidence; TA: Technology appraisal

Key issue: Treatment effect on hospitalisation (1)

Background

- Company applied relative risk of all-cause hospitalisation from the RWE NMA in their base case analysis

Treatment comparison	Relative risk (95% credible interval) – RWE NMAs	
	All-cause hospitalisation (random-effects analysis)	COVID-19 related hospitalisation (fixed-effect analysis)
Molnupiravir versus no treatment	0.79 (0.66-0.92) (company base case)	0.85 (0.49-1.53)
Molnupiravir versus nirmatrelvir plus ritonavir	1.19 (0.98-1.43) (company base case)	1.58 (0.98-2.54)
Molnupiravir versus sotrovimab	Not available	1.64 (0.19-13.04) (company base case)

Source: EAR, Table 19

EAG comments

- No UK studies were included in the RWE NMA for all-cause hospitalisation
- Relative risks for all-cause hospitalisation (molnupiravir vs nirmatrelvir plus ritonavir) and COVID-19 related hospitalisation (molnupiravir vs sotrovimab) from RWE NMA are statistically non-significant
- Uncertain whether all-cause hospitalisation or COVID-19 related hospitalisation should be used
  - UK studies (Zheng et al. 2023 and Tazare et al. 2023) only reported composite hospitalisation/death
  - Composite does not match parameters in model → hospitalisation and mortality modelled separately

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

Key issue: Treatment effect on hospitalisation (2)

EAG comments (continued)

- Unclear whether outpatient treatments have any direct effect on mortality as model does not include any outpatient treatment effect on mortality
  - If not, the composite outcomes reported by Zheng et al. 2023 and Tazare et al. 2023 might be a good proxy for the hospitalisation outcome used in the model
- EAG base case uses same approach as company's base case ➔ Due to the presence of uncertainties explored the following assumptions in scenario analyses:
  1. Relative risk of COVID-19 related hospitalisation from the RWE NMA for all the comparisons;
  2. Relative risk of all-cause hospitalisation or death from Zheng et al. 2023 (OpenSAFELY) for the comparison of molnupiravir against nirmatrelvir plus ritonavir (RR 1.64);
  3. Relative risk of COVID-19 related hospitalisation or death from Zheng et al. 2023 (OpenSAFELY) for the comparison of molnupiravir against nirmatrelvir plus ritonavir (RR 2.22);
  4. Relative risk of COVID-19 related hospitalisation or death based on the conclusions from Tazare et al. 2023 (OpenSAFELY) for the comparison of molnupiravir against no treatment (RR 1.0);
  5. Relative risk of all-cause hospitalisation from the RWE direct meta-analysis for the comparison against no treatment (RR 0.81) and nirmatrelvir plus ritonavir (RR 0.88).

Which are the most appropriate outcomes and sources for the treatment effect on hospitalisation to be used in the economic model?

Abbreviations: NMAs: Network meta-analyses; RR: Relative risk; RWE: Real world evidence

Key issue: Proportion of patients with long-term sequelae

Company uses proportion of patients with long-term sequelae from TA878 and TA791, EAG explores lower proportions in scenario analyses

Company

- Assumes 10% of non-hospitalised patients and 100% of hospitalised patients would experience long-term sequelae for a mean duration of 114 weeks, as in TA878 and TA971

EAG comments

- Clinical advice to the EAG suggests the proportion of patients with long-term sequelae are currently much lower than before
  - EAG considers this is likely due to the reduced risks of the current Omicron variant, increased population immunity and the access to better treatments.
- The mean duration of long-term sequelae is reasonable as it was previously assumed in TA878 and TA971
- Explored scenario analyses assuming lower proportion of patients with long-term sequelae

What proportion of patients should be assumed to experience long-term sequelae?

Abbreviations: TA: Technology appraisal

Key issue: Health state utilities (1)

Company

- Utilities derived from a vignette study conducted by the company in which members of the UK General Public completed EQ-5D-5L questionnaires for each of the health states.

