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Molnupiravir for COVID-19 (ID6340)

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Ines Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Lois Woods critically appraised the company's literature searches, critically appraised the clinical effectiveness systematic

review, and drafted the report; Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Alexander Scott critically appraised the indirect treatment comparisons and drafted the report; Geoff Frampton critically appraised the clinical effectiveness systematic review and indirect treatment comparisons, drafted the report and is the project coordinator and guarantor.

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LIST OF ABBREVIATIONS

AE	Adverse event
A&E	Accident and emergency
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
COVID-19	Coronavirus disease 2019
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DDI	Drug-drug interactions
DSU	Decision Support Unit
EAG	External Assessment Group
eMIT	Drugs and Pharmaceutical Electronic Market Information Tool
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
ITT	Intent to treat
LYG	Life-years gained
mITT	Modified intent to treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services

PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RR	Relative risk/risk ratio
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the Key Issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the Key Issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.7 explain the Key Issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's Key Issues

Table 1 List of the Key Issues identified by the EAG

ID	Summary of issue	Report sections
1	Restriction of the Decision Problem population to non-hospitalised patients	2.3
2	Uncertain size and characteristics of the no-treatment comparator group	2.3
3	Uncertainty around the clinical effectiveness of molnupiravir in the endemic setting of COVID-19	3.2.5, 3.6, 3.7
4	Hospitalisation rates for untreated patients	4.2.6.1.1
5	Treatment effect on hospitalisation	4.2.6.2.1
6	Proportion of patients with long-term sequelae	4.2.6.1.6
7	Health state utilities	4.2.7.2
8	Uncertain benefit / risk profile of molnupiravir in relation to its mechanism of action	3.2.6

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the baseline characteristics, the estimates for hospitalisation rates of untreated patients (overall population), the mortality rate for immunocompromised patients,

the treatment effect of inpatient treatment on time to discharge (except for immunocompromised patients), the health state utilities and the acquisition cost of nirmatrelvir plus ritonavir.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Following their response to the Clarification Questions, the company updated their economic model. The company's revised base case deterministic cost-effectiveness results are shown in Table 2. The pairwise ICER for molnupiravir compared to no treatment is [redacted] per QALY. Nirmatrelvir plus ritonavir, and sotrovimab, have higher costs and QALYs than molnupiravir and the ICERs for these treatments versus molnupiravir are [redacted] and [redacted] per QALY, respectively.

Table 2 Company revised base case results

Technologies	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	1,028	12.873	Reference	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from Table 36 in the Clarification Response document.
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years.
[a] shows the ICER for molnupiravir versus the comparator

For the subgroup of patients aged 70 years and above, the ICER for molnupiravir compared to no treatment is [redacted] per QALY and for nirmatrelvir plus ritonavir compared to molnupiravir is [redacted] per QALY. For patients contraindicated to nirmatrelvir plus ritonavir, the ICER for molnupiravir versus no treatment is [redacted] per QALY and for sotrovimab versus molnupiravir is [redacted] per QALY. For immunocompromised patients, molnupiravir dominates no treatment, and the ICER of nirmatrelvir plus ritonavir and sotrovimab versus molnupiravir is [redacted] and [redacted] per QALY, respectively. For patients with chronic kidney disease, the ICER for

molnupiravir compared to no treatment is [redacted] per QALY and for sotrovimab versus molnupiravir is [redacted] per QALY.

We identified a few errors in the unit costs used by the company in their revised model, which we corrected. Applying the EAG corrections had a minor impact on the model results (for further details, see section 5.3.4).

1.3 The decision problem: summary of the EAG's Key Issues

Issue 1 Restriction of the Decision Problem population to non-hospitalised patients

Report section	2.3
Description of issue and why the EAG has identified it as important	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. The company's Decision Problem is narrower than this, restricted to non-hospitalised adults who meet these criteria. The CS does not explicitly justify this focus but does explain, and the EAG's experts concurred, that there is a lack of relevant data on hospitalised patients. The EAG is uncertain whether non-hospitalised and hospitalised patients would be eligible to receive the same treatments and whether it is clinically appropriate to exclude hospitalised patients (i.e. those who test positive 'incidentally' for SARS-CoV-2 whilst admitted to hospital for a non-COVID reason and who meet the population criteria specified in the NICE scope).
What alternative approach has the EAG suggested?	The EAG sought the opinion of clinical experts. The experts highlighted that there is heterogeneity in how the patients who contract COVID-19 whilst in hospital are diagnosed and treated, due in part to ambiguity in current guidelines, and that there is a lack of robust data for this patient group.
What is the expected effect on the cost-effectiveness estimates?	Uncertain
What additional evidence or analyses might help to resolve this Key Issue?	Wider clinical expert consultation, as the EAG's clinical experts represent one NHS area (Southampton).

Issue 2 Uncertain size and characteristics of the no-treatment comparator group

Report section	2.3
Description of issue and why the EAG has identified it as important	The company have included 'no treatment' as a comparator, although the NICE scope specifies the comparators as 'established clinical management without molnupiravir', and includes nirmatrelvir plus ritonavir, sotrovimab, and if recommended by NICE, remdesivir. The placebo or no-treatment group is the only comparator against which the clinical evidence from randomised controlled trials (RCTs) and real-world evidence (RWE) studies show molnupiravir to be consistently relatively more effective (although results of network meta-analysis of RCTs have major limitations so results of those are highly uncertain). The EAG agrees that a no-treatment group is relevant (i.e. those who are unable to receive any of the active comparator treatments) but we are uncertain of its size and characteristics (and whether it would differ between non-hospitalised and hospitalised people).
What alternative approach has the EAG suggested?	The EAG sought the opinion of clinical experts, who said that, due to a lack of systematic data collection, the size and characteristics of the no-treatment group are uncertain. The experts noted that not all patients who could be contraindicated to nirmatrelvir plus ritonavir because of drug-drug interactions (DDI) necessarily would be precluded this treatment, as clinicians could in some cases temporarily stop the patient's concomitant medication during the antiviral therapy.
What is the expected effect on the cost-effectiveness estimates?	Uncertain
What additional evidence or analyses might help to resolve this Key Issue?	The EAG's clinical experts (consultant virologists and an anti-infectives pharmacist) were not experienced in treating non-hospitalised patients and represent one NHS centre (Southampton). Further clinical opinion may help to clarify the size and characteristics of the no-treatment group for non-hospitalised patients in the NHS.

1.4 The clinical effectiveness and safety evidence: summary of the EAG's Key Issues

Issue 3 Uncertainty around the clinical effectiveness of molnupiravir in the endemic setting of COVID-19

Report section	3.2.5, 3.6, 3.7
Description of issue and why the EAG has identified it as important	The company conducted two sets of network meta-analyses, for RCTs and for RWE studies. The RCT NMAs (which included the UK AGILE-CST and PANORAMIC trials) have major limitations including unaccounted for heterogeneity, risks of bias, and lack of generalisability (section 3.6.1). The RCT NMAs do not provide convincing evidence of the clinical effectiveness of molnupiravir and they do not inform the economic analysis, although one RCT, MOVe-OUT informs a scenario analysis. The company and EAG consider the RWE NMAs more generalisable to current endemic COVID-19 and they inform the economic analysis (see Key Issue 5 below). The RWE NMAs show molnupiravir was statistically more effective at reducing hospitalisation only when compared to no treatment (Appendix 6). However, only one UK study was included in the RWE NMAs (Zheng et al. 2023[1], conducted Feb-Nov 2022). Another UK study using the same OpenSAFELY data platform (Tazare et al. 2023[2], conducted Dec 2021-Feb 2022) showed lack of molnupiravir clinical effectiveness compared to no treatment but was excluded, according to the company's date eligibility criteria. Uncertainty exists around the appropriate time cutoff to ensure current relevance of studies, and generalisability of NMA results, given the lack of UK studies. Furthermore, the evidence provided does not include outcomes for COVID-19 symptom progression or resolution, viral clearance or viral load change, or the requirement for respiratory support (section 3.4.1.3), so clinical effectiveness conclusions for molnupiravir are limited to hospitalisation and death outcomes. A further uncertainty is whether statistically significant reductions in hospitalisation rate would be considered clinically significant.

What alternative approach has the EAG suggested?	We have considered different evidence sources from the NMAs and individual studies in scenario analyses in the economic analysis (see Key Issue 5).
What is the expected effect on the cost-effectiveness estimates?	The excluded UK OpenSAFELY study (Tazare et al. 2023[2]) which showed no difference between molnupiravir and no treatment at reducing the risk of COVID-related hospitalisation or death would have an impact on ICERs (see scenario 4 in Key Issue 5).
What additional evidence or analyses might help to resolve this key issue?	(i) Consideration of the 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. (ii) Consideration of whether RWE NMAs or individual studies are the most appropriate sources of clinical effectiveness evidence. (iii) Clarification on whether observed statistically significant changes in hospitalisation and other outcomes are clinically important.

1.5 The cost-effectiveness evidence: summary of the EAG's Key Issues

Issue 4 Hospitalisation rates for untreated patients

Report section	4.2.6.1.1
Description of issue and why the EAG has identified it as important	In the company's model, the hospitalisation rate for untreated patients was based on the all-cause hospitalisation rate from the company's RWE NMA (3.79%). But we note that for this outcome there were no UK studies in the NMA, which adds uncertainty to the generalisability of these results for the current assessment. A UK RWE study by Zheng et al. 2023[1] was conducted using the OpenSAFELY cohort, although this study did not report data on hospitalisation rates for untreated patients. According to our clinical experts, OpenSAFELY should be a relevant source of information for the current economic model. Moreover, in the previous NICE appraisals of antivirals for COVID-19, TA878 and TA971, the NICE committee considered that hospitalisation rates for untreated patients should be between 2.41% and 2.82%

	based on estimates from OpenSAFELY and DISCOVER-NOW. For subgroup analyses, we found the hospitalisation rates for patients aged ≥70 years and for immunocompromised patients to be very similar to the MOVe-OUT trial values. We are uncertain whether this is reflective of the current clinical practice as MOVe-OUT was conducted during the pandemic period of COVID-19.
What alternative approach has the EAG suggested?	The EAG prefers to use the hospitalisation rates from the OpenSAFELY dataset in our base case, as they are aligned with previous NICE appraisals and clinical expert opinion. We explored the uncertainty around this parameter by conducting scenario analyses using different hospitalisation rates. For subgroup analyses, we explored lower hospitalisation rates in scenario analyses for patients aged ≥70 years and immunocompromised patients.
What is the expected effect on the cost-effectiveness estimates?	Using the hospitalisation rate from OpenSAFELY increases the ICER for: • Molnupiravir versus no treatment from [redacted] to [redacted] per QALY. • Nirmatrelvir plus ritonavir versus molnupiravir from [redacted] to [redacted] per QALY. • Sotrovimab versus molnupiravir from [redacted] to [redacted] per QALY.
What additional evidence or analyses might help to resolve this Key Issue?	Further UK data on hospitalisation rates for the group of patients eligible to receive molnupiravir. Further clinical expert opinion on which are the most appropriate sources for the hospitalisation rates to be used in the economic model.

Issue 5 Treatment effect on hospitalisation

Report section	4.2.6.2.1
Description of issue and why the EAG has identified it as important	The company applied the relative risk of all-cause hospitalisation from the RWE NMA in their base case analysis. However, as noted above, no UK studies were included in the NMA for this outcome. The relative risks for all-cause hospitalisation (molnupiravir versus nirmatrelvir plus ritonavir) and COVID-19 related hospitalisation

	(molnupiravir versus sotrovimab) from the RWE NMA are statistically non-significant. Moreover, we are uncertain whether all-cause hospitalisation or COVID-19 related hospitalisation should be used. The UK studies by Zheng et al. 2023[1] and Tazare et al. 2023,[2] referred to in Key Issue 3 above, did not report either of these outcomes, instead providing composite hospitalisation/death outcomes. The composite outcomes do not match the parameters that inform the economic model, as hospitalisation and mortality were modelled separately within the model. We note that the economic model does not include any outpatient treatment effect on mortality. So, it is unclear whether outpatient treatments have any direct effect on mortality or not. If not, the outcomes reported by Zheng et al. 2023[1] and Tazare et al. 2023[2] combining hospitalisation and death might be a good proxy for the hospitalisation outcome used in the model.
What alternative approach has the EAG suggested?	Due to the uncertainties discussed above, we 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[1] (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[1] (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[2] (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).
What is the expected effect on the cost-effectiveness estimates?	Changing the base case assumptions leads to the following results:

	(1) Molnupiravir versus no treatment from [redacted] to [redacted] per QALY; Nirmatrelvir plus ritonavir versus molnupiravir from [redacted] to [redacted] per QALY. (2) Nirmatrelvir plus ritonavir versus molnupiravir from [redacted] to [redacted] per QALY. (3) Nirmatrelvir plus ritonavir versus molnupiravir from [redacted] to [redacted] per QALY. (4) Molnupiravir versus no treatment from [redacted] to [redacted] per QALY. (5) Molnupiravir versus no treatment from [redacted] to [redacted] per QALY; Nirmatrelvir plus ritonavir versus molnupiravir from [redacted] to [redacted] nirmatrelvir plus ritonavir.
What additional evidence or analyses might help to resolve this Key Issue?	Further clinical expert opinion on which are the most appropriate outcomes and sources for the treatment effect on hospitalisation to be used in the economic model.

Issue 6 Proportion of patients with long-term sequelae

Report section	4.2.6.1.6
Description of issue and why the EAG has identified it as important	The proportion of patients with long-term sequelae is a key driver of the model. The company assumed that 10% of non-hospitalised patients and 100% of hospitalised patients would experience long-term sequelae for a mean duration of 113.60 weeks, as done in previous NICE appraisals TA878 and TA971. The EAG's clinical experts suggested that the proportion of patients with long-term sequelae are currently much lower than before. We consider that this is likely due to the reduced risks of the current Omicron variant, increased population immunity and the access to better treatments. We acknowledge the uncertainty associated with the estimation of this parameter and the impact it has on the model conclusions.
What alternative approach has the EAG suggested?	We explored the following scenario analyses to test the impact of this assumption on model outcomes:

	(1) an exploratory scenario assuming that 1% of non-hospitalised patients and 10% of hospitalised patients experience long-term sequelae; (2) an exploratory scenario assuming that 5% of non-hospitalised patients and 50% of hospitalised patients experience long-term sequelae.
What is the expected effect on the cost-effectiveness estimates?	Assuming a lower proportion of patients with long-term sequelae increases the ICER for: • Molnupiravir versus no treatment from [redacted] to [redacted] per QALY. • Nirmatrelvir plus ritonavir versus molnupiravir from [redacted] to [redacted] per QALY. • Sotrovimab versus molnupiravir from [redacted] to [redacted] per QALY.
What additional evidence or analyses might help to resolve this Key Issue?	Further clinical expert opinion on the estimated proportion of patients experiencing long-term sequelae.

Issue 7 Health state utilities

Report section	4.2.7.2
Description of issue and why the EAG has identified it as important	In the company's base case, the utilities for patients with COVID-19 were 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. The utility values reported by the vignette study are very low and included negative values for the hospitalised patients (meaning that patients experienced states worse than death). We consider that utilities from the vignette study lack face validity. Most importantly, the vignette study does not meet the NICE Reference Case because it used members of the public rather than patients/carers to answer the questionnaires. A study by Soare et al. 2024,[3] which was identified through the systematic literature review of HRQoL studies conducted by the company, reported EQ-5D-5L utilities for patients with mild-to-moderate COVID-19 in the UK for the following health states: pre-COVID, acute COVID,

	post-COVID and long COVID (either for hospitalised or non-hospitalised patients). TA878 and TA971 reported utilities based on studies older than Soare et al. 2024 and not specific for COVID-19 patients.
What alternative approach has the EAG suggested?	We used utility estimates from Soare et al. 2024 in our EAG base case and assumed that the utility of acute COVID-19 for hospitalised patients reported by Soare et al. 2024 reflects the experience of patients in general wards. For intensive care unit stay with mechanical ventilation (not directly reported by Soare et al. 2024), we assumed a utility of zero (same as in TA878 and TA971). Further details of our approach to estimate utilities are discussed in section 4.2.7.2.2 and the values are reported in Table 28.
What is the expected effect on the cost-effectiveness estimates?	Applying the utility values from Soare et al. 2024 increases the ICER for: • Molnupiravir versus no treatment from [redacted] to [redacted] per QALY. • Nirmatrelvir plus ritonavir versus molnupiravir from [redacted] to [redacted] per QALY. • Sotrovimab versus molnupiravir from [redacted] to [redacted] per QALY.
What additional evidence or analyses might help to resolve this Key Issue?	Further discussion on which patient utility estimates are the most appropriate.

1.6 Other Key Issues identified by the EAG

Issue 8 Uncertain benefit / risk profile of molnupiravir in relation to its mechanism of action

Report section	3.2.6
Description of issue and why the EAG has identified it as important	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 and previous NICE appraisal committees have highlighted that viral clearance is

	necessary to avoid transmitting the virus, as well as any viral mutations generated by the mechanism of action of molnupiravir. This could have implications for genotoxicity in humans, the risk of development of new SARS-CoV-2 variants, and/or potential drug efficacy (see sections 3.2.3.3 and 3.2.6). Despite these concerns being raised in the scientific literature, the CS does not discuss them. Limited results for the virological outcomes of the pivotal MOVe-OUT trial were reported in Clarification Response A1, compared to the expected virological endpoints as listed in CS Table 8, and the company virological report was not provided. Virological outcomes could only be analysed in the network meta-analyses of RCTs, which are subject to limitations, whereas we consider the network meta-analyses of RWE studies to be more generalisable to the current endemic phase of COVID-19 (see section 3.4.1.3). The MHRA Public Assessment Report,[4] from the time of the conditional marketing authorisation in November 2021, states that the company has committed to carry out further studies relating to, among other things, the emergence of viral variants, but this information does not yet appear to be available. It is unclear whether these issues were resolved at drug development stage or whether they can be considered ongoing. The EAG consider these concerns around viral clearance as an issue of potential future risk, discussed in report sections 3.2.3.3 and 3.2.6.
What alternative approach has the EAG suggested?	Consideration of these issues may help in determining whether any action would be necessary to help reduce uncertainty in the benefit / risk profile, e.g. post-recommendation viral surveillance of molnupiravir-treated patients.
What is the expected effect on the cost-effectiveness estimates?	This issue is not directly relevant to the cost-effectiveness analysis but might potentially have resource implications for the NHS if additional patient information, monitoring or data collection is deemed appropriate.

What additional evidence or analyses might help to resolve this key issue?	Clarification on whether and how these issues are being addressed and whether any additional data collection is needed to clarify the potential risks relating to the mechanism of action of molnupiravir.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG's critique of the company's model (discussed in section 4), we have identified the following key aspects of the company base case with which we disagree. Our preferred model assumptions for the overall population are the following:

- **Proportion of females at baseline**: 59% based on the PANORAMIC trial rather than 51.3% based on the MOVe-OUT trial (section 4.2.3).
- **Hospitalisation rate of untreated patients**: 2.41% based on COVID-19 related hospitalisation rate from the OpenSAFELY study rather than 3.79% based on RWE NMA (section 4.2.6.1.1.1).
- **Treatment effect of inpatient treatments (time to discharge)**: HR of 1 for both remdesivir and tocilizumab based on previous appraisals TA878 and TA971 rather than a HR of 1.27 for remdesivir and 1.05 for tocilizumab (section 4.2.6.2.3).
- **Health state utilities**: utilities taken from Soare et al.[3] rather than the company's vignettes (see Table 25).

For the subgroups (except the immunocompromised patients), our preferred assumptions include all the above except the change in hospitalisation rate of untreated patients (we use the company's assumptions for this parameters). For the subgroup of immunocompromised patients, our preferred assumptions include the following:

- **Proportion of females at baseline**: 59%, based on PANORAMIC trial.
- **Mortality**: 10.39% based on TA971 rather than 24.98% based on the INFORM study (section 4.2.6.1.4.2).
- **Health state utilities**: utilities taken from Soare et al. [3] rather than the company's vignettes (see Table 25).