EAG comments

- Utilities from the vignette study lack face validity ➔ very low and include negative values for hospitalised patients
- Vignette study does not meet NICE reference case because it used members of the public rather than patients/carers to answer the questionnaires
- EAG's base case uses utilities from Soare et al. 2024 which reported EQ-5D-5L values for patients with mild-to-moderate COVID-19 in the UK for pre-COVID, acute COVID, post-COVID and long COVID
  - Assumed that the utility of acute COVID-19 for hospitalised patients reflects patients in general wards
  - Assumed zero utility for ICU stay with mechanical ventilation (same as TA878 and TA971)
- TA878 and TA971 reported utilities based on studies older than Soare et al. 2024 and not specific for COVID-19 patients

ICU: Intensive care unit; TA: Technology appraisal

Key issue: Health state utilities (2)

Table: Health state utility values used in the model

	Baseline overall population (pre-COVID	Symptomatic outpatient	Hospitalised in general ward	Hospitalised in ICU with MV	Long-term sequelae
Company base case (vignette study)	0.85	0.30	-0.18	-0.38	0.21
EAG base case (Soare et al. 2024)	0.85	0.59	0.28	0	0.67
TA878, TA971 and other sources (company scenario)	0.85	0.57	-0.59 (decrement)	0	0.49
TA878 and TA971 (EAG scenario)	0.85	0.85	0.38[a]	0	0.72[a]
Soare et al. 2024 (EQ-5D-5L)	0.82[b]	0.62[b]	0.38	NR	0.68[c]
Soare et al. 2024 (EQ-5D-3L calculated by the EAG)	0.71	0.49	0.23	NR	0.56

[a] A utility decrement was applied to the baseline overall population utility
[b] Weighted average of pre-COVID utilities for hospitalised and non-hospitalised patients
[c] Weighted average of long COVID utilities for hospitalised and non-hospitalised patients

Source: EAR, Table 25

What is the most appropriate source of utility values to inform the economic model?

Abbreviations: ICU: Intensive care unit; MV: Mechanical ventilation; NR: Not reported TA: Technology appraisal

Differences between company and EAG base case assumptions

Parameter	Company base case	EAG base case
Baseline characteristics (proportion of females)	51.3% based on MOVe-OUT	59% based on the PANORAMIC
Hospitalisation rate (overall population)	3.79% based on all-cause hospitalisation from RWE NMA	2.41% based on COVID-19 related hospitalisation rate from OpenSAFELY
Mortality (subgroup of immunocompromised patients)	24.98% based on INFORM study	10.39% based on TA971
Treatment effect of inpatient treatments (time to discharge)	HR for remdesivir: 1.27 (Beigel et al. 2020) HR for tocilizumab: 1.05 (metaEvidence)	Overall population and subgroups, except immunocompromised patients: • HR of 1 for remdesivir and tocilizumab based on TA878, TA971
Health state utilities	Utilities based on vignette study	General population utilities adjusted for the relative decrements observed in Soare et al.

BNF: British National Formulary; NMA: Network meta-analyses; RWE: Real world evidence; TA: Technology appraisal

Cost-effectiveness results

- All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts
- **Company's base case cost-effectiveness results for overall population:**
  - ICER for molnupiravir versus no treatment is below the £30k threshold
  - Molnupiravir is dominated by nirmatrelvir plus ritonavir
  - ICER for sotrovimab versus molnupiravir is above the £30k threshold
- **EAG's base case cost-effectiveness results for overall population:**
  - ICER for molnupiravir versus no treatment is above the £30k threshold
  - Molnupiravir is dominated by nirmatrelvir plus ritonavir
  - ICER for sotrovimab versus molnupiravir versus is above the £30k threshold

ICER: Incremental cost effectiveness ratio; PAS: Patient access scheme

Molnupiravir for treating COVID-19 (ID6340)

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Other considerations

Potential for managed access

- Managed access not proposed by the company

Severity modifier

- Both the company and the EAG consider severity modifier is not applicable

Molnupiravir for treating COVID-19 (ID6340)

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues and questions for committee

Key issues and questions for committee
Uncertainty around the clinical effectiveness of molnupiravir in the endemic setting of COVID-19 • What is an appropriate time cut-off to distinguish studies that are relevant or not relevant to populations and clinical practices in the current endemic phase of COVID-19? • Is evidence from RWE NMAs or individual studies more appropriate to inform the clinical effectiveness evidence for molnupiravir versus relevant comparators? • Are statistically significant changes in hospitalisation clinically important?
Uncertain viral clearance profile of molnupiravir in relation to its mechanism of action • Are there any potential risks associated with viral clearance outcomes profile of molnupiravir?
Hospitalisation rates for untreated patients • Which are the most appropriate sources for the hospitalisation rates to be used in the economic model?
Treatment effect on hospitalisation • Which are the most appropriate outcomes and sources for the treatment effect on hospitalisation to be used in the economic model?
Proportion of patients with long-term sequelae • What proportion should be assumed for patients experiencing long-term sequelae?
Health state utilities • What is the most appropriate source of utility values to inform the economic model?
Restriction of the decision problem population to non-hospitalised patients • Is it appropriate to restrict NICE scope population to non-hospitalised people only by excluding hospitalised people?

NICE

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

Molnupiravir for treating COVID-19 (ID6340)

Supplementary appendix

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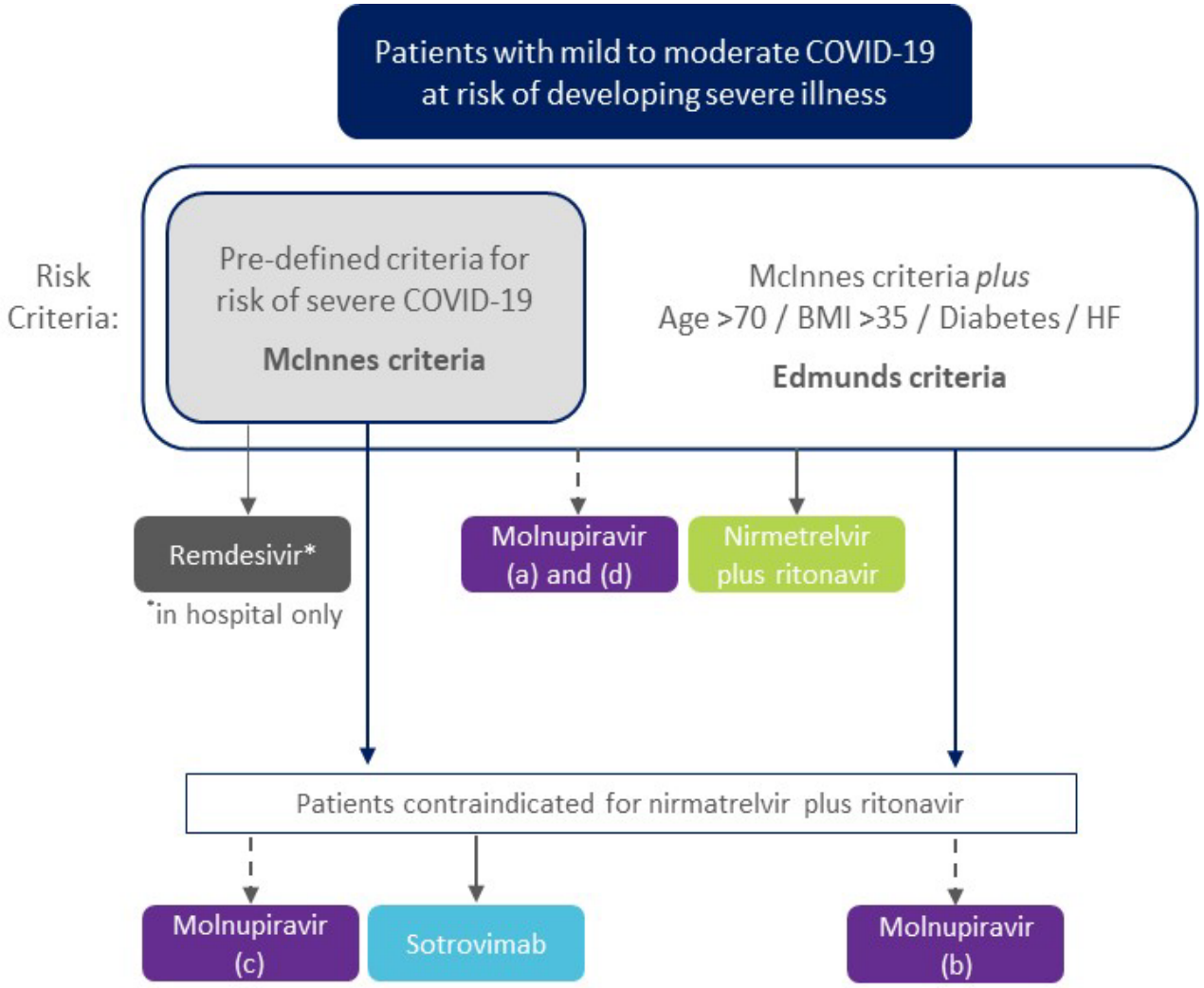
Treatment pathway