Table 3 shows the cumulative cost-effectiveness results of applying the EAG preferred model assumptions to the company's base case for the overall population. Incorporating all the EAG assumptions, the ICER for molnupiravir versus no treatment increases from

[redacted] to [redacted] per QALY, and the ICERs for nirmatrelvir plus ritonavir versus molnupiravir and sotrovimab versus molnupiravir increases from [redacted] to [redacted] per QALY and from [redacted] to [redacted] per QALY, respectively. Incorporating the EAG preferred assumptions leads to an increase in the ICER for all the subgroups (see section 6.4).

The changes that have the most significant impact on the cost-effectiveness results are changing the proportion of patients with long-term sequelae, using alternative relative risks of hospitalisation and alternative utility values.

Table 3 EAG's cumulative model base case results with preferred assumptions, ICER versus molnupiravir (£/QALY)

Scenarios	Treatments	Total Costs	Total QALYs	Pairwise ICER vs molnupiravir
EAG corrected company revised model base case	No treatment	£1,000	12.873	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
+ Proportion of females based on PANORAMIC trial	No treatment	£1,000	12.901	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
+ Overall proportion hospitalised at baseline based on OpenSAFELY	No treatment	£797	12.928	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
+ Treatment effects of inpatient treatments (time to discharge): Using HRs for remdesivir and tocilizumab of 1 and 1 respectively	No treatment	£811	12.928	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
+ Using general population utilities adjusted for the relative decrements observed in Soare et al. 2024[3] (see Table 25)	No treatment	£811	13.042	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
EAG preferred base case	No treatment	[redacted]	[redacted]	[redacted][a]

Scenarios	Treatments	Total Costs	Total QALYs	Pairwise ICER vs molnupiravir
	Molnupiravir	**£1,354**	**13.050**	**Reference**
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]

Source: Analyses conducted by the EAG
HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MOL, molnupiravir; QALYs, quality adjusted life years.
[a] shows the ICER for molnupiravir versus comparator

Modelling errors identified and corrected by the EAG is described in section 5.3.4. For further details of the exploratory and sensitivity analyses done by the EAG, see sections 6.1 and 6.3.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Merck Sharp & Dohme on the clinical effectiveness and cost effectiveness of molnupiravir for treating COVID-19. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 3rd July 2024. A response from the company via NICE was received by the EAG on 22nd July 2024 and this can be seen in the NICE committee papers for this appraisal. A further report on the company's network meta-analyses of real-world evidence studies was received by the EAG on 26th July 2024.

2.2 Background

2.2.1 Background information on COVID-19

Coronavirus disease 2019 (COVID-19) is a viral disease affecting the upper respiratory tract caused by infection with the SARS-CoV-2 coronavirus that emerged in January 2020 creating a global pandemic. Since then, the virus and the nature of the disease and its management (vaccinations, treatment options, precautionary measures) have evolved, shifting to a more endemic state. The company summarise the disease, its history, diagnosis, symptoms, and epidemiology, in relation to the UK setting, accurately in CS section B.1.3.1.

The virus has evolved through various strains and the Omicron variants are now dominant. The Office for National Statistics states that the Omicron variant has been the dominant variant in the UK since 20 December 2021.[6] Clinical experts advising the EAG noted that the course of the disease from transmission to symptoms is now shorter with about 48 hours from exposure to symptoms, and patients can become oxygen dependent after about five days. Since October 2021 most of the UK population has been vaccinated (85%), and booster vaccinations in the UK are now only received by a clinically vulnerable population (CS section B.1.3.1.1): vaccination and previous COVID-19 infection can reduce mortality (CS section B.1.3.1.7). Two English cohort studies have found that the risks of hospitalisation or death following SARS-CoV-2 infection were substantially lower for Omicron variant cases than for delta variant cases, and that the BA.2 Omicron subvariant has lower

risk of severe outcomes than the earlier BA.1 Omicron subvariant.[7, 8] Therefore, the EAG agrees it is appropriate that the CS emphasises evidence from the most recent studies for generalisability to the current, more endemic setting.

COVID-19 can be asymptomatic or symptomatic, with symptoms that range from mild (fever, sore throat, cough, fatigue, gastrointestinal), to moderate (pneumonia without hypoxemia), to severe (pneumonia with hypoxemia) and to critical (including acute respiratory distress syndrome, organ injury or organ failure) as discussed in CS section B.1.3.1.2. COVID-19 symptoms that persist or start three months after the initial infection and that last for at least two months without any other explanation are defined as long-COVID-19; they include fatigue, breathing difficulties, joint pain and chest pain, and organ dysfunction, at any degree of severity (CS section B.1.3.1.4).

The risk of developing severe COVID-19 disease has been associated with older age, male sex, and various comorbidities.[9] Two reports in the UK, the McInnes Report[10] and the Edmunds Report,[11] have listed factors (comorbidities and an older age group) for high risk of progression to severe disease and both have informed recent clinical decision-making. The McInnes Report lists adults with Down's syndrome, solid cancer, haematological diseases and HSCT recipients, renal disease, liver diseases, solid organ transplant recipients, immune-mediated inflammatory disorders, respiratory disease, immune deficiencies, HIV/AIDS, and neurological disorders; the Edmunds Report lists the same and adds age $\geq$70 years, diabetes, obesity, and heart failure (CS Table 4). Therefore, the Edmunds Report extends the list of comorbidities in the earlier McInnes Report, which increases the number of people classified as being at risk for progression to severe disease by 1.4 million to a total of 5.3 million (CS section B.1.3.1.5). It is also thought that people of older age are more likely to have one or more of these comorbidities or a weakened immune system, so there is potential for some overlap of people with these risk factors. The EAG's clinical experts noted that a high-risk population according to the comorbidities listed in the Edmunds Report is a very broad population and applies to most people they see in practice (note that the EAG's clinical experts are hospital-based).

CS section B.1.3.1 discusses the economic burden of COVID-19 from the current literature relevant to the UK or England, and therefore gives an appropriate description of the disease burden for this appraisal. To update the May 2024 statistics reported in the CS, the number of weekly cases up to 24th July 2024 was 3,625 and the number of weekly deaths up to 19th July 2024 was 211.[12] We agree that incidence is likely to be underestimated due to changes in testing, though the extent of underestimation is unknown. However, we also note that the

Gov.UK COVID-19: testing from 1 April 2024 document states that from April [2024] onwards testing using free lateral flow devices will be provided to individuals at highest risk from COVID-19 via their local pharmacy.[13] The list of people who may be at highest risk is reported on the nhs.uk website: the list is broad, including all comorbidities on the Edmunds Report list and more, e.g. sickle cell disease, certain blood conditions, and states that the list does not cover everything,[14] although the older age category is smaller, at ≥85 years rather than ≥70 years.

2.2.2 Background information on molnupiravir

Molnupiravir, brand name Lagevrio, is an antiviral medication that causes an accumulation of errors in the viral ribonucleic acid (RNA) of RNA viruses, including SARS-CoV-2, ultimately inhibiting replication of the virus. The precise mechanism of action is summarised in CS Table 2 and described in detail in the scientific literature.[15-17]

Molnupiravir is administered orally as four 200 mg hard capsules twice a day for five days. If nirmatrelvir plus ritonavir is contraindicated, this is the only remaining oral treatment for COVID-19 and therefore suitable for non-hospitalised patients. The EAG's clinical experts noted that the capsules are very large (21.7 mm x 7.6 mm[18]) and that some patients find them difficult to swallow. The UK public assessment report advises the capsules should not be opened, crushed or chewed, but we are not aware that this would cause any significant issues.

The Summary of Product Characteristics (SmPC) states that molnupiravir is Indicated for 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.[18] The SmPC does not specify the risk factors, although it does refer to the "limits of the clinical trial population" listing the at-risk subgroups in the pivotal clinical trial (MOVe-OUT) for which there is evidence, and it does not limit molnupiravir to non-hospitalised patients.[18]

A Conditional Marketing Authorisation in Great Britain was granted on 4 November 2021 (CS Table 2).[4]

2.2.3 The position of molnupiravir in the treatment pathway

The Interim Clinical Commissioning Policy for remdesivir and molnupiravir for non-hospitalised patients with COVID-19,[19] aims to provide clarity on the access to molnupiravir for the period of the appeal process, as molnupiravir did not receive a positive recommendation in TA878.[20] It shows molnupiravir as a fourth-line option for non-hospitalised adults with symptomatic COVID-19 at high risk of progressing to severe disease

(high risk of severe disease is defined according to the updated Independent Advisory Group Report, i.e. the Edmunds Report, discussed above in section 2.2.1):[11]

- First-line: nirmatrelvir plus ritonavir (as per published NICE guideline TA878)
- Second-line: sotrovimab (as per published NICE guideline TA878)
- Third-line: remdesivir (where supply is available)
- Fourth-line: molnupiravir (if the above treatments are contraindicated or not clinically suitable, and if treatment commences within five days of symptom onset)
- Where patients were ineligible for any of these treatments, they could have been recruited to the PANORAMIC trial.

The EAG's clinical experts do not refer to this policy as they treat hospitalised patients and the EAG is unable to confirm this pathway for non-hospitalised patients in practice. Currently patients in the community need to self-refer to a GP or the NHS 111 service since the COVID Medicine Delivery Units no longer proactively contact patients. There appears to be regional variation according to how the units operate. Additionally, the PANORAMIC trial is no longer recruiting and there are no further options after consideration of these treatments.

The NICE COVID-19 rapid guideline (NG191)[21] states that molnupiravir may be considered for adults ≥18 years of age with COVID-19 who do not need supplemental oxygen, are within five days of symptom onset, and are thought to be at high risk of progression to severe disease. NG191 states that the molnupiravir recommendation is based on clinical trials conducted before emergence of the Omicron (B.1.1.529) variant, which enrolled patients not vaccinated against COVID-19 and there is uncertainty about the generalisability of the evidence. [21] The guideline refers to the Interim Clinical Commissioning Policy (above) for a list of people at high risk of progression, which is based on the risk factors listed in the Edmunds Report. [11] NG191 does not provide any further detail on treatment with molnupiravir than the Interim Clinical Commissioning Policy.

The company outline the following treatment pathway for patients with mild to moderate COVID-19 at risk of developing severe disease in CS Figure 1, reproduced below in Figure 1.

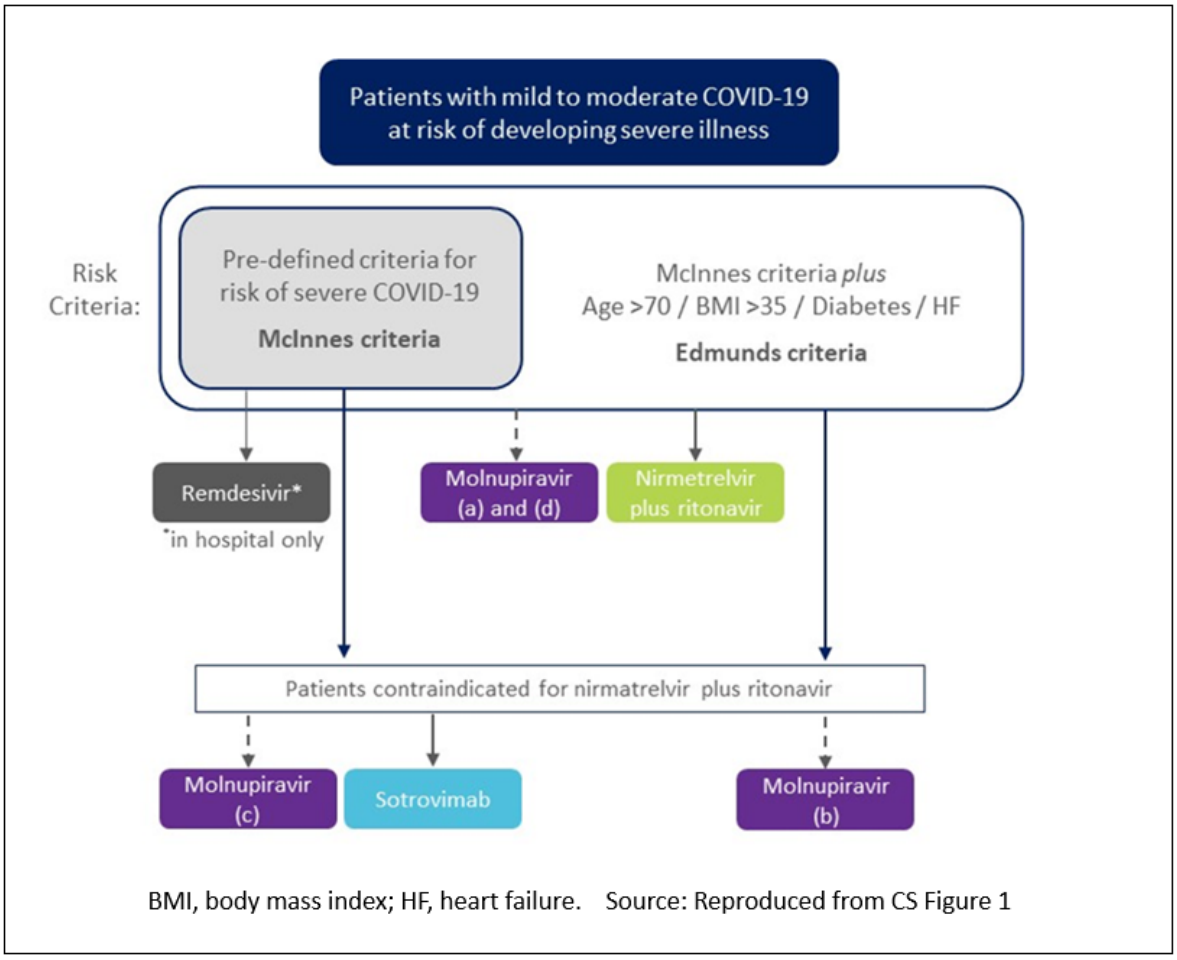

Figure 1 Care pathway with proposed positions for molnupiravir

The company propose four positions where patients would be eligible for treatment with molnupiravir (a), (b), (c) and (d) in Figure 1. The diagram of the pathway is not intuitive, and we discuss each proposed position below.

Position (a): for treating patients at risk of severe illness according to the Edmunds criteria, (which includes the McInnes criteria). This positions molnupiravir as an alternative to nirmatrelvir plus ritonavir, which is different from the interim guidance where nirmatrelvir plus ritonavir must be contraindicated before molnupiravir can be considered and therefore expands the population eligible for treatment with molnupiravir relative to the Interim Clinical Commissioning Policy for antiviral therapies.[19].

Position (b): for treating patients at risk of severe illness according to the Edmunds criteria who are contraindicated to nirmatrelvir plus ritonavir.

Position (c): for treating patients at risk of severe illness according to the McInnes criteria where nirmatrelvir plus ritonavir is contraindicated. This position is unclear because the McInnes criteria is subset of the Edmunds criteria, so these patients are already included at position (b).

Position (d): for treating patients at risk of severe disease with incidental COVID-19 acquired in hospital as an alternative to nirmatrelvir plus ritonavir, sotrovimab or remdesivir. Remdesivir is positioned for in-hospital treatment only, for patients at risk of severe disease according to the McInnes criteria which is in accordance with current guidance for remdesivir (TA971).[22] Interim guidance for treating non-hospitalised patients with remdesivir is given in the same Interim Clinical Commissioning Policy as for molnupiravir[19] where remdesivir must be considered before treatment with molnupiravir. The position for remdesivir for non-hospitalised patients, as per the company Decision Problem and Interim Clinical Commissioning Policy, is not included in the proposed treatment pathway, although the current position of remdesivir for non-hospitalised patients is currently being appealed in the NICE appraisal process and is not certain. However, position (d) is irrelevant to this appraisal because the company Decision Problem is for non-hospitalised patients.

EAG conclusion on the company's positioning of molnupiravir

The company has positioned molnupiravir as an alternative to nirmatrelvir plus ritonavir or sotrovimab, in addition to when nirmatrelvir plus ritonavir is contraindicated or when sotrovimab is unsuitable, which increases the potential population who could receive treatment with molnupiravir compared to the pathway in the Interim Clinical Commissioning Policy. The difference between positions (b) and (c) is unclear, and position (d) is irrelevant to this appraisal according to the company's Decision Problem.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE, together with the EAG's comments on this.

The EAG has noted two key uncertainties in relation to the company's Decision Problem which we have specified as Key Issues for further discussion and clarification (Table 4):

- The company's Decision Problem population is limited to non-hospitalised patients whereas the NICE scope does not make a distinction between non-hospitalised and hospitalised patients. The rationale for this is not explicitly stated, although the company consider that there are no data available on treatments for COVID-19 contracted while a patient is in hospital for another reason (i.e. incidental COVID-19) (CS section B.1.3.2.1). We are uncertain whether the exclusion of hospitalised patients is clinically appropriate, although there appear to be limited data available for this group (Key Issue 1).

- The company have included a no-treatment group as a comparator, which is not specified in the NICE scope. The EAG and our clinical experts agree that there is likely to be a group of patients who could not receive either nirmatrelvir plus ritonavir or sotrovimab, but we are uncertain of the size and characteristics of this group in clinical practice (Key Issue 2). The experts commented that the size of this group would be important in relation to the number needed to treat, to achieve an overall benefit for this group.

A further difference between the NICE scope and the company's Decision Problem is that remdesivir (specified as a comparator in the scope) is not included in the Decision Problem, i.e. not included as a comparator for non-hospitalised patients. The company say this is because remdesivir is not currently recommended for non-hospitalised patients (Table 4 below), which the EAG agrees is appropriate. Remdesivir can be used later in the treatment pathway, for treating patients hospitalised with severe COVID-19. It is therefore relevant to those patients in the Decision Problem population who become hospitalised with severe COVID-19, and the company's economic model takes this in-hospital use of remdesivir into consideration (see section 4.2.2 below).