Company's proposed positioning for molnupiravir



Source: CS, Figure 1

BMI: Body mass index; HF: Heart failure

a) Alternative to nirmatrelvir plus ritonavir for people at risk of severe disease as per McInnes+Edmunds criteria

b) When nirmatrelvir plus ritonavir is contraindicated for people at risk of severe disease as per Edmunds criteria, where there is currently no treatment option available

c) When nirmatrelvir plus ritonavir is contraindicated for people at risk of severe disease as per McInnes criteria, as an alternative to sotrovimab

d) People at risk of severe disease with incidental COVID-19 acquired in hospital as an alternative to nirmatrelvir plus ritonavir, sotrovimab or remdesivir – no analysis presented for this population

Back to: Treatment pathway and McInnes definition and Edmunds report

Decision problem

Uncertainties related to population and comparators in the company's decision problem

	Final NICE scope	Company	EAG comments
Population	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	Limited to non-hospitalised people	Uncertain whether the exclusion of hospitalised people is clinically appropriate
Comparators	Established clinical management without molnupiravir including: • Nirmatrelvir plus ritonavir • Sotrovimab for people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable • Remdesivir (subject to NICE evaluation)	• No treatment • Nirmatrelvir plus ritonavir • Sotrovimab	• Exclusion of remdesivir appropriate because it is not recommended in the population in company's decision problem • Agree inclusion of no treatment comparator as there is likely to be a group of patients who could not receive either nirmatrelvir plus ritonavir, or sotrovimab ➔ Size and characteristics of this group is uncertain

Back to: Treatment pathway

Decision problem

Uncertainties related to population and comparators in the company's decision problem

	Final NICE scope	EAG comments	
Outcomes	The outcome measures to be considered include: • Mortality • Requirement for respiratory support • Time to recovery • Hospitalisation • Time to return to normal activities • Virological outcomes • Symptoms of post-COVID-19 syndrome • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)	• Mortality • Requirement for respiratory support • Time to recovery • Hospitalisation (requirement and duration) • HRQoL • AEs of treatment Outcomes included during clarification stage: • Virological outcomes • Requirement for respiratory support	The EAG agrees that there are insufficient data in the included studies for time to return to normal activities and symptoms of post-COVID-19 syndrome to be included as outcomes

Back to: Treatment pathway

McInnes definition and Edmunds report

McInnes: People more likely to develop severe COVID-19*

Some people have a health condition that may increase their risk of getting seriously ill from COVID-19, such as:

- 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 (multiple sclerosis, 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

Other issue: Restriction of the decision problem population to non-hospitalised patients

Background

- The population specified in the NICE scope is adults who have mild to moderate COVID-19 with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness