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	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	The company state "As per final scope". However, the company's Decision Problem population is narrower than the NICE scope population – see EAG comments column.	The company state "N/A".	The company's Decision Problem is limited to non-hospitalised patients (CS section B.3.2.1). The EAG is uncertain whether the exclusion of hospitalised patients is clinically appropriate (see Issue 1). The EAG's clinical experts said there is a lack of data on the incidence of COVID-19 in hospitalised patients and a lack of data on their outcomes, so limiting the appraisal to non-hospitalised patients may be appropriate on pragmatic grounds. However, the experts do not believe that patients hospitalised for a reason other than COVID-19 who then become infected with COVID-19

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
				while in hospital would differ from non-hospitalised patients in their prognosis or treatment.
Intervention	Molnupiravir	As per final scope	N/A	The intervention is 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)	As per final scope, with the addition of placebo or no active treatment as a comparator on the basis of clinical expert feedback that there remains a group of patients that may not receive either nirmatrelvir plus ritonavir or sotrovimab, for reasons explained in Section B.1.3.2.	The company's response was extensive (see CS Table 1 for full details). The EAG have therefore summarised the company's key points here: **Exclusion of remdesivir:** ● The final NICE recommendation for remdesivir in the management of COVID-19 limits its use to the in-patient setting, for either mild-to-moderate or severe COVID-19 (TA971). ● The only situation in which comparison with molnupiravir is	The company have excluded remdesivir as a comparator for non-hospitalised patients, which the EAG agree is appropriate because remdesivir is not recommended in this population. The EAG also agree in principle with the company's inclusion of a no-treatment group as there is likely to be a group of patients who could not receive either nirmatrelvir plus ritonavir, or sotrovimab. However, the EAG and our clinical experts are uncertain of the size and

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
			relevant is in-hospital for incidental COVID-19. ● To our knowledge there is no study reporting on the effects of treatments for incidental COVID-19 acquired in hospital. ● The impact of remdesivir on the key clinical outcome of rate of hospitalisation is not relevant to the pharmacoeconomic assessment of specified comparators. **Inclusion of no treatment as a comparator:** MSD present estimates for molnupiravir versus placebo or no treatment, as we consider that there is a group of patients who fall outside the criteria for treatment with nirmatrelvir plus	characteristics of this roup and have noted this as a Key Issue for further consideration (see Issue 2). Nirmatrelvir plus ritonavir would be contraindicated if patients have severe hepatic or renal impairment or drug-drug interactions (DDI), but the EAG's clinical experts said that clinicians could in some cases temporarily suspend the patient's concomitant medication to overcome DDI. Patients unable to receive nirmatrelvir plus ritonavir could be eligible for sotrovimab but this is subject to having access to an outpatient clinic. The NICE committee for TA878 noted that due to its mode of action sotrovimab may

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
			ritonavir and sotrovimab, and who thus do not currently receive treatment for mild/moderate disease unless they deteriorate and are subsequently hospitalised.	be particularly susceptible to loss of efficacy with the emergence of new SARS-CoV-2 variants so might not be as suitable as the other comparators for COVID-19 treatment in future.
Outcomes	The outcome measures to be considered include: ● Mortality ● Requirement for respiratory support ● Time to recovery ● Hospitalisation (requirement and duration) ● Time to return to normal activities ● Virological outcomes (viral shedding and viral load)	● Mortality ● Requirement for respiratory support ● Time to recovery (referred to as 'length of stay' in the model) ● Hospitalisation (requirement and duration) ● Health-related quality of life ● Adverse effects of treatment	Data did not allow for the following outcome measures to be included: ● Time to return to normal activities ● Virological outcomes (viral shedding and viral load) ● Symptoms of post-COVID-19 syndrome	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 (as noted in section 4.2.6.1.5 below, the economic analysis models the duration of outpatient symptoms). However, viral shedding and viral load were reported in some of the included studies and were subsequently provided in Clarification Responses A1 and A11.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	● Symptoms of post-COVID-19 syndrome ● Adverse effects of treatment ● Health-related quality of life			The CS does not include any results for the requirement for respiratory support. These were subsequently provided in Clarification Response A2.
Subgroups	If evidence allows, the following subgroups will be considered: ● People with risk factors for severe COVID-19 as described in TA878 ● People with broader risk factors for severe COVID-19 than those described in TA878 which may include: ○ Age as a risk factor (for example age over 50 years with one risk factor for	A subgroup for patients with immunosuppression has been added to the analysis, in addition to subgroups based on the final scope which have been more clearly defined. Subgroups included in the analysis are: ● People aged > 70 years ● People contraindicated to nirmatrelvir plus ritonavir ● People with immunosuppression	Patients with immunosuppression are at particularly high risk of severe COVID-19 illness. Chronic kidney disease constitutes a more strictly defined patient group that may be precluded from receiving currently approved treatments for mild to moderate disease.	The company focus on four subgroups in their economic analysis which are consistent with the NICE scope: people aged >70 years; people contraindicated to nirmatrelvir plus ritonavir; people with immunosuppression; and people with chronic kidney disease (CS section B.3.2.1 and CS Appendix E). The company do not discuss whether a systematic approach was used to identify data for subgroup analyses and whether any further subgroups could

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	severe illness or age over 70 years) ○ Specific risk factors (for example a body mass index (BMI) of 35 kg/m^2 or more, diabetes, or heart failure) ● People for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable	● People with chronic kidney disease		have been analysed (e.g. other comorbidities relevant to the NICE scope). However, the EAG agrees that these are appropriate subgroups and likely to be sufficiently representative of patents with risk factors for developing severe COVID-19.
Special considerations including issues related to equity or equality	The impact of vaccination status or SARS-CoV-2 seropositivity on the clinical evidence base of the intervention, generalisability to clinical practice and interaction with other risk factors will	As per the final scope – MSD supports the need for alternative easy to administer oral COVID-19 therapeutics for mild to moderate disease to provide options for patients and clinicians to eliminate any residual and	N/A. While these aspects cannot be directly modelled, they remain particularly relevant for decision making in the endemic phase.	Vaccination status and SARS-CoV-2 seropositivity were not specifically investigated as covariates in assessments of clinical effectiveness. However, the CS states that to ensure the evidence base was representative of the UK setting, only studies conducted in

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	be considered in the context of the appraisal. The impact of different variants of concern of COVID-19 on the clinical evidence base of the intervention will be considered in the context of the appraisal. The scope notes that some people are at a higher risk of severe COVID-19 outcomes because of underlying risk factors. These risk factors have been defined within an Independent Advisory Group report commissioned by the Department of Health	unobserved aspects of access inequality. Treatment at home reduces the onward risk of transmission within a hospital setting, where there are substantial numbers of vulnerable individuals as well as health care professionals, limiting any absenteeism due to infection.		countries with vaccination rates comparable to the UK were prioritised for full data extraction and assessed for inclusion in the RWE NMAs (CS sections B.2.1.2.2 and B.2.9.4.2). In practice, patients' vaccination status varied considerably across the included RWE studies (as summarised in Appendix 4 of this report), although the EAG's clinical experts said that vaccination status alone may not be particularly informative since vaccine efficacy and duration of effectiveness can vary considerably among patients. Key risk factors for severe COVID-19 are considered in the

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	and Social Care. Data from the UK also suggest that mortality due to COVID-19 is strongly associated with older age, male gender, deprivation and black, Asian and minority ethnic family background.			analyses of subgroups, discussed above.
N/A, not applicable				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS includes two systematic literature reviews (SLRs) of clinical effectiveness evidence, one for randomised controlled trials (RCTs) and one for real-world evidence (RWE) studies. Key points are below, with a summary EAG critique of each review in Appendix 1.

3.1.1 RCT systematic literature review

The company SLR to identify relevant RCTs, reported in CS Appendix D, was generally well-conducted. Searches were carried out in a broad range of sources including MEDLINE, Embase, and Cochrane, including supplementary searching, from database inception up to 1st February 2024, and the EAG do not believe any relevant studies would have been missed in the search results. Study selection and data extraction methods were broadly appropriate but, as noted below, some aspects of reporting were incomplete.

The SLR identified 23 RCTs, of which 15 RCTs were judged of high relevance to this appraisal (PRISMA flow diagram in CS Appendix Figure 1). The EAG agree that the 15 trials that progressed to the feasibility assessment (section 3.4.2.1) all met the original eligibility criteria and evaluated interventions relevant to this appraisal; however, we cannot confirm that the other eight trials that made up the set of 23 eligible trials were excluded appropriately as a discrete list was not provided. Two of the 15 RCTs of high relevance were the company-sponsored MOVe-OUT trial[23] (discussed below in section 3.2) which informs some baseline characteristics and a scenario analysis in the company's economic model, and the UK PANORAMIC trial which informs some baseline characteristics in the model (as described in section 4 of this report). The remaining 13 RCTs and the RCT NMAs do not inform the economic analysis.

3.1.2 RWE systematic literature review

CS Appendix D.2 reports a comprehensive SLR to identify evaluations of real-world evidence of molnupiravir and comparator treatments. A peer reviewed literature search was performed in the main healthcare databases from database inception to 15th December 2023, with additional searches for recent material from four relevant conferences and several preprint servers. The aim was to identify studies that are generalisable to the current endemic phase of COVID-19 which the company did at the 'prioritisation' stage, after initial screening for eligibility, by excluding studies with a recruitment period of 2021-2022 (CS Appendix Figure 14). Although the prioritisation process is not fully transparent the EAG believe that all relevant, recent studies are likely to have been captured by the searches.

However, the EAG is uncertain whether the 2021-2022 date cutoff achieves an appropriate balance between optimising the available evidence and ensuring that the evidence is generalisable to current clinical practice (see section 3.7.5).

The RWE SLR identified 82 studies according to the PICOTS criteria in CS Appendix Table 35. Of these studies, 52 were excluded for reasons summarised in CS Appendix D.2.1.4 and the PRISMA flow diagram in CS Appendix Figure 14. The EAG agrees that all exclusion reasons appear appropriate.

Therefore 30 studies proceeded to the feasibility assessment for inclusion in the RWE NMA, discussed further in 3.4.2.2 of this report.

3.2 Critique of MOVe-OUT

MOVe-OUT is the company-sponsored trial that supported the marketing authorisation for molnupiravir. It informs values for some input parameters in the company's economic model (discussed in section 4.2.6.1 of this report) and values for treatment effects in a scenario analysis of the economic model (section 4.2.6.2). MOVe-OUT is also included in the company's RCT NMAs, although these do not inform the economic analysis.

3.2.1 Study characteristics

3.2.1.1 Study design characteristics

MOVe-OUT was an international, multicentre, double-blind, randomised controlled trial comparing molnupiravir against placebo. Study characteristics are summarised in CS sections B.2.3 and B.2.4.

The eligible population is relevant to the NICE scope, including non-hospitalised adults aged ≥18 years who tested positive for SARS-CoV-2 and presented with mild or moderate symptomatic COVID-19 and had at least one of the following risk factors for progression to severe disease: age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart condition, or diabetes mellitus (details in CS Table 7). We agree that the company's risk factors align with the Edmunds Report criteria (discussed in section 2.2.1 above) as they include an older age group, serious heart conditions and diabetes. The MOVe-OUT trial population is narrower than the population described in the NICE scope because it is limited to non-hospitalised patients, but it is consistent with the company's Decision Problem population which is also limited to non-hospitalised patients (see section 2.3 above).

MOVe-OUT included 1433 participants from 20 different countries across North America, Latin America, Europe and Asia, who were randomised 1:1 to molnupiravir (n=716) or placebo (n=717). CS section B.2.12.1 states there were six UK sites. The company specified the six sites in their Factual Accuracy Check but only five of these UK sites are listed in the clinicaltrials.gov update (June 2023) cited by the company. From the company's Factual Accuracy Check statement we understand that four sites recruited patients although the number of UK participants is not reported. CS section B.2.3.6 describes a diverse population and CS section B.2.6.1.2 comments that the inclusion of trial sites from countries with different COVID-19 disease burdens that could not be kept constant is one of several potential factors influencing the change in efficacy results between the interim and final analyses.

The trial recruitment period was 6 May 2021 to 2 October 2021 thus patients were recruited in the 'pre-Omicron' era (i.e. prior to 20 December 2021; see section 2.2.1 above). Due to the mechanism of action of molnupiravir the SARS-CoV-2 variant should not affect the efficacy of molnupiravir. However, the changes in care and also the speed of progression of the disease during the pandemic may be of less relevance to the current Omicron era of endemic disease (see section 2.2.1).

3.2.1.2 Patients' baseline characteristics

Patient baseline characteristics in MOVe-OUT are summarised in CS Table 10. All reported demographic and disease characteristics were similar between the molnupiravir and placebo groups, except there were slightly fewer males in the molnupiravir group (46.4%) than in the placebo group (51.0%) (CS Table 10). As the male sex is more likely to develop severe COVID-19 disease this could bias the molnupiravir arm results favourably, however, this difference is not likely to be significant. Additionally, all demographic and disease characteristics matched the eligibility criteria and are likely to be typical of patients with mild to moderate COVID-19 disease.

The most commonly reported risk factors were obesity (BMI $\geq$30: 73.7%), age >60 years (17.2%), diabetes mellitus (15.9%) and serious heart condition (11.7%) (CS section B.2.3.6) which correspond with the EAG's clinical experts' opinion that the largest populations leading to an at-risk decision are older age, obesity and diabetes. MOVe-OUT may not provide sufficient evidence for the at-risk subgroups included in the company's economic model (section 5.2.4) since patients contraindicated to nirmatrelvir plus ritonavir, immunocompromised patients, and those aged >70 years are not specified in MOVe-OUT,

although active cancer patients and chronic kidney disease patients were respectively 2.0% and 5.9% of the overall trial population.

Participants were described as being 'predominantly' unvaccinated (CS section B.2.12.1.3) although CS section B.2.3.2 says that SARS-CoV-2 vaccines were prohibited at any time prior to randomisation through to Day 29. COVID-19 variant status was non-evaluable for 44.7% of participants; 32.1% had the Delta variant, and the other variants were Alpha, Beta, Gamma, Lambda and Mu[23] which reflect the trial recruitment dates. The EAG concludes that the vaccination status and the COVID-19 variant status of participants is not generalisable to the current NHS population in the UK. The COVID-19 variant should not affect the effectiveness of molnupiravir due to its mechanism of action; however, lack of vaccination status could increase risk of progression to severe disease compared to the mostly vaccinated current UK population and antiviral therapies could appear more effective in a more vulnerable population such as the unvaccinated MOVe-OUT participants.

3.2.2 Risk of bias assessment

The company assessed the MOVe-OUT trial as being at low risk of bias using the Cochrane RoB2 tool[24] (CS Table 12 and CS Appendix Table 26). Justifications for the decisions for each domain of bias are reported in the spreadsheet of assessments made for all the trials included in the RCT NMA provided in Clarification Response A7. A summary of the EAG's assessment is in Appendix 2 and we agree that the trial has a low risk of bias.

3.2.3 Outcomes assessment

Outcomes reported in MOVe-OUT included hospitalisation and death outcomes, COVID-19 related symptom outcomes, and virological outcomes (CS Table 8). Respiratory support outcomes were assessed in a post hoc analysis.[25] Adverse events, serious adverse events, treatment discontinuation due to adverse events are reported appropriately. Details of the main outcomes are discussed below.

3.2.3.1 Hospitalisation and death

The primary outcome in MOVe-OUT was a composite of all-cause hospitalisation or death at Day 29 and at Month 7. Results for each component (i.e. hospitalisation and death) are also reported separately. MOVe-OUT additionally reports COVID-19 related hospitalisation or death as an exploratory outcome. Hospitalisation and death are the most appropriate measures of progression to severe COVID-19 disease, and an International Consortium for Health Outcomes Measurement (ICHOM) COVID-19 Working Group suggest all-cause hospitalisation as a core clinical outcome.[26] It is unclear what would constitute a clinically meaningful difference in hospitalisation rate; the UK Clinical Pharmacy Association

consultee submission for this appraisal suggests a 5% reduction in hospitalisation rate would be clinically meaningful. However, the EAG's clinical experts noted that the number needed to treat (i.e. 100 patients to prevent fewer than 5 hospital admissions) would entail a substantial investment. Uncertainty around what is clinically meaningful for this outcome contributes to Key Issue 3 (section 1.4).

MOVe-OUT also reported results for the WHO 11-point ordinal scale which measures the health states of patients with COVID-19, including hospitalisation and death. This is a clinical progression scale where the patient state is described using a score of 0–10 where 0 means uninfected, 1-3 means ambulatory mild disease, 4-5 means hospitalised with moderate disease, 6-9 means hospitalised with severe disease, and 10 means dead. Hospitalisation status is subcategorised by the level of respiratory support.[27] The proportions of patients in the hospitalised categories in MOVe-OUT informed a scenario analysis in the economic model (CS section B.3.3.1.2 and section 4.2.6.1.4.1 of this report),. The EAG has not identified any literature that validates this outcome measure.

The proportion of patients requiring respiratory support was also reported in MOVe-OUT as a post-hoc analysis. The requirement for respiratory support can indicate disease severity, usually once the patient is hospitalised (and has cost implications due to the resource use). Different types of respiratory support can indicate severity, e.g. non-invasive or invasive ventilation methods, and this was reported for MOVe-OUT in a separate trial publication, Johnson et al. 2022.[25]

3.2.3.2 COVID-19 symptoms

The NICE scope specifies post-COVID symptoms as a relevant outcome but does not mention early symptoms of COVID-19 (as noted in section 4.2.6.1.5 below, the economic analysis models the duration of outpatient symptoms). MOVe-OUT used a daily 15-item symptom diary completed by participants and reviewed by study staff at study visits to record symptom resolution and/or progression up to Day 29. Our clinical experts confirmed that COVID-19 symptoms can last for between five to 15 days so the diaries cover a sufficient time-span to capture disease symptoms over the normal course of the disease. It is not reported whether this is a study-specific symptom diary or a validated symptom diary, the full list of 15 items is not reported, nor the severity scale used. A validated instrument would have been preferable to improve certainty of the results, e.g. FLU-PRO as suggested by the ICHOM COVID-19 Working Group[26] which is a 32-item patient reported outcome measure of symptom severity across six body systems relevant to respiratory disease that has been validated in patients with influenza and influenza-like disease. However, the COVID-19

symptoms outcomes do not inform the company's economic model and so the company approach to assessing symptoms does not affect the cost-effectiveness aspect of this appraisal.

3.2.3.3 Virological outcomes

Virological outcomes (viral shedding and viral load) are relevant, as specified in the NICE scope. Recent NICE Committee discussions (TA971 and TA878) noted that a treatment unable to clear the infection may increase the risk of future variants developing.[22, 28] This may indicate a safety concern (see also section 3.2.6). Virological outcomes are more of a measure of the pathogen burden in response to treatment rather than an insight into the clinical status of a patient.[27] Clarification Response A1 reports mean change from baseline in SARS-CoV-2 nasopharyngeal RNA titre at Day 3 and Days 14/15 for the MOVe-OUT trial. The other exploratory virological outcomes stated in CS Table 8 are not reported. The EAG's clinical experts explained there are no nationally agreed levels for virus clearance due to limitations on the detection capabilities of different test devices and different centres aim for different levels.

3.2.4 Statistical methods

The statistical methods of the MOVe-OUT trial are provided in CS section B.2.4 with further details in the statistical analysis plan (section 9 of the study protocol). The EAG note that the study was adequately statistically powered for the primary outcome (i.e. all-cause hospitalisation or death), although it is unclear whether the power calculation considers clinical significance, and that analyses were carried out on appropriate populations. For the efficacy results a modified intention-to-treat (modified ITT) analysis where all randomised participants who received at least one dose of study intervention and were not hospitalised before receiving that dose were analysed, and for the safety results, all randomised participants who received at least one dose of study intervention were analysed (CS section B.2.4.1).

The interim analyses were conducted when 50% of the trial population reached Day 29, and since the primary endpoint was met at this analysis, the company considers the efficacy evaluation was complete and that the final analysis results are supportive (CS section B.2.4.2). The trial protocol states that the reason for the interim analysis for the efficacy evaluation was, if the efficacy results were smaller than the original assumption but still clinically meaningful, to check whether the overall sample size could be adjusted upwards to n=2000 without inflating the type I error, and to check potential to stop the study early if there was overwhelming efficacy (or futility) of molnupiravir (study protocol section 9). However,

the sample size was not increased, nor was the study was stopped, and there is no mention that the statistical testing of the primary outcome at the final analysis was intended to be inferior to or invalidated/superseded by a positive result in the interim analysis.

Multiplicity was not accounted for beyond controlling for type I error in the interim analysis, because the success of the study was based on the single composite primary endpoint (hospitalisation or death) (Statistical Analysis Plan section 9.8). The other outcomes were not evaluated for statistical significance, except for COVID-19 symptom resolution or progression and the WHO-11 point scale score. Missing, i.e. unknown, data for the primary outcome was imputed as hospitalised or dead which is conservative and appropriate. The data for the WHO 11-point scale score was “sparse” (CS Table 11) which implies missing data. The Miettinen-Nurminen method for estimating confidence intervals for predefined events, and Cox regression with Efrons’ method of tie handling, are appropriate to the trial outcomes.

Overall, the EAG find that the statistical methods for MOVe-OUT are appropriate, and that the primary outcome of the MOVe-OUT trial is the only statistically robust trial outcome.

3.2.5 Clinical efficacy results

3.2.5.1 MOVe-OUT main results

Table 5 below summarises the topline results for each outcome in the MOVe-OUT trial that is relevant to the Decision Problem and/or included in the RCT NMA networks. All outcomes are reported for Day 29 and for the final analysis, unless otherwise stated.

Table 5 MOVe-OUT main results

Outcome	Comparison: molnupiravir versus placebo	Source
Primary outcome: All-cause hospitalisation or death at Day 29	Interim analysis: Favours molnupiravir (statistically significant) Molnupiravir 7.3% vs placebo 14.1% Adjusted difference (95% CI); p-value -6.8 (-11.3 to -2.4); p=0.0012 Final analysis:	CS section B.2.6.1

Outcome	Comparison: molnupiravir versus placebo	Source
	Favours molnupiravir (statistically significant) Molnupiravir 6.8% vs placebo 9.7% Adjusted difference (95% CI); p-value -3.0 (-5.9 to -0.1); p=0.0218	
All-cause hospitalisation or death at Month 7	Statistical significance not reported; not reported as a composite outcome.	CS section B.2.6.1
Sustained resolution or improvement of COVID-19 symptoms	No statistically significant difference	CS section B.2.6.2
Progression of each targeted self-reported sign/symptom of COVID-19	No statistically significant difference	CS section B.2.6.3
WHO 11-point ordinal scale	No statistically significant difference	CS section B.2.6.4
EOT, end of treatment; NMA, network meta-analysis; RCT, randomised controlled trial; WHO, World Health Organization.		

COVID-19 hospitalisation was not reported in the CS, although it informs the RCT NMA network for that outcome in CS Table 21.

The following MOVe-OUT outcomes were not tested statistically, and the results should not be interpreted further: all-cause hospitalisation and all-cause death separately at Day 29 and all-cause hospitalisation or death at Month 7 (CS section B.2.6.1); COVID-19-related hospitalisation or death (Jayk Bernal et al. 2022, Figure S2 [23]; informs the RCT NMA network for that outcome); viral load change (Jayk Bernal et al. 2022, Table S6 [23]; Clarification Response A1a); and the requirement for respiratory support (Johnson et al. 2022[25]; Clarification Response A2a).

The primary outcome reported a 6.8 percentage-point difference in all-cause hospitalisation or death between molnupiravir and placebo, which is probably clinically meaningful according to a consultee submission for this appraisal which suggests a 5% reduction would be clinically meaningful (section 3.2.3.1 above), however, this would suggest that the 3.0 percentage-point difference at the final analysis was not clinically meaningful. The CS does

not discuss the minimum important clinical difference, or any threshold that might suggest clinically meaningful change, for any outcome.

Overall, molnupiravir was favoured over placebo for the primary outcome up to Day 29, but at Month 7 the difference was only 3% and marginally statistically significant. For all other outcomes the results were either not statistically significant or no statistical testing was done. This contributes to the uncertainty of the clinical effectiveness evidence for the efficacy of molnupiravir (Key issue 3, section 1.4).

3.2.5.2 MOVe-OUT subgroup analyses

Pre-specified subgroups of MOVe-OUT were: sex (male/female), days since onset of symptoms (≤3/>3), baseline COVID-19 severity (mild/moderate), baseline SARS-CoV-2 nucleocapsid antibody status (positive/negative), risk factors for severe COVID-19 (>60 years of age; obese; diabetes; serious heart condition), race (4 classes), and whether baseline SARS-CoV-2 qualitative assay was detectable, undetectable or unknown (CS Figure 5).

For the primary outcome, hospitalisation or death at Day 29, results associated molnupiravir with improvement for the obesity, age >60 years, and serious heart conditions subgroups. However, the confidence intervals reported in CS Figure 5 are wide and not significant. Results were not significant for any of the other subgroups (CS section B.2.7.1).

The NICE subgroups of interest are, age >70 years, contraindicated to nirmatrelvir plus ritonavir, immunosuppressed and chronic kidney disease. Thus, the most relevant result from the MOVe-OUT subgroups is for the older age group >60 years which, as noted above, showed molnupiravir to be associated with improvement but was not significant as the confidence interval is wide and crosses the null: absolute risk reduction -2.4 (95% CI -10.6 to 5.8) (CS Figure 5).

3.2.6 Safety results

The CS reports safety in terms of adverse reactions. Adverse events were assessed during treatment and after a 14-day follow-up period in all participants who received at least one dose of study treatment. Results are reported in CS section B.2.10 and summarised in Table 6 below.

Table 6 MOVe-OUT safety results

Outcome	Comparison: molnupiravir versus placebo	Source
Any adverse events	Day 14: similar (less than 3% difference for all adverse events reported) Month 7: not assessed.	CS section B.2.10.1.1
Serious adverse events	Day 14: similar (less than 3% difference; only one drug-related serious adverse in the placebo group, none in the molnupiravir group) Month 7: one drug-related serious adverse event in the placebo group, none in the molnupiravir group.	CS sections B.2.10.1.1 and B.2.10.1.2
Treatment discontinuation due to adverse events	Day 14: similar (less than 2% difference) Month 7: not assessed.	CS section B.2.10.1.1
Adverse events leading to death	Day 14: 12 (1.7%) in the placebo group and 2 (0.3%) in the molnupiravir group (estimated difference -1.4 percentage points (95% CI -2.7 to -0.5)	CS Table 47

The EAG query whether virus clearance should be considered important for the safety of a treatment with a mechanism of action that 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 (see virological outcomes in section 3.2.3.3 above for previous Appraisal Committee opinion). CS Table 8 shows that three exploratory outcomes were measured (SARS-CoV-2-RNA, viral RNA sequences, and infectious SARS-CoV-2), and the CSR references a separate virology report, but results were not provided with the CS. We also note concerns in the scientific literature on the mutagenic potential of molnupiravir in humans.[29] It is the EAG's opinion that it could be too early to say whether molnupiravir is safe in this respect and some reviews advise caution.[30-32] The EAG's clinical experts noted that due to its mode of action, it is possible that molnupiravir could have genotoxic effects in humans if the β-d-N4-Hydroxycitadine triphosphate (NHC-TP) were to cause damage to human DNA. However, we note that the MHRA Public Assessment Report[4] and SmPC[18] considered data from animal studies to show molnupiravir would be of low risk for genotoxicity or mutagenicity in clinical use. Given molnupiravir's mode of action we consider the limited evidence and discussion of virological outcomes to be an uncertainty in the evidence and have noted this as an issue for consideration in section 1.6 (Key Issue 8).

In summary, molnupiravir has been demonstrated to be tolerable with no concerns regarding reported adverse events. However, viral clearance, virus transmission and genomic safety concerns do not appear to be addressed in the MOVe-OUT outcomes, nor discussed by the company, and it is unclear to the EAG how important this is.

EAG conclusion on MOVe-OUT

MOVe-OUT was a well-conducted RCT at low risk of bias therefore conveying with 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. The participants are unlikely to be generalisable to the current UK population due to differences in vaccination status and there is limited evidence available for some of the specified at-risk subgroups in the economic model. There is also limited evidence available to support the usefulness of molnupiravir in reducing the requirement for respiratory support or in reducing the viral load compared to placebo.

3.3 Pairwise meta-analysis of intervention studies

3.3.1 Pairwise meta-analysis of RCTs

Pairwise meta-analyses comparing molnupiravir against placebo are feasible but were not conducted. The CS points out (CS section B.2.8) that pairwise meta-analyses is unnecessary since the direct comparison of molnupiravir against placebo is included in the NMAs.

3.3.2 Pairwise meta-analysis of real-world evidence studies

For the real-world evidence studies the company have reported “direct meta-analysis” results alongside those of the NMAs of RWE studies, i.e. pairwise meta-analyses comparing molnupiravir against either nirmatrelvir plus ritonavir, sotrovimab, remdesivir, or no treatment, where sufficient RWE studies are available for each of these comparisons. The pairwise meta-analyses were included to provide supporting information for the company’s primary (base case) Bayesian NMAs (Clarification Response A16b).

EAG conclusion on pairwise meta-analysis

The company’s approaches for pairwise meta-analysis are appropriate.

3.4 Critique of studies included in the company's network meta-analyses (NMAs)

The company conducted two sets of NMAs for a range of outcomes, for randomised controlled trials, which we refer to as "RCT NMAs"; and for real-world evidence studies, which we refer to as "RWE NMAs".

The CS presents a relatively superficial description of the NMA methods (CS section B.2.9 and CS Appendix D). The company provided the following reports on the NMAs which provide more extensive methodological details:

- A confidential company report on the RCT NMAs was provided in response to Clarification Question A11. We refer to this as the "RCT NMA Report".

- A confidential company systematic literature review report for the RWE studies was provided with the company's Clarification Responses, dated July 2024, which also includes information on the company's RWE NMA methods and results. We refer to this as the "RWE SLR Report".

- A confidential company report on the RWE NMAs was not included in the Clarification Responses but was subsequently provided by the company on request from the EAG. We refer to this as the "RWE NMA Report".

3.4.1 Rationale for the NMAs

3.4.1.1 Rationale for the NMAs of randomised controlled trials

The RCT NMAs were conducted to enable molnupiravir to be compared indirectly against nirmatrelvir plus ritonavir, sotrovimab, and remdesivir, since no RCTs have directly compared molnupiravir against these therapies. The EAG agrees this rationale is appropriate.

3.4.1.2 Key limitations of the NMAs of randomised controlled trials

The RCT NMAs do not inform the economic analysis for this technology appraisal and have substantial limitations, as follows:

- The company acknowledges that the RCTs were conducted during the pre-Omicron era and their populations and results are unlikely to be generalisable to the current endemic phase of COVID-19. The EAG agrees that the RCTs may have limited generalisability to

current patient populations, COVID-19 disease characteristics and clinical practice for COVID-19 treatment.

- The RCT NMAs were based on fixed-effect models which underestimate heterogeneity, potentially giving a false picture of treatment effectiveness (inappropriately narrow credible intervals for the outcome point estimates) (see 3.5.2.1.1.1 below).
- The company did not adequately assess the sensitivity of the RCT NMAs to risks of bias and declined to do so in Clarification Response A7. The EAG considered that several of the RCTs have high risk of bias (see section 3.4.4.1 below) but the impact of this for the RCT NMA results has not been explored.

Due to these limitations, and the company's preference to focus on RWE studies, which we agree is appropriate, the RCT NMAs are not discussed in detail in this report.

3.4.1.3 Rationale for the NMAs of real-world evidence studies

The company conducted RWE NMAs in addition to the RCT NMAs "due to the continual changes in COVID-19 epidemiology" (CS section B.2.9). Notably, the most recent RCTs had been conducted during the pandemic phase of COVID-19 (prior to the emergence of Omicron variants of the SARS-CoV-2 virus) and would not be expected to reflect clinical management of COVID-19 in the current endemic phase of the disease. The company's study selection criteria identified RWE studies conducted during the endemic phase of COVID-19 which should be generalisable to people who currently experience COVID-19. NMAs of RWE studies were required due to a lack of individual RWE studies that had compared molnupiravir against all the relevant comparators.

The RWE NMAs included the same hospitalisation/death outcomes as the RCT NMAs. However, due to a lack of consistent data in the RWE studies, virological, respiratory support and safety outcomes were only included in the RCT NMAs. The EAG checked the RWE studies and we confirm that these outcomes were not reported frequently enough to be included in the RWE NMAs.

The EAG agrees that the RWE NMAs are more generalisable to the current endemic phase of COVID-19, and we note that results of the RCT NMAs are not used in the economic analysis. Furthermore, the company stated in Clarification Response A7 that they wish to focus on the RWE NMAs for their evidence submission as they were unable to conduct an investigation of the sensitivity of the RCT NMAs to bias.

3.4.2 Identification, selection and feasibility assessment of studies for NMAs

3.4.2.1 Feasibility assessment of RCTs

The company's process for identifying and selecting relevant RCTs for this technology appraisal is summarised in CS section B.2.1.2.1, CS Appendix D.1 and in the 'Feasibility' and 'NMA methodology' sections of the RCT NMA Report and is critiqued above in section 3.1.1 of this report. As noted in section 3.1.1 above, the company identified fifteen RCTs to undergo a feasibility assessment for inclusion in the RCT network meta-analysis (NMA).

During the feasibility assessment four RCTs were excluded by the company, leaving 11 eligible for inclusion in the NMAs. The EAG conducted a detailed critique of the company's feasibility assessment and we agree broadly with the company's rationale for including these 11 RCTs.

Two of the included RCTs were conducted in the UK: PANORAMIC[33] and AGILE-CST-2.[34] PANORAMIC had a large sample size and 94% of participants had received three doses of vaccine, however both the company and EAG find it to be at high risk of bias; we note that it is open label (no blinding), and that unlike the other RCTs the comparator was not placebo but 'usual care' and there was potential that participants in the usual care group could have received other antivirals. Nevertheless, the company included it in the networks where feasible, which was for all-cause death and for serious adverse events. Fifty percent of participants in AGILE-CST-2 were vaccinated, however the eligibility criteria required participants to be free of uncontrolled chronic conditions which may have affected their risk status compared to the populations of the other included RCTs.

3.4.2.2 Feasibility assessment of RWE studies

The company's process for identifying and selecting relevant RWE studies for inclusion in network meta-analyses is described in CS section B.2.1.2.2, CS Appendix D.2, and in Appendix I of the RWE SLR Report and is summarised and critiqued above in section 3.1.2 of this report. Thirty studies were identified as relevant (section 3.1.2), listed in Table 7 below, and these entered the company's feasibility assessment for inclusion in NMAs.

The EAG queried why eight studies had been excluded during the selection process, since the exclusion reasons given for these studies in CS Appendix Figure 15 are not specific. Following the company's explanation in Clarification Response A5 the EAG agrees that these exclusions were appropriate (in the case of Mazzitelli et al. 2023 we agree with the exclusion but not the reason) (Table 7). After the company's feasibility assessment, 22 RWE

studies were therefore considered eligible for inclusion in NMAs (CS section B.2.9; CS Appendix Table 36).

Table 7 RWE studies included in the RWE NMA feasibility assessment

RWE study / publication	Study design	Treatment comparison(s)	Included in NMA?
Aggarwal et al. 2023[35]	Retrospective cohort	Nirmatrelvir plus ritonavir vs no treatment	Included
Arbel et al. 2022[36]	Retrospective cohort[a]	Molnupiravir vs no molnupiravir	Included
Bajema et al. 2023[37]	Retrospective matched cohort	Nirmatrelvir plus ritonavir vs no treatment Molnupiravir vs no treatment Nirmatrelvir plus ritonavir vs molnupiravir	Included. Note that the direct and indirect treatment effect estimates were handled as two separate studies in the NMA.
Basoulis et al. 2023[38]	Prospective cohort	Nirmatrelvir plus ritonavir vs remdesivir	Included
Bruno 2022[39]	Retrospective cohort	Molnupiravir vs nirmatrelvir plus ritonavir	Excluded: incompatible study design. EAG: agree, it was subject to confounding because only unadjusted comparative data were reported (CS Appendix D.2.3).
Butt et al. 2023a[40]	Retrospective cohort (matched)	Molnupiravir vs no molnupiravir/no nirmatrelvir plus ritonavir	Included
Butt et al. 2023b[41]	Retrospective cohort (matched)	Nirmatrelvir plus ritonavir vs no molnupiravir/no nirmatrelvir plus ritonavir	Included
Cegolon et al. 2023[42]	Retrospective case control	Molnupiravir or nirmatrelvir plus ritonavir	Included

RWE study / publication	Study design	Treatment comparison(s)	Included in NMA?
		or sotrovimab vs standard of care	
Cowman et al. 2023[43]	Retrospective cohort	Nirmatrelvir plus ritonavir vs molnupiravir	Included
Del Borgo et al. 2023[44]	Prospective cohort	Remdesivir vs molnupiravir vs nirmatrelvir plus ritonavir	Excluded: no common outcomes. EAG agrees with company rationale (Clarification Response A5).
Dryden-Peterson et al. 2023[45]	Retrospective cohort	Nirmatrelvir plus ritonavir vs no nirmatrelvir plus ritonavir	Included
Gentry et al. 2023[46]	Retrospective cohort (propensity-matched analysis).[b]	Molnupiravir or nirmatrelvir plus ritonavir vs no oral antivirals	Included
Kabore et al. 2023[47]	Retrospective cohort	Nirmatrelvir plus ritonavir vs no nirmatrelvir plus ritonavir	Included
Lin et al. 2023[48]	Retrospective cohort	Nirmatrelvir plus ritonavir vs molnupiravir	Excluded: no common outcomes. EAG: agree, time to hospitalisation or death was reported but not the event rates.
Manciulli et al. 2023[49]	Retrospective cohort	Remdesivir vs sotrovimab vs molnupiravir vs nirmatrelvir plus ritonavir	Included
Martin-Blondel et al. 2023[50]	Prospective cohort	Sotrovimab vs nirmatrelvir plus ritonavir	Excluded: incompatible study design. EAG: agree, it was subject to confounding because it only reported unadjusted

RWE study / publication	Study design	Treatment comparison(s)	Included in NMA?
			comparative data (CS Appendix D.2.3).
Mazzitelli et al. 2023[51]	Retrospective case control	Remdesivir vs no treatment	Excluded: no common outcomes. EAG agrees with the exclusion but not with the reason (COVID-19 related hospitalisation is reported, but imbalances in prognostic factors were not adjusted for appropriately).
Minoia et al. 2023[52]	Prospective cohort	Nirmatrelvir plus ritonavir vs molnupiravir	Excluded: high proportion of patients receiving concomitant treatments. EAG: agree, the cohort comprised patients with haematological malignancies who were able to receive monoclonal antibodies in association with the antivirals.
Najjar-Debbiny et al. 2023[53]	Retrospective case control	Molnupiravir vs no molnupiravir	Included
Najjar-Debbiny et al. 2023[54]	Retrospective cohort	Nirmatrelvir plus ritonavir versus no nirmatrelvir plus ritonavir	Included
Paraskevis et al. 2023[55]	Retrospective cohort	Molnupiravir vs nirmatrelvir plus ritonavir	Included

RWE study / publication	Study design	Treatment comparison(s)	Included in NMA?
Petrakis et al. 2023[56]	Retrospective case control (matched-pairs)	Nirmatrelvir plus ritonavir vs no oral antiviral treatment	Excluded: incompatible study design. EAG: agree, only the treated cohort was at increased risk of progression to severe disease whereas the untreated cohort was not.
Qian et al. 2023[57]	Retrospective cohort	Any treatment vs nirmatrelvir plus ritonavir vs monoclonal antibodies	Excluded: population heterogeneity. EAG: agree, the groups were not balanced for comorbidities or age, i.e. risk factors.
Schwartz et al. 2023[58]	Retrospective case control	Nirmatrelvir plus ritonavir vs no nirmatrelvir plus ritonavir	Included
Tiseo et al. 2023[59]	Prospective cohort	Nirmatrelvir plus ritonavir vs molnupiravir vs remdesivir	Included
Zheng et al. 2022[60]	Retrospective cohort	Sotrovimab vs molnupiravir	EAG: Incorrectly listed by the company as included but had previously been excluded which the EAG agrees was appropriate.
Zheng et al. 2023[1]	Retrospective cohort	Nirmatrelvir plus ritonavir vs sotrovimab vs molnupiravir	Included

RWE study / publication	Study design	Treatment comparison(s)	Included in NMA?
Van Heer et al. 2023[61]	Retrospective cohort	Nirmatrelvir plus ritonavir vs molnupiravir vs no oral antivirals [c]	Included
Torti et al. 2023[62]	Retrospective cohort	Nirmatrelvir plus ritonavir vs molnupiravir	Included
Xie et al. 2023[63]	Retrospective cohort	Molnupiravir vs no treatment	Included

[a] The study publication indicates Arbel 2022 was a retrospective study, although CS Appendix Table 36 notes it as a prospective cohort study.
[b] CS Appendix Table 36 notes Gentry 2023 as a matched case control study.
[c] antivirals were added to the no-treatment group during analysis (section 3.4.4.2.2).
Table source: EAG. For study references see Table 7.

Five of the 22 studies listed as eligible for inclusion in NMAs (CS Appendix Table 36) were not subsequently included in any of the NMAs reported in the CS (Butt et al. 2022a, Butt et al. 2022b, Najjar-Debbiny et al. 2023a, Najjar-Debbiny et al. 2023b, Zheng et al. 2022) but neither the CS, CS Appendices nor Appendix I of the RWE SLR Report explain this. However, we agree that these studies should be excluded, for the following reasons:

- Zheng et al. 2022: This study had been excluded by the company because the population had a specific comorbidity, kidney disease, that was not comparable between studies, but the study was included in the kidney disease sensitivity analysis (Clarification Responses A5 and A9). We also note that this study included patients recruited in 2021-2022 so for consistency should have been excluded before feasibility assessment according to the company's criteria for selecting studies most relevant to current endemic-phase COVID-19 (CS Appendix D.2.1.4).