Company

- NICE scope population restricted to non-hospitalised adults only

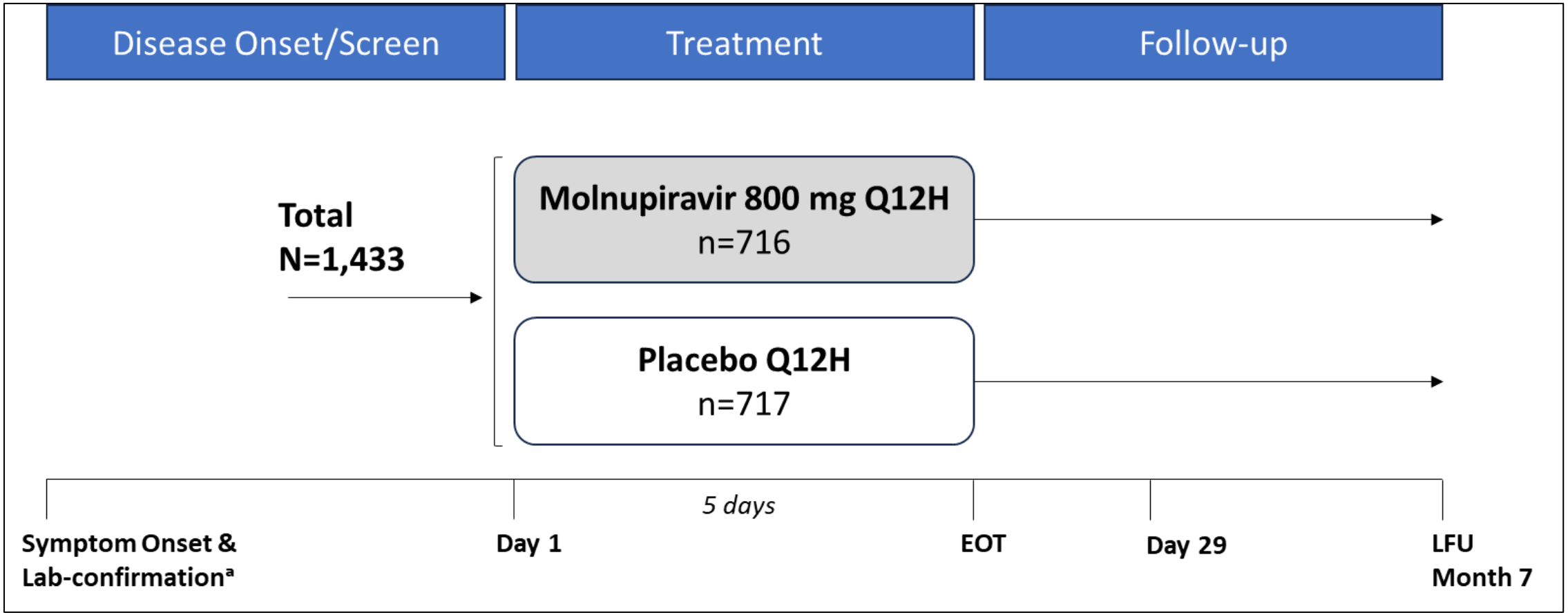
EAG comments

- Uncertain whether non-hospitalised and hospitalised patients would be eligible to receive the same treatments and whether it is clinically appropriate to exclude hospitalised people
- Clinical advice to EAG suggests there is lack of data on the incidence of COVID-19 in hospitalised people and a lack of data on their outcomes ➔ Limiting population to non-hospitalised people may be pragmatic
- Clinical advice also suggests it is unlikely that people hospitalised for a reason other than COVID-19 who then become infected with COVID-19 while in hospital would differ from non-hospitalised people in their prognosis or treatment

Is it appropriate to restrict NICE scope population to non-hospitalised people only by excluding hospitalised people?

MOVe-OUT study design

Figure: MOVe-OUT study schematic



Source: CS, Doc B, Figure 2

Back to: Clinical effectiveness evidence: Overview and MOVe-OUT – Results

EOT = End-of-treatment; LFU = Late follow-up; Q12H: Every 12 hours

MOVe-OUT – baseline characteristics (1)

Table: Patient characteristics in the MOVe-OUT trial (final analysis)