- Butt et al. 2022a, Butt et al. 2022b, Najjar-Debbiny et al. 2023a, and Najjar-Debbiny et al. 2023b: We note that (as indicated in Appendix I of the RWE SLR Report) some patients in the no-treatment group of these studies might have received antivirals. As such this is not a strict no-treatment group (contrary to the information reported in CS Appendix Table 36) and we believe these studies are at high risk of confounding and should be excluded. CS Appendix Figure 17 does show that the Butt and Najjar-Debbiny studies are connected to a separate node "no nirmatrelvir + ritonavir or molnupiravir" in the evidence networks, acknowledging the 'uncertain no-treatment' group in these studies although the nature of this group is not clearly communicated in the CS or Appendices.

After excluding these five studies, 17 RWE studies were included by the company in the RWE NMAs.

However, in addition to the Butt and Najjar-Debbiny studies, as shown in Appendix I of the RWE SLR Report and CS Appendix Figure 17, three further studies had 'no-treatment' groups in which some patients might have received antivirals and therefore these studies also have a high risk of confounding (Arbel et al. 2023, Kabore et al. 2023, Schwartz et al. 2023). (NB This contamination of the no-treatment groups is not shown in CS Appendix Table 36 where the studies are summarised). The EAG requested the company to conduct a sensitivity analysis removing the "no nirmatrelvir + ritonavir or molnupiravir" node from the evidence networks to exclude these studies (Clarification Question A15). Removing this node from the networks had negligible impact on NMA results, presumably because these studies had not contributed to the "true" no-treatment node (for results, see Appendix 6).

Of the 17 RWE studies that were included in the company's RWE NMAs (Table 8), only one study, Zheng et al. 2023,[1] had been conducted in the UK. This study compared molnupiravir and sotrovimab each against nirmatrelvir plus ritonavir using data from the OpenSAFELY electronic health record platform. This is a substantial dataset of direct relevance to UK clinical practice (and earlier data cuts from it provided evidence in the previous NICE Technology Appraisals of antivirals for COVID-19, TA878 and TA971). We present the results of the Zheng 2023 study alongside those of the overall RWE NMA results in Appendix 6, and this study informs scenario analyses on hospitalisation rates in the economic evaluation (see section 4.2.6.1.1.1).

Table 8 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	Aggarwal et al. 2023	Cegolon et al. 2023

	Cegolon et al. 2023 Gentry et al. 2023 Paraskevis et al. 2023 Van Heer et al. 2023 Xie 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	
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: EAG table. For study references see Table 7

3.4.3 Clinical heterogeneity assessment

3.4.3.1 Heterogeneity assessment in NMAs of randomised controlled trials

The RCT NMA Report refers to heterogeneity assessment as part of the NMA feasibility assessment process and the report provides tables comparing the study designs, study inclusion and exclusion criteria, baseline characteristics, and comparability of outcomes across the RCTs. Overall, the RCTs were heterogeneous in their population characteristics, which in several RCTs were uncertain due to lack of consistent reporting (Appendix 3). However, as noted above (section 3.4.1.2) the RCT NMAs have major limitations that likely limit their validity and generalisability to the current technology appraisal and they do not inform the economic analysis. We therefore do not discuss heterogeneity within these NMAs further in this report.

3.4.3.2 Heterogeneity assessment in NMAs of real-world evidence studies

Heterogeneity of study characteristics was considered in detail during the company's NMA feasibility assessment (section 3.4.2.2 above). However, it was difficult to identify an homogeneous set of RWE studies and those included in the RWE NMAs varied in several respects, including in how comorbidities were defined and reported (see Appendix 4). The company conducted a range of scenario (i.e. subgroup) analyses to explore the impact of these differences in the RWE NMAs (Clarification Responses A9 and A18).

The Statistical Analysis Plan (SAP) for the RWE NMAs (Appendix C of the company's RWE SLR Report) lists 11 scenario analyses (SAP Table 4). These were: (1) direct & indirect network; (2) base case network plus the Butt 2023a and Butt 2023b studies (outliers in terms

of symptomatic disease distribution between arms); (3) subgroup aged ≥60 years; (4) subgroup aged ≥70 years; (5) subgroup of cancer patients; (6) subgroup of cardiovascular disease patients; (7) subgroup of chronic kidney disease patients; (8) subgroup of immunocompromised patients; (9) subgroup of obese patients; (10) subgroup of diabetic patients; and (11) sensitivity analysis of vaccination status. Results of these scenario analyses are summarised briefly alongside the base case NMA results in Appendix 6 of this report.

Detailed results of heterogeneity assessment for the NMA base case and scenario analyses are provided in Table 39 (Appendix K) of the RWE SLR Report for both fixed-effect and random-effects models. As noted in CS section B.2.9.4.2, there was 'significant and notable' heterogeneity for some outcomes in the overall active treatment/control network, particularly for analysis of all-cause hospitalisation or death. The subgroup analyses of prognostic factors for severe COVID-19 in some cases eliminated the heterogeneity for certain comorbidity-treatment comparison combinations but heterogeneity generally remained present in most of the subgroup analyses. An exception is all-cause death, which had little or no statistical heterogeneity in the base case and subgroup analyses. These results highlight the challenge of controlling for statistical heterogeneity in the RWE NMAs despite the detailed consideration of the sources of heterogeneity and systematic application of subgroup analyses.

3.4.4 Risk of bias assessment for studies included in the NMAs

3.4.4.1 Risk of bias in the RCTs

The company assessed the risk of bias for each of the RCTs included in the NMAs using the Cochrane RoB 2 tool (CS section B.2.5.1). The EAG requested that the company investigate the sensitivity of the RCT NMA results to risks of bias, but the company did not do so (Clarification Response A7). We note that, for the molnupiravir versus no treatment comparison, viral clearance outcomes up to Day 5 and up to Day 10 (NMA Report Tables 49 and 53) appear particularly sensitive to risk of bias since all three RCTs which informed these outcomes were judged to have high risk of bias. Removing the RCTs at high risk of bias from the NMAs would eliminate these outcomes from the analysis. Given that the RCT NMAs have several major limitations as noted above (section 3.4.1.2), we did not explore the sensitivity of all RCT NMA outcomes and treatment comparisons to risks of bias.

3.4.4.2 Risk of bias in the RWE studies

3.4.4.2.1 Company assessments

The company conducted a risk of bias assessment for the RWE studies which CS section B.2.5.2 states was based on NICE criteria.[64] The company rated three of the 30 RWE studies included in the feasibility assessment as having risk of bias concerns (CS Table 13 and CS Appendix Table 40). The EAG queried whether it was plausible that only 10% of the observational studies were considered to have risk of bias issues for concern, whereas 50% of the RCTs were deemed to have at least some risk of bias concerns (CS Table 12). The company clarified that the RWE studies considered at risk of confounding had already been excluded from the list in CS Table 13 and CS Appendix Table 40 during the NMA feasibility assessment (Clarification Response A8).

However, as noted in section 3.4.2.2 above, several studies were at high risk of confounding because the no-treatment group could have received antiviral therapies (Arbel et al. 2023, Butt et al. 2023a,b, Kabore et al. 2023, Najjar-Debbiny et al. 2023a,b, Schwartz et al. 2023) yet the company had rated these all as having low concern relating to bias (CS Table 13). The impact of risk of bias in these studies on the interpretation of NMA results was investigated through a company sensitivity analysis requested by the EAG, as explained in section 3.4.2.2 above.

NICE's guidance on assessing the risk of bias in non-randomised evidence is not exhaustive and recommends that "an appropriate and validated quality assessment instrument" should be used.[65] The EAG asked the company to assess the risk of bias in the RWE studies using the ROBINS-I tool which has been validated for assessing risks of bias in non-randomised comparative studies.[66]. We also requested that the company provide a brief rationale for each judgement and explore the sensitivity of the NMA results to the inclusion of any studies deemed to have high risk of bias (Clarification Question A8). In their response to Clarification Question A8 the company reiterated their original assessment using the NICE criteria.

3.4.4.2.2 EAG assessments

It was not feasible for the EAG to assess the risk of bias in detail in all 17 studies included in the RWE NMAs. We prioritised assessing the six studies that inform the molnupiravir versus no-treatment comparison (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) to test how sensitive this comparison is to potential bias in the studies. Our assessment was based on the bias domains and criteria in the ROBINS-I tool,[66] but to expedite the process in the time available we made judgements directly against these criteria rather than running through the full tool

and signalling questions. Of the six studies, we rated four to have moderate overall risk of bias. This implies, according to the ROBINS-I criteria, a well-conducted observational study with no serious risks of bias (a low risk of bias judgement can rarely be made with observational studies unless they are exceptionally well-conducted to well emulate a target RCT). We judged the remaining two studies, Paraskevis et al. 2023 and Van Heer et al. 2023 as having serious risk of bias overall, in both cases due to issues with confounding:

- Paraskevis et al. 2023: (i) Data on comorbidities were not available and these might have differed between the study groups. (ii) the molnupiravir and nirmatrelvir plus ritonavir groups were for successive (and unequal) time periods so clinical decisions might have differed between these groups according to unknown time-varying factors.

- Van Heer et al. 2023: Data on comorbidities were not available and these might have differed between the study groups; the authors used prior hospitalisation during the immediate three-year period as a proxy, but this would reflect only uncontrolled comorbidities, and not all hospitalisations would have been for comorbidities.

We investigated the impact of these studies with serious bias risks on the overall NMA results by re-running the company's NMAs reported in CS Figures 16 and 22 without these studies included, for all-cause hospitalisation or death (Paraskevis et al. 2023 excluded), and for all-cause hospitalisation (Van Heer et al. 2023 excluded). Removing these studies had a relatively small impact on the risk ratios but did slightly widen the credible intervals (see Appendix 6). As part of the checking process we were able to replicate the company's base case NMA results (see Appendix 6). Overall, removing the serious risk of bias studies does not alter the NMA conclusions and would have no substantive impact on the economic analysis.

As noted above (section 3.4.2.2) the study by Zheng et al. 2023 is of interest (the only UK study included in the RWE NMAs, and which informs economic model scenario analyses). We assessed this study using the same criteria and found it to have no serious risk of bias concerns (rated as moderate risk of bias according to the ROBINS-I criteria).

3.5 Critique of the NMAs

Overall, the NMAs appear generally to have been well conducted, according to the RCT NMA and RWE NMA Reports, and the RWE SLR Report, provided by the company at the clarification stage of this appraisal.

3.5.1 Data inputs to the NMAs

Overall, the data inputs to the RCT NMAs and RWE NMAs are clearly reported and traceable to the individual studies.

3.5.2 Statistical methods for the NMAs

The company conducted Bayesian NMAs with a non-informative prior, using appropriate methods. For the RWE analyses two sets of Bayesian NMAs were provided, one containing only active treatment comparisons in the network ("active network") and the other containing both active treatments and no-treatment as the comparators ("active/control" network") (CS section B.2.9.2). The company also provided direct pairwise meta-analysis results where possible alongside the Bayesian NMA results. Overall, the results are presented clearly and intuitively, using both forest plots and tables. The EAG was able to replicate some of the company analyses, although substantive information on the NMAs (three separate reports; listed in section 3.4 above) was not available until the clarification stage (Clarification Questions A11 and A17) which limited the extent of checking possible.

The company explored inconsistency between direct and indirect evidence using appropriate methods, as reported in Clarification Response A16. No strong evidence of inconsistency was identified, although there was significant statistical heterogeneity, reflective of the clinical heterogeneity (section 3.4.3.2 above). NMA model fit was assessed appropriately, as reported in Appendix L of the RWE SLR Report.

Overall, the statistical methods of the NMAs were appropriate. As noted in section 3.5.2.1 below, random-effects models were used where feasible but fixed-effect models were employed for the NMAs of RCTs due to networks being generally sparse. Random-effects models were feasible for all outcomes in the RWE NMAs except for the COVID-19 related hospitalisation outcome and some of the scenario analyses conducted, which had sparse networks (Appendix 6). The CS and NMA Reports do not discuss whether heterogeneity could have been modelled in these networks using an informative prior.

3.5.2.1 Choice between random-effects and fixed-effect models

3.5.2.1.1.1 NMAs of RCTs

In contrast to the approach for the RWE studies, the company employed a fixed-effect model for their RCT NMAs. The company's rationale is that a random-effects model "was deemed unsuitable because most networks consisted of a limited number of studies" and the fixed-

effect model provided “more stable results (i.e. more reliable posterior distributions and generally a better fit to the data” (CS section B.2.9).

We agree that the fixed-effect analysis is appropriate for most of the outcomes since there was only one study per comparison for most outcomes. But the credible intervals for the fixed-effect results would underestimate any between-study heterogeneity that would likely be present if more studies had been available per comparison.

3.5.2.1.1.2 NMAs of RWE studies

The CS states that for the RWE NMAs a random-effects analysis was chosen a priori for the base case since there was a considerable amount of clinical heterogeneity across studies (CS section B.2.9). A fixed-effect analysis would be presented in cases where there is only one study per comparison or only one instance of two studies for a comparison (CS Appendix D.2.1.7). In practice, a fixed-effect analysis was only necessary for the COVID-19 related hospitalisation outcome (CS section B.2.9.2.4), which the EAG agrees is appropriate. For this outcome, the credible intervals for the fixed-effect results would underestimate any between-study heterogeneity that would likely be present if more studies had been available per comparison.

3.5.3 Summary of EAG critique of the NMAs

The company’s NMAs followed appropriate statistical methods. The main limitations of the NMAs relate to issues of generalisability, bias, and heterogeneity:

- Lack of generalisability (RCT NMAs only) – these NMAs included studies conducted before the endemic phase of COVID-19 and are unlikely to reflect current populations, disease characteristics, vaccination rates and clinical decisions relevant to COVID-19. Also, the RWE NMAs included only one UK study.

- Failure to account for risks of bias (RCT NMAs).
- Underestimation of heterogeneity (all RCT NMAs and some aspects of RWE NMAs) – fixed-effect models underestimate between-study heterogeneity in the RCT NMAs and in the COVID-19 related hospitalisation outcome RWE NMA.

- The most generalisable evidence (RWE NMAs) is available for a limited set of outcomes only – networks were only feasible for hospital and/or death related outcomes.

3.6 Results from the NMAs

3.6.1 Results from the NMAs of RCTs

A summary of the RCT NMA results across all treatment comparisons for 15 outcomes is provided in Appendix 5. The RCT NMAs indicate that molnupiravir was not clinically superior to any comparator other than placebo (apart from viral clearance outcomes which, as noted above in section 3.4.4.1 are at high risk of bias). However, these results are subject to considerable uncertainty due to the significant limitations and likely lack of generalisability of the RCT NMAs noted above (section 3.4.1.2) and their uncertain risk of bias (section 3.4.4.1). For the RCT NMA results to be fit for decision-making a more thorough assessment of their risks of bias and generalisability would need to be made, although the RCT NMAs are not influential in this technology appraisal as they do not inform the company's economic analysis.

3.6.2 Results from the NMAs of real-world evidence studies

Results of the company's NMAs of RWE studies are summarised across outcomes and comparisons in Table 9. Note that (as summarised in section 3.7 below) these results are subject to uncertainty.

Results were generally consistent between the "active only" and "active/control" networks, except for the COVID-19 related hospitalisation outcome (where the company employed a fixed-effect analysis, as discussed in section 3.5.2.1.1.2 above); all other analyses used a random-effects model). Inconsistency in results from the two networks for this outcome (Appendix 6) does not affect the overall treatment efficacy conclusion.

As shown in Table 9, molnupiravir was only favoured when compared against no treatment. We have included results from two studies on the UK OpenSAFELY platform, Zheng 2023[1] and Tazare et al. 2023[2] in Table 9 for comparison alongside the NMA results. The relevance of these studies is explained in section 3.7.5 and Key Issue 3. The full data (relative risks and posterior probabilities) for the NMA results shown in Table 9 are given in Appendix 6.

Table 9 Overview of results of the real-world evidence NMAs and UK OpenSAFELY cohort study

Outcome	Comparison, molnupiravir versus…			
	Nirmatrelvir plus ritonavir	Sotrovimab	Remdesivir	No treatment
All-cause hospitalisation or death [a]	NMA: No significant difference Zheng et al. 2023[1] OpenSAFELY study: comparator favoured	NMA: No significant difference	No data	NMA: Molnupiravir favoured
COVID-19 related hospitalisation or death [a, b]	NMA: No significant difference Zheng et al. 2023[1] OpenSAFELY study: comparator favoured	NMA: No significant difference	NMA: No significant difference	NMA: No significant difference Tazare et al. 2023[2] OpenSAFELY study: no significant difference
All-cause hospitalisation	NMA: No significant difference	No data	NMA: No significant difference	NMA: Molnupiravir favoured
COVID-19 related hospitalisation (fixed-effect analysis)	NMA: No significant difference	NMA: No significant difference	No data	NMA: No significant difference
All-cause death	NMA: Comparator favoured	No data	No data	NMA: Molnupiravir favoured

[a] Zheng et al. 2023 was included in the NMAs. Results from Zheng et al. are also presented separately as this was the only UK study in the NMAs.

[b] A second UK study, Tazare et al. 2023, was not included in the NMAs (for explanation see section 3.7.5)

As noted above (section 3.4.2.2) and in Clarification Question A15, the EAG requested the company to conduct a sensitivity analysis omitting the 'uncertain no-treatment' node (which the company referred to as the 'no nirmatrelvir plus ritonavir or no molnupiravir' group). This had negligible impact on the NMA results (Appendix 6).

Insufficient RWE studies reporting adverse events were available to conduct NMAs of adverse event outcomes. The available adverse events results are summarised in Table 10 below. Generally, rates of adverse events were low across the active therapies, although the Italian studies Tiseo 2023 and Torti 2023 showed higher rates for people treated with nirmatrelvir plus ritonavir, and molnupiravir in the Tiseo 2023 study.[59, 62] The only UK study, Zheng 2023, did not report adverse events.[1] Due to the overall sparsity of data and the relatively short duration of follow up it is difficult to draw firm conclusions regarding adverse events.

Table 10 Adverse events in real-world evidence studies

	Molnupiravir	Nirmatrelvir plus ritonavir	Sotrovimab	Remdesivir	No treatment
Cegolon et al. 2023 AE	Stated none	Stated none	Stated none	No data	No data
Manciulli et al. 2023 AE	Stated the range was 3% to 5% across treatments				No data
Paraskevis et al. 2023 AE	3.82%	1.33%	No data	No data	No data
Tiseo et al. 2023 Any AE Discontinuation [a]	21.1% 3.7%	49.2% 2.1%	No data	4.6% 0%	No data
Torti et al. 2023 At least 1 AE	4.1%	11.4%	No data	No data	No data
[a] discontinuations due to adverse events AE, adverse event(s); SAE, serious adverse events					

3.7 Conclusions on the clinical effectiveness evidence

3.7.1 Treatment pathway

In their proposed treatment pathway, the company has positioned molnupiravir as an alternative to nirmatrelvir plus ritonavir or sotrovimab, in addition to when nirmatrelvir plus ritonavir is contraindicated or when sotrovimab is unsuitable. This increases the potential population who could receive treatment with molnupiravir when compared to the pathway in the NHS Interim Clinical Commissioning Policy for Remdesivir and Molnupiravir.[19] The active treatment comparators included in the company's Decision Problem are appropriate for this positioning of molnupiravir.

3.7.2 Population

The population specified in the NICE scope for this appraisal 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. The company's Decision Problem is narrower than this, restricted to non-hospitalised adults who meet these criteria. The EAG is uncertain whether non-hospitalised and hospitalised patients would be eligible to receive the same treatments and whether it is clinically appropriate to exclude hospitalised patients (i.e. those who test positive 'incidentally' for SARS-CoV-2 whilst admitted to hospital for a non-COVID reason and who meet the population criteria specified in the NICE scope). We have raised this as a Key Issue for further consideration (see Key Issue 1).

3.7.3 Comparators

The company have included a no-treatment comparator (i.e. patients who have not received antiviral therapies) although this is not specified as a comparator in the NICE scope. The EAG agrees that this is a relevant population group for patients unable to receive nirmatrelvir plus ritonavir, or sotrovimab, but we and our clinical experts are uncertain of the characteristics and size of this group in clinical practice. We therefore suggest that the nature and significance of the no-treatment comparator group is a Key Issue for further consideration (see Key Issue 2).

3.7.4 Outcomes

- Hospitalisation rate is an important outcome that informs the economic analysis, both as the baseline hospitalisation rate in untreated patients (section 4.2.6.1.1), and as the treatment effect on the risk of hospitalisation (section 4.2.6.2.1). The CS focuses on the statistical significance of treatment effects and does not discuss what would be a clinically meaningful reduction in the risk of hospitalisation. The EAG has queried this as

part of a Key Issue regarding uncertainty in the clinical effectiveness of molnupiravir (see Key Issue 3).

- The studies included in the company's network meta-analyses varied in their hospitalisation outcomes, which were defined as all-cause hospitalisation, COVID-related hospitalisation, all-cause hospitalisation or death, or COVID-related hospitalisation or death, and data is not consistently available across all treatment comparisons for any one of these definitions (Appendix 6). The economic analysis models hospitalisation and death separately, but studies which appear most relevant to clinical practice, including those based on the UK OpenSAFELY platform, employed composite hospitalisation or death outcomes. The EAG is uncertain which of these definitions if any can be considered comparable in the context of this appraisal, to help address data gaps in model inputs. We have raised this as a Key Issue related to the economic modelling for further consideration (see Key Issue 5).

3.7.5 Clinical effectiveness of molnupiravir

- The MOVe-OUT RCT showed molnupiravir as statistically superior to placebo in an unvaccinated population, and only for the primary outcome of all-cause hospitalisation or death, symptom related outcomes, and viral clearance at Days 3, 5, and 10 (not at day 29). The difference between the results for the primary outcome at interim analysis and final analysis are substantially different, although molnupiravir was still statistically superior to placebo at the final analysis it was probably not a clinically meaningful difference. (Section 3.2.5)

- The company conducted two sets of network meta-analyses, for RCTs and for RWE studies. The RCT NMAs (which included the UK AGILE-CST and PANORAMIC trials that were discussed in detail in previous NICE technology appraisals) have major limitations including unaccounted for heterogeneity, risks of bias, and lack of generalisability (section 3.6.1). As such, the RCT NMAs do not provide convincing evidence of the clinical effectiveness of molnupiravir and they do not inform the economic analysis.

- The company and EAG consider the RWE NMAs more generalisable to the current endemic phase of COVID-19 and these do inform the economic analysis. Results of the RWE NMAs indicate that molnupiravir was not more clinically effective than any active treatment comparator, and in some cases was less clinically effective than nirmatrelvir

plus ritonavir, at reducing the risk of hospitalisation and composite hospitalisation/death outcomes (Appendix 6). According to the RWE NMAs molnupiravir was statistically more effective at reducing the risk of hospitalisation or hospitalisation/death only when compared against no antiviral treatment.

- However, the generalisability of the RWE NMAs to NHS practice is questionable since only one UK study was included (Zheng et al. 2023,[1] which was based on the OpenSAFELY platform, but did not include a no-treatment comparison). Given the shift from pandemic to endemic COVID-19, there is uncertainty around the "ideal" cutoff date for including studies to ensure generalisability to current clinical practice. The EAG assumed that the company's cut-off date for selecting studies (2021-2022; CS Appendix Figure 14) excluded a further UK study that demonstrates lack of clinical effectiveness of molnupiravir (Tazare et al. 2023 [2]). However, the company informed the EAG in their Factual Accuracy Check that the study by Tazare et al. 2023 was not retrieved by the literature search due to incorrect indexing in Embase, nor, the EAG notes, was it identified by the company's supplementary searches of medRxiv (CS Appendix D.1.1.1). The EAG are uncertain whether this study should have been excluded due to lack of generalisability to current clinical practice. If not, there may be other relevant studies that could be included. We have highlighted this uncertainty around the appropriate time limits for evidence inclusion as a Key Issue for consideration (see Key Issue 3). In their Factual Accuracy Check the company stated that they would have included the Tazare et al. 2023 study due to its UK relevance, had it been identified.

3.7.6 Benefit / risk considerations in relation to the mechanism of action of molnupiravir

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. This could have implications for genotoxicity in humans, the risk of development of new SARS-CoV-2 variants, and/or potential drug efficacy (see sections 3.2.3.3 and 3.2.6). Despite these concerns being raised in the scientific literature, the CS does not discuss them. The EAG is uncertain whether any activities are ongoing or may be necessary for monitoring viral transmission and its impact in molnupiravir-treated patients to address these issues and we query whether sufficient information has been provided to adequately assess the benefit / risk profile of molnupiravir. We have identified the limited evidence and discussion of virological outcomes as a Key Issue for consideration in section 1.6 (see Key Issue 8).

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company reports their economic search strategy in CS section B.3.1 and CS Appendix G. They conducted searches for published economic evaluations of therapies for patients with COVID-19 with a date cut-off of 22 January 2024. CS Appendix G Table 58 presents the inclusion and exclusion criteria.

The company identified five studies relevant to the UK setting, including four cost-effectiveness analyses[5, 67-69] and one study denominated by the authors as a cost-calculator study including the estimation of clinical and cost outcomes [70] (described in CS Appendix G Table 60). The company also described the relevant previous NICE technology appraisals in CS section B.3.1.2: TA878[20, 28] assessed nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19, and TA971[22] assessed remdesivir and tixagevimab plus cilgavimab for treating COVID-19. Both used the same cost-effectiveness analysis approach (including the model structure and most of the model inputs and assumptions) which is presented in CS Table 48.

In the EAG's view, the cost-effectiveness searches were quite narrow, but they included appropriate terms for the main healthcare databases and are reasonably up to date. However, the reporting of the search strings is unclear so we are uncertain which of the search terms were applied, and whether the subject heading terms were mapped across the different databases. We have done additional searches to check whether relevant studies might have been missed by the company. We found three US cost-effectiveness studies assessing molnupiravir or other outpatient treatments for COVID-19 (Goswami et al. 2022[71] Jovanoski et al. 2022[72] and Yeung et al. 2022 (ICER assessment)[73]) but we consider that all relevant UK cost-effectiveness studies were included by the company.

Of the identified and reported studies in the company's search, we agree that the NICE technology appraisals TA878 and TA971 [20, 22, 28] are the most relevant to the UK as they assess all the treatments being compared with molnupiravir in the current appraisal and have been discussed and accepted by previous appraisals' NICE committees. We consider that the US cost-effectiveness studies of Goswami et al. 2022[71] Jovanoski et al. 2022[72] and Yeung et al. 2022(ICER assessment)[73] are also informative for the model structure in the current appraisal (see section 4.2.2 below). We note that the clinical parameters used in these three US studies were mostly obtained from sources reporting data from the pandemic period of COVID-19.

EAG conclusion on the company's review of cost-effectiveness evidence

Although reporting of the cost-effectiveness searches is not entirely clear, it is not likely that any relevant studies conducted in the UK setting were missed. We consider the NICE appraisals TA878 and TA971[20, 22, 28] to be relevant for the current assessment. Moreover, although not conducted in the UK, three economic evaluations which assessed outpatient COVID-19 treatments in the US[71-73] are informative for the model structure of the current assessment.

4.2 Summary and critique of the company's submitted economic evaluation

The company developed a de novo economic model to assess the cost-effectiveness of molnupiravir in the treatment of non-hospitalised patients with mild to moderate COVID-19 at risk of developing severe illness.

4.2.1 NICE reference case checklist

The company economic model fulfils the requirements of NICE's reference case (Table 11), except for:

- the estimation of utilities where general population participants, rather than patients, completed the EQ-5D questionnaires (section 4.2.7).

Table 11 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes

Element of health technology assessment	Reference case	EAG comment on company's submission
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, reported by general population participants
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: EAG assessment based on the company submission
NHS, National Health Service; PSS, Personal Social Services; QALY, quality adjusted life-year

4.2.2 Model structure

The company developed a de novo cost-effectiveness model, which is described in CS section B.3.2.2. The model parameters are presented in CS sections B.3.3 to B.3.5, the base case inputs in CS Table 70, and the model assumptions in CS Table 71. The company developed a hybrid model, comprising a decision tree for the acute phase of the disease (30 days) and a Markov model to follow the patients who survive the acute phase through their

lifetime (see schematic of the model structure in Figure 2 below). The cycle length of the Markov model was one week for the first year followed by a yearly cycle until death (or 100 years of age). In the model:

- Patients enter the decision tree in the outpatient setting and start treatment with molnupiravir or one of the comparators.
- Patients can then stay in the outpatient setting, or go to hospital due to severe disease, either to a general ward, high dependency unit or intensive care unit with mechanical ventilation (according to the highest level of care received in hospital).
    - The treatment effects of molnupiravir and the comparators include prevention of progression to hospitalisation and reduction in the duration of symptoms, which are further discussed in sections 4.2.6.2.1 and 4.2.6.2.2 below.
    - Once hospitalised, the treatment effect of inpatient drugs is applied (remdesivir and tocilizumab), which is discussed in section 4.2.6.2.3.
- Patients who survive the acute phase of COVID-19 and are discharged from the hospital enter the Markov model and can either recover or experience long-term sequelae before recovering.
    - Readmission to hospital after discharge was not directly modelled by the company although this was captured in the costs of long-term sequelae which include costs of readmission, discussed in section 4.2.8.3 below.
- All patients might die from any reason, although deaths among hospitalised patients and from those with long-term sequelae were assumed to be due to COVID-19.
    - A COVID-19 mortality rate is applied for hospitalised patients, discussed below in section 4.2.6.1.4.
    - The company applied a standardised mortality ratio to the background mortality for the duration of long-term sequelae, which is discussed in section 4.2.6.1.6.

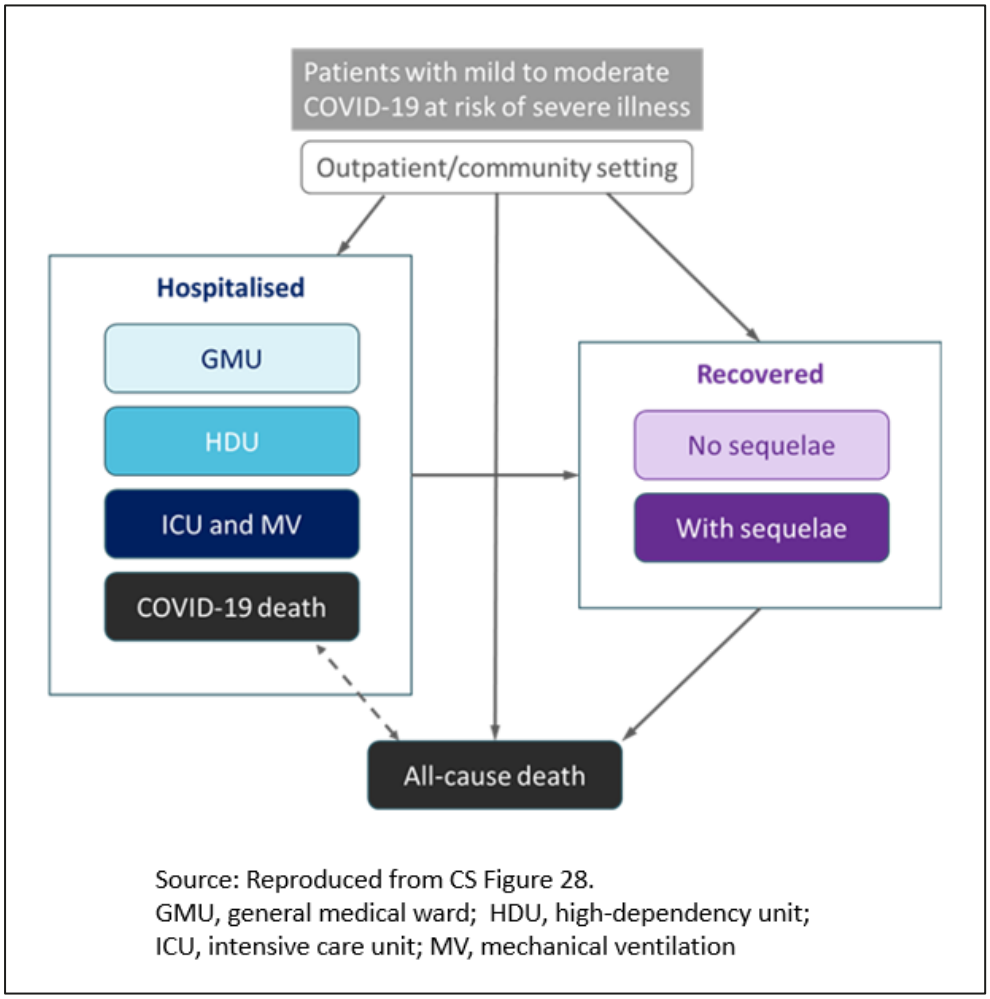

Figure 2 Schematic of the model structure

The current model structure is similar to the model structure used in previous cost-effectiveness models for molnupiravir.[71] and other outpatient treatments for COVID-19.[72, 73] It is also closely aligned with the decision tree of previous NICE appraisals (TA878 and TA971) for non-hospitalised patients. However, to model hospitalised patients, the previous appraisals used a partitioned survival model including three mutually exclusive health states: (a) discharged from hospital and alive; (b) hospitalised with or without COVID-19; and (c) death from any cause (including COVID-19). For the current appraisal, the company opted for a simpler approach to model hospitalised patients, as molnupiravir is positioned as an outpatient treatment and molnupiravir and the other outpatient treatment comparators are not expected to impact the downstream inpatient treatment effectiveness for patients developing severe COVID-19. The EAG's clinical experts consider that the use of early

outpatient treatments does not appear to negatively impact the efficacy of later treatments for COVID-19.

The acute phase of COVID-19 in the model lasts for 30 days, and the company assumes that all patients are discharged after this period. Although this might not be true in clinical practice, this assumption is not expected to significantly impact the cost-effectiveness conclusions as the proportions of patients estimated to be in hospital at day 30 is relatively small. Moreover, previous cost-effectiveness studies for outpatient COVID-19 treatments made a similar assumption.[72, 73]

The EAG notes that remdesivir and tocilizumab were the drugs considered to treat hospitalised patients with severe COVID-19. Tocilizumab was recommended for treatment of severe COVID-19 when patients need supplemental oxygen, as reported in the TA878 guidance.[20] According to the TA971 guidance, remdesivir was recommended to treat adults with COVID-19 in hospital and at risk of severe illness.[22] The EAG's clinical experts explained that the guidance in NG191 and TA971 lacks detail and does not refer to the different therapy indication details given in the SmPC, not specifying which of three ways remdesivir should be used nor whether it is indicated for mild or severe symptoms. Moreover, the experts clarified that they very rarely use remdesivir in their clinical practice, although we note that their view only reflects the practice in a single hospital. Therefore, it is unclear to us whether remdesivir is used for (a) patients with mild to moderate COVID-19 at risk of severe illness diagnosed in hospital (i.e., incidental COVID-19), (b) patients in the community admitted to hospital with severe COVID-19, or (c) both.

The EAG's clinical experts commented that the model structure does not appear to capture patients who start the treatment pathway while already in hospital (i.e., incidental COVID-19). The company explained that they did not model the population with incidental COVID-19 while in hospital due to lack of specific data for this group of patients. The EAG's clinical experts were not able to give us an estimate of the proportion of patients that contract incidental COVID-19 in hospital as there are no available records for this, but they suggested that this is quite a significant number. The experts also explained that asymptomatic patients can be admitted to hospital (as patients are no longer tested before admission) and transmit the infection to others, increasing the likelihood of incidental COVID-19 among hospitalised patients.

The model did not capture the potential impact of antiviral treatments on the risk of transmission of COVID-19. The company submission suggests that molnupiravir is expected to reduce transmission and not capturing this is potentially underestimating the benefits of

molnupiravir. The EAG's clinical experts are not aware of any evidence to support the company's statement.

EAG conclusion on the model structure

The EAG considers the model structure to be appropriate for the decision problem, and in line with previous cost-effectiveness studies for molnupiravir and other outpatient COVID-19 treatments.[71-73] Given the nature of the disease, it is reasonable to assume a weekly cycle length in the first year after discharge (as the disease changes rapidly) and then a yearly cycle as most patients would have fully recovered after that period. Although the model assumes that all patients are discharged at 30 days (acute phase), which might not happen in real world practice, the EAG consider this assumption to have a minor impact on the model conclusions. The appropriateness of assuming that remdesivir is used to treat patients admitted to hospital due to COVID-19 is unclear. Our clinical experts mentioned that the guidance in NG191 and TA971 lacks detail and that they rarely use remdesivir in their practice. The model does not capture the pathway of patients with incidental COVID-19 due to lack of specific data for this group of patients. For the same reason, the EAG was unable to address this issue. Our clinical experts suggested that patients with incidental COVID-19 are quite a significant number.

4.2.3 Population

The population considered in the company model is described in CS section B.3.2.1 and consists of non-hospitalised adults with mild to moderate COVID-19 at risk of progression to severe illness leading to hospitalisation. This is aligned with the modified intention-to-treat (mITT) population in the MOVe-OUT trial (i.e. effectively the whole trial population).[23] The licensed population and the population defined in the NICE scope for molnupiravir is broader, as it is not restricted to non-hospitalised adults. This suggests to us that patients with incidental mild to moderate COVID-19 while in hospital are also part of the licensed population and the population defined in the NICE scope. As mentioned in section 4.2.2 above, the company did not model the population with incidental COVID-19 while in hospital due to a lack of specific data for this group of patients. Instead, the company assumed that hospitalisation for patients treated in the outpatient setting is due to progression of COVID-19 and therefore patients would experience a COVID-19 treatment escalation with remdesivir and tocilizumab. We are uncertain if excluding hospitalised patients is clinically appropriate and whether the current model structure and assumptions, data inputs and

model outputs could be generalisable to the population with incidental COVID-19 while in hospital (see Key Issue 1 and section 2.3 above). Although our clinical experts could not provide a quantitative estimate, they believed the proportion of patients with incidental COVID-19 in hospital to be relatively large.

The company's criteria for risk of progression to severe illness are based on the those used in the MOVe-OUT trial, which closely align with the Edmunds criteria of high risk[11] (section 3.2.1.1 above).

The company's analyses were conducted for four subgroups: patients aged over 70 years, patients contraindicated to nirmatrelvir plus ritonavir, immunocompromised patients and patients with chronic kidney disease. Immunocompromised patients were defined as having prior use of systemic corticosteroids for ≥ 4 weeks before treatment, or prior and/or concomitant use of immune suppressants, and/or medical history of immunocompromising conditions, such as HIV, haemopoietic stem cell or solid organ transplant recipient or active cancer. As discussed in section 2.3 above, the CS does not mention whether other relevant subgroups could have been included, but we consider that those included are relevant subgroups and likely to reflect a reasonable range of high-risk patients.

The baseline characteristics of the population used in the company's model are presented in CS section B.3.9.1 and Table 12 below. Mean age was taken from PANORAMIC trial[33] and the proportion of females from the MOVe-OUT trial.[23] The EAG is unclear on why these characteristics were obtained from different sources. The company explained that the mean age was taken from the PANORAMIC trial as that was considered more representative of the overall at-risk population than the MOVe-OUT trial, due to the broader definition of high-risk (Clarification Response B2). The company did not explain why the proportion of females was taken from the MOVe-OUT trial.