		Molnupiravir (N=716)	Placebo (N=717)
Male sex, n (%)		332 (46.4)	366 (51.0)
Age, yearsMean (standard deviations [SD])		44.4 (14.6)	45.3 (15.0)
Geographic region, n (%)	North America	45 (6.3)	46 (6.4)
	Latin America	331 (46.2)	330 (46.0)
	Europe	230 (32.1)	239 (33.3)
	Asia Pacific	20 (2.8)	17 (2.4)
	Africa	90 (12.6)	85 (11.9)
Time from onset of symptoms (Mean [SD]		3.5 (1.0)	3.5 (1.0)
Risk factors for severe illness, n (%)	At least one risk factor	712 (99.4)	712 (99.3)
	Age > 60 years	119 (16.6)	127 (17.7)
	Active Cancer	13 (1.8)	16 (2.2)
	Chronic kidney disease (CKD)	38 (5.3)	46 (6.4)
	Coronary obstructive pulmonary disease	22 (3.1)	35 (4.9)
	Obesity (BMI ≥ 30)[a]	538 (75.1)	518 (72.2)
	Serious Heart Condition	86 (12.0)	81 (11.3)
	Diabetes Mellitus	107 (14.9)	121 (16.9)

Source: CS, Doc B, Table 10

Back to: Clinical effectiveness evidence: Overview and MOVe-OUT – Results

NICE

BMI: Body mass index

MOVe-OUT – baseline characteristics (2)

Table: Patient characteristics in the MOVe-OUT trial (final analysis)

		Molnupiravir (N=716)	Placebo (N=717)
Baseline COVID-19 severity, n (%)	Mild	395 (55.2)	390 (54.4)
	Moderate	315 (44.0)	323 (45.0)
	Severe	3 (0.4)	1 (0.1)
	Unknown	3 (0.4)	3 (0.4)
SARS qualitative assay viral load (VL) at baseline	High VL (> 106 copies/mL)	389 (54.3)	383 (53.4)
	Low VL (500 to ≤ 106 copies/mL)	162 (22.5)	163 (22.7)
	Undetectable VL (< 500 copies/mL)	64 (8.9)	71 (9.9)
	Unknown	102 (14.2)	100 (13.9)

Source: CS, Doc B, Table 10

Back to: Clinical effectiveness evidence: Overview and MOVe-OUT – Results

NMAs of RCTs – Results for virological outcomes

Table: Results of the NMAs of RCTs – virological outcomes

Outcome	Results for molnupiravir versus each comparator unless stated otherwise the statistic is an odds ratio (95% credible interval)			
	Nirmatrelvir plus ritonavir	Sotrovimab	Remdesivir	Placebo
Viral clearance by Day 5	9.30 (7.35 to 11.81) Favours molnupiravir	No data for this comparison	No data for this comparison	12.09 (10.02 to 14.64) Favours molnupiravir
Viral clearance by Day 10	5.10 (3.87 to 6.77) Favours molnupiravir	No data for this comparison	No data for this comparison	7.23 (5.79 to 9.11) Favours molnupiravir
Viral clearance by Day 14/15	1.14 (0.85 to 1.55) Favours molnupiravir	No data for this comparison	No data for this comparison	1.49 (1.21 to 1.84) Favours molnupiravir
Viral clearance by Day 29	No data for this comparison	2.20 (0.35 to 13.95) Favours molnupiravir	No data for this comparison	2.47 (0.84 to 8.33) Favours molnupiravir
Viral load change to Day 3	No data for this comparison	No data for this comparison	Median difference: -0.11 (-0.38 to 0.16) No significant difference	Median difference: -0.24 (-0.40 to -0.08) Favours molnupiravir
Viral load change to Day 14/15	No data for this comparison	No data for this comparison	Median difference: -0.16 (-0.60 to 0.29) No significant difference	Median difference: -0.13 (-0.37 to 0.11) No significant difference

Source: EAR appendix 5

Back to: Key issue: Uncertainty around the clinical effectiveness of molnupiravir in the endemic setting of COVID-19