For consistency, we consider that age and sex should be based on the same source. Data from the PANORAMIC trial was used in the EAG base case, as it is a national study and likely to be more aligned with the current endemic setting since it is more recent than the MOVe-OUT trial (see Table 12 below). Mean patient weight was obtained from TA878 as this information is not reported in the PANORAMIC or MOVe-OUT trials. The EAG's clinical experts were not able to comment on whether the baseline characteristics considered for the company's and EAG base case are representative of the patients who may receive molnupiravir treatment in clinical practice as our experts don't have data on the characteristics of the patients at high risk of COVID-19 in the community.

Table 12 Baseline characteristics of the model population

	Company's base case		EAG base case	
Mean age, years	57	PANORAMIC trial[33]	57	PANORAMIC trial[33]
Proportion of females, %	51.3%	MOVe-OUT trial[23]	59%	PANORAMIC trial[33]
Mean weight, kg	78	Assumption in TA878	78	Assumption in TA878

Source: Partly reproduced from CS Table 70; MOVe-OUT trial [23, 33]; PANORAMIC trial.[33]

EAG conclusion on the model population

The patient population included in the cost-effectiveness analysis aligns with the modified-ITT population of the MOVe-OUT trial. However, the licensed population and the population defined in the NICE scope are broader, as they do not exclude hospitalised patients. The company did not explore the cost-effectiveness of molnupiravir for patients with incidental disease in hospital in the current appraisal due to lack of specific data for this group of patients. We are unclear about the generalisability of the model conclusions to the broader population (see Key Issue 1). We consider the definition of risk of severe illness to be appropriate. The four subgroups included in the analyses are relevant and representative of a reasonable range of high-risk patients. We note that the mean age and proportion of female patients were based on different trials without a clear rationale. We used the same source (the PANORAMIC trial) for both parameters in our base case.

4.2.4 Interventions and comparators

CS sections B.1.2 and B.3.2.3 describe the intervention and comparators. Molnupiravir is an oral treatment administered at a recommended dose of 800mg twice daily for five days. The economic model compares molnupiravir against nirmatrelvir plus ritonavir, sotrovimab and no treatment.

For the subgroup analysis, the following comparators were used:

- Patients aged over 70 years: nirmatrelvir plus ritonavir, and no treatment.
- Patients contraindicated to nirmatrelvir plus ritonavir: sotrovimab and no treatment.
- Patients immunocompromised: nirmatrelvir plus ritonavir, sotrovimab, and no treatment.
- Patients with chronic kidney disease: sotrovimab and no treatment.

Although remdesivir is listed as a comparator in the NICE scope, it was not included as a comparator in the company submission. The EAG requested that the company run a scenario analysis including remdesivir as a comparator for completeness (Clarification Question B1). The company declined to run a scenario with remdesivir as they consider formal modelling of remdesivir in the outpatient setting to be inappropriate. They argued that remdesivir is recommended by NICE for the treatment of COVID-19 in hospital but does not form part of the outpatient treatment pathway, in contrast to molnupiravir. The company added that the technologies are not fully interchangeable for the overall population under consideration for this appraisal and therefore formal inclusion of this comparator in the model engine alongside the other comparators would be invalid. In addition, 'no treatment' is not listed as comparator in the NICE scope, but the company included it.

The appropriateness of the comparators used in the model is discussed in section 2.3 above. We consider that 'no treatment' is relevant as a comparator when a patient is unable to receive any of the other comparator treatments, but we are uncertain of the size and characteristics of this group, which is noted as a Key Issue (see Key Issue 2). It is unclear whether remdesivir would be used for non-hospitalised patients as NICE have not yet reached a recommendation for remdesivir in this subgroup of patients.

EAG conclusion on the intervention and comparators

The intervention and comparators in the economic model are consistent with the NICE scope, except for the exclusion of remdesivir and inclusion of no treatment as comparators in the company's model. The EAG is uncertain whether the exclusion of remdesivir is appropriate. The EAG's clinical experts agreed with the comparators used for each of the subgroup analyses conducted by the company.

4.2.5 Perspective, time horizon and discounting

The perspective of the analysis is the National Health Service (NHS) and Personal Social Services (PSS) in England and the discounting rate for costs and outcomes is 3.5% per year, in line with the NICE reference case.[74] A lifetime horizon was applied.

EAG conclusion on the perspective, time horizon and discounting

The company uses the recommended perspective and discounting rates and an appropriate time horizon, which are all in line with NICE guidelines.[74]

4.2.6 Clinical parameters

The clinical parameters are described in CS section B.3.3 and were obtained from two main sources: published RWE studies identified from the systematic literature review of RWE and included in the RWE network meta-analysis (see section 3.4 above) that informed the company's base case; and the MOVe-OUT trial (see section 3.2 above) that informed some of the company's scenario analyses. The clinical parameters for subgroups are presented in CS Appendix E.

4.2.6.1 Disease characteristics

Disease characteristics are discussed in CS section B.3.3.1. These include hospitalisation rate, the distribution of hospitalised patients by hospital care settings, length of stay according to hospital care settings, mortality, outpatient parameters (symptom duration, number of outpatient visits, proportion of outpatients with accident and emergency visits, and number of accident and emergency visits), and the rates and duration of long-term sequelae.

Specific data for the subgroups were available for hospitalisation rates, mortality rates and length of stay according to hospital care settings.

4.2.6.1.1 Hospitalisation rate

4.2.6.1.1.1 Hospitalisation rate for the overall population

The hospitalisation rate for the overall population of patients with mild to moderate COVID-19 at high risk of severe disease is discussed in CS section B.3.3.1.1. The hospitalisation rate for untreated patients in the company's base case uses the pooled all-cause hospitalisation rate from the untreated arms of the studies included in the company's RWE network meta-analysis (see Table 13 below). The approach for calculating this is not fully clear (the company refer to a random-effects pairwise meta-analysis of all "no treatment" event rates for the hospitalisation rate outcome for studies included in the NMA which would imply a comparative analysis). For each study that included more than one no-treatment cohort, the company used the weighted average of the all-cause hospitalisation rate across the cohorts for that study (see section 3.6.2 above).

Outcomes in the NMAs included all-cause hospitalisation rates and COVID-19 related hospitalisation rates. In their base case, the company used all-cause hospitalisation rather than COVID-19 related hospitalisation rates as they argue that all-cause hospitalisation was the primary treatment effect assessed across the studies included in the NMA. The EAG notes that the COVID-19 related hospitalisation rate is lower than the all-cause

hospitalisation rate and that using a lower hospitalisation rate leads to a higher ICER for molnupiravir versus no treatment.

Hospitalisation rates (all-cause and COVID-19 related) from the placebo arm of the MOVe-OUT trial[75, 76] are also presented in Table 13 below and were used in a company scenario analysis. The EAG notes that the hospitalisation rates from MOVe-OUT were much higher than the estimates reported by the RWE NMAs.

There were no RWE UK studies included in the NMA that reported all-cause or COVID-19 related hospitalisation rates for untreated patients. Therefore, it is uncertain how generalisable these studies (and hence the NMAs) are for the current assessment. Zheng et al. 2023[1] is a UK RWE study included within the RWE NMAs and was conducted using the OpenSAFELY cohort, but did not report data on this outcome as it did not include an untreated cohort.

In the previous appraisals TA878 and TA971, the NICE committee considered that the hospitalisation rate for a mild COVID-19 setting should lie between 2.41% and 2.82%, based on estimates from OpenSAFELY[28] and DISCOVER-NOW.[77]

In our base case, we therefore use the hospitalisation rate of 2.41% from OpenSAFELY (see Table 13 below). The EAG's clinical experts considered the OpenSAFELY dataset to be relevant to the current appraisal. More recent data from OpenSAFELY would be preferable but were not reported by Zheng et al. 2023, so we used the OpenSAFELY data considered relevant in TA878 and TA971. We explored using the COVID-19 related hospitalisation rate of 2.93% from the company's RWE NMA in a scenario analysis.

Table 13 Overall population: hospitalisation rates for untreated patients

Parameter	RWE NMA	MOVe-OUT trial (company's scenario)	OpenSAFELY (used in TA878 and TA971)	DISCOVER-NOW (used in 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

Parameter	RWE NMA	MOVe-OUT trial (company's scenario)	OpenSAFELY (used in TA878 and TA971)	DISCOVER-NOW (used in TA878 and TA971)
hospitalisation rate, %				
Source: Partly reproduced from CS Tables 50, 51 and 52[28, 75-77] NMA, network meta-analysis; RWE, real-world evidence.				

4.2.6.1.1.2 Hospitalisation rate for subgroups

Hospitalisation rates for the subgroups are described in CS Appendix E. For the subgroup of patients aged over 70 years, a hospitalisation rate of 12.84% was used in the company's base case, based on a Canadian retrospective cohort study[47] identified through the RWE SLR conducted by the company (Table 14). In TA878, the NICE committee considered the hospitalisation rate from people aged over 70 years in the PANORAMIC trial to be appropriate to inform the hospitalisation rate for the subgroup of untreated patients aged over 70 years.[20] However, these data are confidential and are not publicly available. Alternative sources for the hospitalisation rate are presented in Table 14 below, including data from the MOVe-OUT trial.[76] We note that the hospitalisation rates used in the company's base case (12.84%) are similar to the hospitalisation rates reported in the MOVe-OUT trial ([redacted] for all-cause and COVID-19 related hospitalisation respectively). It is uncertain whether this occurs in practice given the current endemic setting.[7] An exploratory scenario with a lower hospitalisation rate of 8% was tested by the EAG**.**

For the subgroup of patients contraindicated to nirmatrelvir plus ritonavir, a hospitalisation rate of 4% was used in the company's base case, based on what was previously assumed in TA878 (Table 14).[20] The hospitalisation rates from MOVe-OUT are also presented in Table 14 below.[76]

For the subgroup of immunocompromised patients, a hospitalisation rate of 22.47% was used in the company's base case, based on the RWE data from Kabore et al. 2023(Table 14).[47] Alternative sources for the hospitalisation rate in this subgroup are presented in Table 14 below, including data from the MOVe-OUT trial.[76] We note that the hospitalisation rates used in the company's base case (22.47%) are again similar or higher than the hospitalisation rates reported in the MOVe-OUT trial ([redacted]% and [redacted]% for all-cause and

COVID-19 related hospitalisation respectively). However, it is unclear whether the hospitalisation rates of immunocompromised patients have changed in the endemic setting, given the characteristics of these individuals (e.g., lower efficacy of the vaccines). A further consideration is that the definition of immunocompromised patients is not consistent across studies. Kabore et al. 2023[47] defined immunocompromised patients as "receiving high-dose immunosuppressive drugs (immunosuppressive drugs in solid organ transplants, anti-cell B therapy, alkylating agents, systemic corticosteroids) with a treatment duration which encompassed the index date or having received a haematological cancer diagnosis (leukaemia, lymphoma, multiple myeloma)" while Shields et al. 2022[78] defined immunocompromised as "receiving immunoglobulin replacement therapy or they had a serum IgG concentration less than 4g/L and were receiving regular antibiotic prophylaxis to prevent infections". We tested the lower hospitalisation rate (15.90%), as reported by Shields et al. 2022, in a scenario analysis.

For the subgroup of patients with chronic kidney disease, a hospitalisation rate of 4.4% was used in the company's base case, based on the rate from the DISCOVER-NOW study for patients with chronic kidney disease (Table 14).[77] Alternative sources for the hospitalisation rate are presented in Table 14 below, including data from the MOVe-OUT trial.[76]

Table 14 Subgroups: hospitalisation rates for untreated patients

	All-cause hospitalisation rate, %	**COVID-19 related hospitalisation rate, %**
Patients aged over 70 years		
Kabore et al. 2023[47]	-	12.84 (company's base case)
Andersen et al. 2023}[79]	13.0	-
MOVe-OUT trial[76]	[redacted]	[redacted]
Patients contraindicated to nirmatrelvir plus ritonavir		
TA878[20, 28]	-	4 (company's base case)
MOVe-OUT trial[76]	[redacted]	[redacted]
Immunocompromised patients		
Kabore et al. 2023[47]	-	22.47 (company's base case)
Shields et al. 2022[78]	-	15.90
MOVe-OUT trial[76]	[redacted]	[redacted]
Patients with chronic kidney disease		

	All-cause hospitalisation rate, %	COVID-19 related hospitalisation rate, %
DISCOVER-NOW[77]	-	4.4 (company's base case)
OpenSAFELY[20, 28]	-	4.15
MOVe-OUT trial[76]	[redacted]	[redacted]
Source: Partly reproduced from CS Appendix E Tables 41, 42, 45, 47, 48, 50 and 51		

EAG conclusion on the hospitalisation rate

The company obtained the hospitalisation rates for untreated patients from RWE studies to reflect the current endemic COVID-19 situation. For the overall population, a pooled estimate for all-cause hospitalisation from the RWE NMA was used in the company's base case. We consider the hospitalisation rate from the UK OpenSAFELY cohort to be more appropriate as this is aligned with the NICE committee conclusions in the previous NICE appraisals TA878 and TA971. Therefore, we use this rate in the EAG base case, but explore alternative values in scenario analyses. We note that the latest OpenSAFELY study by Zheng et al. 2023 could not be used, as this did not report hospitalisation rates of untreated patients. For subgroup analyses, we are uncertain whether the company's hospitalisation rates for patients aged over 70 years and for immunocompromised patients should be so high and therefore we explored lower values in scenario analyses. We agree with the company's base case inputs for the other subgroups. Hospitalisation rates for untreated patients have a significant impact on the model results and we consider this to be a Key Issue (see Key Issue 4).

4.2.6.1.2 Distribution of hospitalised patients by hospital care settings

The distribution of patients by hospital care settings is discussed in CS section B.3.3.1.2. The model allows patients to enter in three alternative hospital settings – general ward, high dependency unit and intensive care unit with mechanical ventilation, according to the highest level of care received in hospital (i.e., the most advanced care level reached by a patient in the sequence from general ward to high dependency unit to intensive care unit). The company assumed, based on their clinical experts' advice, that all patients with COVID-19 were either in the general ward or intensive care unit with mechanical ventilation and nobody was in high a dependency unit. The EAG's clinical experts advised that most hospitalised patients are in a general ward and admissions to a high dependency unit or intensive care unit are very rare. Data from the NHS on COVID-19 hospital activity[80] were considered the

most up-to-date source by the company and the EAG agrees with the appropriateness of this source. Moreover, clinicians advising the company suggested similar proportions to those reported by the NHS website (85% in general wards and 15% in intensive care units receiving mechanical ventilation).[81] The proportion of patients in intensive care units receiving mechanical ventilation was calculated by dividing the number of COVID-19 patients in intensive care units by the total number of inpatients being treated primarily for COVID-19 (see Table 15 below). The remaining patients were assumed to be in a general ward.

The distribution of patients by hospital care settings from the MOVe-OUT trial is also presented in Table 15 below and was used in a company scenario analysis.[75] Data from the molnupiravir and placebo arms were pooled to calculate the proportion of patients in each hospital care setting.

TA878 and TA971 reported data on the distribution of patients according to supplemental oxygen and hospitalisation requirements based on an 8-point ordinal scale used to define progression of COVID-19 severity in the model. However, the split of patients requiring or not requiring supplemental oxygen is not clearly reported.[20, 22] Therefore, we agree with the source used in the company's base case.

The EAG notes that the same model inputs on the distribution of patients by hospital care setting, according to the highest level of care received in hospital, were used for the overall population and each of the four subgroups. The proportions in each hospital care setting may vary for the most vulnerable subgroups, but we consider the company's simplified approach to be appropriate as the evidence is poor and this has little impact on the cost-effectiveness estimates.

Table 15 Distribution of hospitalised patients by hospital care settings, according to the highest level of care received in hospital

Proportion by hospital care settings, %	NHS data (company's base case)	MOVe-OUT trial (company's scenario analyses)
General ward	85.6	[redacted]
High dependency unit	-	[redacted]
ICU with MV	14.4	[redacted]

Source: Partly reproduced from CS Table 53 and 54.[75, 80]
ICU, intensive care unit; MV, mechanical ventilation.

EAG conclusion on the distribution of patients by hospital care settings

The EAG considers that the NHS data is the most appropriate source to inform the distribution of patients by hospital care settings for the overall population and subgroups.

4.2.6.1.3 Length of stay

4.2.6.1.3.1 Length of stay for the overall population

Length of stay is described in CS section B.3.3.1.3. The study by Yang et al. 2023[82] reported healthcare resource use and costs associated with COVID-19 in patients at high risk of severe illness in England between August 2020 and March 2021. Although data was collected in the pandemic context, the company identified this study as the best source of evidence for length of stay as it reports critical care duration and assesses different high-risk definitions, age and subgroups. The study directly reports duration in critical care but not the mean length of stay in general wards, which was calculated as the overall mean length of stay (including general ward and critical care) minus the product of the proportion of patients in critical care and length of stay in critical care (see Table 16). However, we were not able to obtain the same input values as the company for length of stay, even after receiving their clarification response (Clarification Question B5). The company assumed that duration in critical care was a reasonable proxy for the length of stay in an intensive care unit with mechanical ventilation.

Although not reported in the company's submission, the length of stay from the MOVe-OUT trial is also presented in Table 16 below.[71] Previous cost-effectiveness studies of molnupiravir or other outpatient COVID-19 treatments present similar or a slightly higher length of stay for critical care with ventilation than the company's base case, although all the studies used data from the pandemic period.[71-73] The EAG notes that changing this assumption appears to have a minor impact on the model results and therefore we consider the company's input values to be reasonable.

Table 16 Overall population: length of stay by hospital setting

	Yang et al. 2023	MOVe-OUT trial
General ward, days	8.29	10
ICU with MV, days	11.40	14
Source: Partly reproduced from CS Table 55[82] and Goswami et al. Table 1.[71] ICU, intensive care unit; MV, mechanical ventilation.		

4.2.6.1.3.2 Length of stay for the subgroups

Length of stay for the subgroups is described in CS Appendix E. For the subgroup of patients aged over 70 years, a length of stay of 10.22 days for general wards and 10.00 for intensive care units were used in the company's base case, based on the same study by Yang et al. that informed this parameter for the overall population.[82, 83] This study reported data for patients aged between 74 and 85 years. The company used the data on length of stay for patients aged over 70 years as a proxy for the length of stay of the other subgroups (patients contraindicated to nirmatrelvir plus ritonavir, immunocompromised, and with chronic kidney disease).

EAG conclusion on the length of stay

Although the sources to inform length of stay are not ideal, as they reflect a different period of COVID-19, we consider the company's input values for the overall population and subgroups to be reasonable, as the impact of changing this assumption is minor.

4.2.6.1.4 Mortality

4.2.6.1.4.1 Mortality for the overall population

Mortality data related to COVID-19 are presented in CS section B.3.3.1.4. The baseline in-hospital mortality from COVID-19 used in the company's model was based on the UK OpenSAFELY database (see Table 17 below).[84] The company used the OpenSAFELY 28-day mortality rates for all people hospitalised in 2023, stratified by intensive care admission and whether COVID-19 was the primary cause for admission.

Overall mortality and mortality data by hospital care setting (general ward, high dependency unit and intensive care unit with mechanical ventilation) from the MOVe-OUT trial, also presented in Table 17, were used in a company scenario analysis.[75] Data from molnupiravir and placebo arms were pooled to calculate the proportion of patients that died in each hospital care setting.

The EAG notes that, in TA971, the NICE committee considered that OpenSAFELY was of most relevance and generalisable to UK clinical practice. Alternative sources were also considered in TA971 for baseline mortality, presented in Table 17 below.[22]

The same model inputs on mortality were used for the overall population and all the subgroups, except for the subgroup of immunocompromised patients.

Table 17 Overall population: COVID-19 related mortality for patients under usual care

	OpenSAFELY (company's base case)	MOVe-OUT trial (company's scenario analysis)	Clinical expert opinion from TA971
Overall mortality in hospital, %	-	[redacted]	-
General ward, %	1.71	[redacted]	2
HDU, %	-	[redacted]	-
ICU with MV, %	4.15	[redacted]	6-12

Source: Partly reproduced from CS Tables 56 and 57[22, 75, 84]
HDU, high dependency unit; ICU, intensive care unit; MV, mechanical ventilation.