NMAs: Network meta-analyses; RCTs: Randomised controlled trials

NMAs of RCTs – Results for respiratory support and adverse events

Table: Results of the NMAs of RCTs – respiratory support and adverse events

Outcome	Results for molnupiravir versus each comparator unless stated otherwise the statistic is an odds ratio (95% credible interval)			
	Nirmatrelvir plus ritonavir	Sotrovimab	Remdesivir	Placebo
Requirement for respiratory support	4.08 (1.85 to 9.88) Favours nirmatrelvir plus ritonavir	2.74 (1.10 to 7.53) Favours sotrovimab	No data for this comparison	0.63 (0.42 to 0.94) Favours molnupiravir
Any adverse events	No data for this comparison	1.01(0.71 to 1.45) No significant difference	1.09 (0.73 to 1.62) No significant difference	0.93 (0.75 to 1.15) No significant difference
Severe adverse events	No data for this comparison	2.71 (1.30 to 6.00) Favours sotrovimab	3.65 (1.36 to 11.94) Favours remdesivir	0.88 (0.66 to 1.16) No significant difference
Treatment discontinuation due to adverse events	1.15 (0.48 to 2.72) No significant difference	No data for this comparison	1.53 (0.26 to 13.57) No significant difference	0.55 (0.27 to 1.08) No significant difference

Source: EAR appendix 5

Back to: Key issue: Uncertainty around the clinical effectiveness of molnupiravir in the endemic setting of COVID-19

NMAs: Network meta-analyses; RCTs: Randomised controlled trials

NMAs of RWE – relevant studies and comparisons

Table: Studies and treatment comparisons in the real-world evidence NMAs

	Molnupiravir	Nirmatrelvir plus ritonavir	Sotrovimab
Molnupiravir	-	Bajema et al. 2023, Cowman et al. 2023, Torti et al. 2023, Zheng et al. 2023	No studies
Nirmatrelvir plus ritonavir	Bajema et al. 2023, Cowman et al. 2023, Torti et al. 2023, Zheng et al. 2023	-	Zheng et al. 2023
Sotrovimab	No studies	Zheng et al. 2023	-
Remdesivir	Manciulli et al. 2023, Tiseo et al. 2023	Basoulis et al. 2023, Manciulli et al. 2023, Tiseo et al. 2023	Manciulli et al. 2023
No treatment	Bajema et al. 2023, Cegolon et al. 2023, Gentry et al. 2023, Paraskevis et al. 2023, Van Heer et al. 2023, Xie et al. 2023	Aggarwal et al. 2023, Bajema et al. 2023, Cegolon et al. 2023, Dryden-Peterson et al. 2023, Gentry et al. 2023, Paraskevis et al. 2023, Van Heer et al. 2023	Cegolon et al. 2023
No nirmatrelvir plus ritonavir or no molnupiravir [a]	Arbel et al. 2023	Kabore et al. 2023, Schwartz et al. 2023	No studies

[a] This comparator reflects a 'no treatment' group that did not receive molnupiravir or nirmatrelvir plus ritonavir but an unspecified proportion of patients in each study may have received remdesivir and/or monoclonal antibodies. This was a separate node from the no-treatment group in evidence networks and is referred to in this report as the 'uncertain no-treatment group'.

Source: EAR Table 8

Back to: Key issue: Uncertainty around the clinical effectiveness of molnupiravir in the endemic setting of COVID-19 and NMAs of RWE - Results

NICE

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

Hospitalisation rates for untreated patients

Table: Hospitalisation rates for untreated patients – Subgroups

		All-cause hospitalisation rate	COVID-19 related hospitalisation rate
Patients aged over 70 years	Kabore et al. 2023	-	12.84 (company's base case)
	Andersen et al. 2023	13.0%	-
	MOVe-OUT trial	[redacted]	[redacted]
Patients contraindicated to nirmatrelvir plus ritonavir	TA878	-	4 (company's base case)
	MOVe-OUT trial	[redacted]	[redacted]
Immunocompromised patients	Kabore et al. 2023	-	22.47% (company's base case)
	Shields et al. 2022	-	15.90%
	MOVe-OUT trial	[redacted]	[redacted]
Patients with CKD	DISCOVER-NOW	-	4.4% (company's base case)
	OpenSAFELY	-	4.15%
	MOVe-OUT trial	[redacted]	[redacted]

Source: EAR Table 14

Back to: Key issue: Hospitalisation rates for untreated patients

CKD: Chronic kidney disease