4.2.6.1.4.2 Mortality for the subgroup of immunocompromised patients

Mortality for the subgroups is described in CS Appendix E. For the subgroup of immunocompromised patients, an overall mortality rate of 24.98% was used in the company's base case, based on the retrospective cohort INFORM study.[85]

We note that different mortality rates for the immunocompromised patients were discussed by the NICE committee in the previous appraisal TA971, including the published rate of 24.98% from the INFORM study. The committee considered this to be an overestimation and concluded that estimating a mortality rate for immunocompromised patients in hospital is uncertain, but that evidence suggests that it may be between 10.39% and 14%. The NICE committee preferred the lower rate of 10.39%.[22] Therefore, in our base case, we use a mortality rate of 10.39% for immunocompromised patients. A rate of 14% is explored in a scenario analysis.

EAG conclusion on mortality

The EAG considers that OpenSAFELY is the most appropriate source to inform the underlying in-hospital mortality, as it is reports data by hospital care settings and is based on a large UK database. It was also considered a relevant source for mortality in the previous NICE appraisal TA971.[22] For the subgroup of immunocompromised patients, a mortality rate of 10.39% is used in the EAG base case in line with the committee's preference for NICE appraisal TA971.[22]

4.2.6.1.5 Outpatient parameters

Outpatient parameters are described in CS section B.3.3.1.5 and include duration of outpatient symptoms, number of outpatient visits, proportion of outpatients with accident and emergency visits and the number of accident and emergency visits.

The company noted that very few studies provide data on duration of outpatient symptoms, and they used data from the PANORAMIC trial in their base case although they mentioned some limitations of this study.[33] Based on the PANORAMIC trial, the company used a duration of nine days for outpatient symptoms for untreated patients in their base case.

The clinical experts advising the EAG considered that the current duration of outpatient symptom is likely to be shorter for immunocompetent patients but longer for vulnerable groups when compared to the duration from the PANORMIC trial. But we note that our experts have no experience in managing outpatient patients with COVID-19 as they work in hospital. We tested the duration of symptoms in a scenario analysis: 15 days for the group of immunocompromised patients and five days for the overall population. For the remaining subgroups, the EAG's clinical experts would expect that symptoms last around 9 days.

In line with the previous NICE appraisal TA971,[22] the company assumed that patients with mild to moderate COVID-19 at high risk of severe illness in the outpatient setting would not have any outpatient visit or outpatient accident and emergency visit. The EAG's clinical experts consider this to be a reasonable assumption if NHS is working well, but added that when primary care breaks down, patients might go to outpatient or accident and emergency visits to access care.

The EAG's clinical experts explained that usually patients in the outpatient setting have a phone call with a prescriber from the COVID Medicines Delivery Unit (CMDU) who will check for symptoms, risk factors and drug-drug interactions and, if needed, prescribe the relevant outpatient treatments. The experts also added that vulnerable outpatients (including those with a stem cell transplant, with malignancy or using CAR-T cell therapy) are usually assessed in an outpatient clinic by their specialist team, either remotely or in person. We note that adding these costs to the subgroup of vulnerable patients would have a minimal impact on the ICER because it will cancel-out across treatment arms as no treatment effect on the number and proportion of patients having outpatient visits is applied in the model. Therefore, we consider the company's assumptions to be reasonable.

The EAG notes that the same model inputs on the outpatient parameters were used for the overall population and each of the four subgroups. As explained above, we tested a scenario

where a different duration of symptoms for the subgroup of immunocompromised patients was used (15 days).

EAG conclusion on the outpatient parameters

Our clinical experts considered that the PANORAMIC trial data used in the company's base case overestimates the current duration of outpatient symptoms observed in practice for immunocompetent patients, though the duration can be longer for immunocompromised patients. We therefore tested the impact of changing the duration of symptoms to five days for immunocompetent patients and 15 days for immunocompromised patients in a scenario analysis.

We consider the assumption of no outpatient or accident and emergency visits to be reasonable.

4.2.6.1.6 Long-term sequelae

Information on long-term sequelae is discussed in CS section B.3.3.1.6. The company confirmed in the Clarification Teleconference held on 10th July 2024 that long-term sequelae should be interpreted as being the same as long COVID.

For the company's base case, the proportion of patients with long-term sequelae and the duration of long-term sequelae were obtained from the previous NICE appraisals TA878 and TA971 (see Table 18 below).[20, 22] The company assumed that 10% of non-hospitalised patients and 100% of hospitalised patients would experience long-term sequelae for a mean duration of 113.60 weeks.

The EAG's clinical experts noted that the proportion of patients with long-term sequelae are currently much lower than before. The EAG consider that this is likely to be related with the reduced risks of the current Omicron variant, increased population immunity and the access to better treatments.

Our clinical experts explained that there are some patients experiencing persistent viral infection with SARS-CoV-2 (mainly immunocompromised patients whose immune system cannot control the virus for long periods of time), but added that according to NICE guidance NG188[86] for managing the long-term effects of COVID-19, the long-term carriage of SARS-CoV-2 by immunosuppressed patients for more than three months after initial infections is not covered.

Based on the EAG's clinical experts opinion, we explored alternative assumptions in scenario analyses:

- (1) an exploratory scenario assuming that 1% of non-hospitalised patients and 10% of hospitalised patients experience long-term sequelae;
- (2) an exploratory scenario assuming that 5% of non-hospitalised patients and 50% of hospitalised patients experience long-term sequelae;

The company added a standardised mortality ratio of 7.7 for hospitalised patients with long-term sequelae for the duration of long-term sequelae, according to the approach used in previous appraisals TA878 and TA971.[20, 22]

The EAG notes that the same model inputs for long-term sequelae were used for the overall population and each of the four subgroups. The proportion of patients experiencing long-term sequelae may vary for the most vulnerable subgroups, and therefore we tested scenario analysis (1) above in the subgroup analyses.

Table 18 Long-term sequelae

	TA878 and TA971
Proportion of patients with long-term sequelae, %	
Non-hospitalised patients	10
Hospitalised patients	100
Duration of long-term sequelae, weeks	113.60
Source: Partly reproduced from CS Table 59[20, 22]	

EAG conclusion on the long-term sequelae

In our experts' opinion, the proportion of patients with long-term sequelae is currently much lower than the company's estimates. We consider that this is likely due to the reduced risks of the current Omicron variant, increased population immunity and the access to better treatments. Therefore, we tested scenario analyses assuming that 1% and 5% of non-hospitalised patients and 10% and 50% of hospitalised patients experience long-term sequelae. The proportion of patients with long-term sequelae is a key driver of the model and we consider this to be a Key Issue based on the uncertainties described above (Key Issue 6Table 1). We consider the mean duration of long-term sequelae to be reasonable as it was previously assumed in TA878 and TA971.

4.2.6.2 Treatment effectiveness

Treatment effectiveness is discussed in CS section B.3.3.2 and comprises the relative risks of hospitalisation and symptom duration resolution for molnupiravir and the comparators. It also includes relative risks of mortality and discharge for the inpatient treatments (remdesivir and tocilizumab).

Specific data for the subgroups were only available for the relative risk of hospitalisation.

4.2.6.2.1 Treatment effect on hospitalisation

Clinical effectiveness evidence for hospitalisation in the company's base case is informed by results from the RWE NMAs which, as explained in section 3.4.1 above, the EAG agrees is appropriate. The company's model is intended to utilise all-cause hospitalisation as the key clinical effectiveness outcome. However, as discussed below, NMA results for this outcome are not available for all treatment comparisons.

4.2.6.2.1.1 Treatment effect on hospitalisation in the overall population

The treatment effect on hospitalisation is presented in CS section B.3.3.2.1. The company applied the relative risk of hospitalisation from the RWE NMAs in their base case. The relative risks of all-cause hospitalisation from the RWE NMA used in the company's base case are shown in Table 19 below. However, this outcome is not available for the comparison of molnupiravir against sotrovimab. Instead, the company used COVID-19 related hospitalisation in their base case for this comparison. We have provided the relative risks for both all-cause and COVID-19 related hospitalisation where available in Table 19. A limitation of the COVID-19 related hospitalisation outcome is that it was based on a fixed-effect analysis due to sparsity of the evidence network (see section 3.5.2.1.1.2 above). As such, the credible intervals for the relative risks of COVID-19 related hospitalisation do not capture between-study heterogeneity and therefore would underestimate the heterogeneity present.

Table 19 Overall population: treatment effect of molnupiravir versus comparators on hospitalisation

Treatment comparison	Relative risk (95% credible interval)	
	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: Partly reproduced from CS Table 61		

It is unclear from a clinical point of view whether the treatment effect for all-cause hospitalisation or COVID-19 related hospitalisation should be used in the economic model (Key Issue 5). We note that the COVID-19 related hospitalisation rate from OpenSAFELY informs the baseline hospitalisation rate in TA878 and TA971 as well as in the EAG base case for the current appraisal.[20, 22]

There were no UK studies in the RWE NMAs that reported all-cause or COVID-19 related hospitalisation, which adds uncertainty to the generalisability of these results for the current assessment. A UK RWE study by Zheng et al. 2023 [1] was conducted using the OpenSAFELY cohort and reports relative risks of all-cause hospitalisation or death and COVID-19 related hospitalisation or death for the comparison of molnupiravir against nirmatrelvir plus ritonavir. The results from Zheng et al. 2023 have narrower confidence intervals and therefore less uncertainty than the estimates from the RWE NMA (see Appendix 6). However, these composite outcomes combining hospitalisation and death do not match the input parameters that inform the current economic model, where hospitalisation and mortality were modelled separately.

Although not clearly stated in the CS, we note that the economic model does not include any outpatient treatment effect on mortality. In the current model, only inpatient treatments (remdesivir and tocilizumab) influence mortality. Based on that, it is unclear to the EAG whether outpatient treatments have any effect on mortality or not. If not, outcomes

combining hospitalisation and death might be a reasonable proxy for the hospitalisation outcomes alone. The EAG's clinical experts agree with this assumption.

Tazare et al. 2023[2] used data from OpenSAFELY records up to 10 February 2022, so it was not included in the company's RWE SLR according to the eligibility criteria. However, it provides a comparison of molnupiravir versus no treatment that is not available from the Zheng et al. 2023 OpenSAFELY study, showing no difference in effectiveness of molnupiravir compared to no treatment for the outcome COVID-19 related hospitalisation or death (Key Issue 3).

As there is high uncertainty associated with estimation of the treatment effect on hospitalisation and none of the alternatives is ideal, the EAG has kept the company's base case, but we tested the following estimates in scenario analyses:

- (1) Using the relative risk of COVID-19 related hospitalisation from the RWE NMA for all the comparisons (see Table 19);
- (2) Using the relative risk of all-cause hospitalisation or death from Zheng et al. 2003[1] for the comparison against nirmatrelvir plus ritonavir (RR 1.64);
- (3) Using the relative risk of COVID-19 related hospitalisation or death from Zheng et al.[1] for the comparison against nirmatrelvir plus ritonavir (RR 2.22);
- (4) Using the relative risk of COVID-19 related hospitalisation or death based on the conclusions from Tazare et al. 2023[2] for the comparison against no treatment (RR 1.0);
- (5) Using the relative risk of all-cause hospitalisation from the RWE direct meta-analysis: for the comparison against nirmatrelvir plus ritonavir (RR 0.88), for the comparison against no treatment (RR 0.81).

Scenario (5) was explored by the EAG because the results from the direct pairwise meta-analyses for all-cause hospitalisation do not concur with the results of the Bayesian NMA (see Appendix 7).

4.2.6.2.1.2 Treatment effect on hospitalisation in the subgroups

The treatment effects on hospitalisation in the subgroups are described in CS Appendix E. For the subgroup of patients aged over 70 years, the relative risk of all-cause hospitalisation from the RWE NMA was used in the company's base case for molnupiravir versus no treatment and molnupiravir versus nirmatrelvir plus ritonavir (see Table 20 below). The

company did not report the relative risks of COVID-19 related hospitalisation for the subgroup of patients aged over 70 years.

The company used the relative risks of hospitalisation for patients aged over 70 years as a proxy for the relative risks of hospitalisation for the other subgroups (patients contraindicated to nirmatrelvir plus ritonavir, immunocompromised and with chronic kidney disease) in their base case. For the comparison of molnupiravir versus sotrovimab, data from the overall population was used. The EAG is unclear whether this is appropriate. Results from the MOVe-OUT trial showed a lower treatment effect for molnupiravir versus no treatment for the subgroup of patients aged over 70 years compared to the other subgroups. We note that these results are associated with high uncertainty and that the MOVe-OUT trial was conducted during the COVID-19 pandemic setting. However, according to these results, we consider the company's approach to be conservative and favouring no treatment. For the comparison of molnupiravir versus nirmatrelvir plus ritonavir and sotrovimab, the approach taken by the company may have underestimated the effects on hospitalisation of the comparators.

Table 20 Subgroups: treatment effect of molnupiravir versus comparators on hospitalisation

	RWE NMA
All-cause hospitalisation, RR	
Molnupiravir versus no treatment	0.71
Molnupiravir versus nirmatrelvir plus ritonavir	1.18
Source: Partly reproduced from CS Appendix E Table 44. NMA, network meta-analysis; RWE, real-world evidence.	

Data from MOVe-OUT trial were used in a company scenario analysis for all the subgroups for the comparison of molnupiravir versus no treatment (CS Appendix E Tables 43, 46, 49 and 52).[87]

EAG conclusion on the treatment effect for hospitalisation

The treatment effects on hospitalisation in the company's base case are taken from the RWE NMAs, which is appropriate, but the outcomes are uncertain because all-cause hospitalisation was not available for all the treatment comparisons. We are also uncertain which hospitalisation outcome is most appropriate from a clinical perspective. We conducted scenario analyses to explore the impact of using

different treatment effects on hospitalisation from the NMAs, and the Zheng et al. 2023 and Tazare et al. 2023 UK RWE studies. The COVID-19 related hospitalisation outcome is limited to a fixed-effect analysis which underestimates heterogeneity. The treatment effect on hospitalisation has a significant impact on the model results and, based on the uncertainties associated with this input, we consider this to be a Key Issue (Key Issue 5).

4.2.6.2.2 Treatment effect on outpatient symptom duration

The treatment effect on outpatient symptom duration is presented in CS section B.3.3.2.2. The company used a hazard ratio for median days to symptom resolution of 1.36 for the comparison of molnupiravir versus no treatment (converted to 0.74 for no treatment versus molnupiravir) from the PANORAMIC trial[33] as they argue this is the only source reporting the effect of outpatient treatments on the duration of outpatient symptoms (see Table 21 below). For clarity, we note that in the current model a HR for outpatient symptom duration of 0.74 for no treatment versus molnupiravir means that molnupiravir results in a lower duration of symptoms than no treatment.

No data are available on symptom duration for nirmatrelvir plus ritonavir or sotrovimab. In the company's base case, the effect of these two treatments was assumed to be the same as for molnupiravir, i.e., a hazard ratio of 1 (see Table 21 below).

Data to inform this input parameter are very limited and therefore we explored alternative values in scenario analyses:

- We changed the hazard ratio for the comparison of molnupiravir versus no treatment within the range of its 95% credible interval from the PANORAMIC trial (1.32 to 1.40) (see Table 21 below). The inverse numbers were used in the model for no treatment versus molnupiravir, as explained above.
- For the comparison against nirmatrelvir plus ritonavir and against sotrovimab, the treatment effect on symptom duration is uncertain. For that reason, we tested an arbitrary range of hazard ratios in scenario analyses (0.7 and 1.3) (see Table 21 below).

Table 21 Hazard ratio for outpatient symptom duration

	Company's base case	EAG scenario: lower bound	EAG scenario: higher bound
No treatment versus molnupiravir, HR	0.74 (molnupiravir versus no treatment 1.36)	0.71 (molnupiravir versus no treatment 1.40)	0.76 (molnupiravir versus no treatment 1.32)
Nirmatrelvir plus ritonavir versus molnupiravir, HR	1	0.7	1.3
Sotrovimab versus molnupiravir, HR	1	0.7	1.3

Source: Partly reproduced from CS Table 62
EAG, External Assessment Group; HR, hazard ratio

The same estimates of the treatment effect for symptom duration were used for the overall population and the four subgroups.

EAG conclusion on the treatment effect on outpatient symptom duration

Data to inform the treatment effect on outpatient symptom duration is limited and therefore we use the available evidence for molnupiravir versus no treatment in our base case, as the company did. It is very uncertain whether nirmatrelvir plus ritonavir and sotrovimab have a similar treatment effect as molnupiravir since there is no evidence. The EAG considered the company's approach to be reasonable in the absence of better data, and we tested different hazard ratios in scenario analyses to show the impact of this assumption on the model conclusions.

4.2.6.2.3 Effect of inpatient treatments

The effect of inpatient treatments is described in CS section B.3.3.2.3. The company assumed that 50% of patients in a general ward will have treatment with remdesivir and 100% of patients in an intensive care unit with mechanical ventilation will have treatment with tocilizumab.

According to the EAG's clinical experts, once patients start with oxygen they are initially treated with dexamethasone and then with tocilizumab if dexamethasone is not effective. The experts added that remdesivir is rarely used in their hospital trust. We are aware that remdesivir could be used more widely in other hospitals in the English NHS. We note that

the company included the cost of systemic steroids (dexamethasone) for patients admitted to intensive care units with mechanical ventilation. Changing the distribution of inpatient treatments has a minimal impact on the model results.

The relative risks of mortality and discharge with remdesivir and tocilizumab used in the company's base case were taken from TA971 and TA878, respectively (see Table 22 below).[20, 22]

The EAG notes that in previous appraisals TA878 and TA971, the NICE committee concluded that, due to lack of strong evidence for the current endemic period, removing any treatment effects on time to discharge was reasonable. In our base case, we do not apply any treatment effect for time to discharge (i.e., we use a hazard ratio of 1 for both remdesivir and tocilizumab).

In TA971,[22] the NICE committee also concluded that available data did not show a meaningful difference in mortality for remdesivir versus standard of care. The committee considered that the hazard ratios for mortality would be between 0.85 and 1.00 but tending to 1.00. We used a relative risk of 1 for mortality of remdesivir in a scenario analysis. We note that changing the value of either of these parameters (relative risk for mortality or for time to discharge) has a minimal impact on the model results.

Table 22 Effect of inpatient treatments used in the company's base case model

Treatment	Parameter	Value	95% CI	Source
Remdesivir	RR mortality	0.91	0.81, 0.94	COVID-NMA (7 studies)[28 22 88]
	HR discharge	1.27	0.88, 1.25	Beigel et al. 2020 [89]
Tocilizumab	RR mortality	0.88	0.74, 1.11	COVID-NMA (18 studies) [28 22 88]
	HR discharge	1.05	1.10, 1.46	metaEvidence (2 studies) [28 22 90]

Source: Reproduced from CS Table 63
CI, confidence interval; HR, hazard ratio; RR, relative risk.

The EAG notes that the same model inputs for the effect of inpatient treatments were used for the overall population and each of the four subgroups in the company's base case. In TA971, the NICE committee noted that time to discharge might be different for immunocompromised patients as they usually have longer hospital stays and therefore assuming no treatment effect for time to discharge is potentially not capturing some treatment benefits for this subgroup of patients.[22] In the EAG base case, we used the hazard ratios in Table 22 above for the subgroup of immunocompromised patients and assumed no treatment effect on time to discharge for the remaining subgroups.

EAG conclusion on the effect of inpatient treatments

The company's distribution of inpatient treatments is not consistent with the feedback from our clinical experts. But we note that changing the distribution of inpatient treatments has a minimal impact on the model results. In TA878 and TA971, the NICE committee concluded that the available evidence was insufficient to apply a treatment effect for time to discharge. Therefore, we applied a hazard ratio of 1 for time to discharge for remdesivir and tocilizumab for the overall population and subgroups, except for the subgroup of immunocompromised patients for whom we kept the company's base case values. We note that changing the treatment effect for time to discharge or mortality have very low impact on the model results.

4.2.6.2.4 Adverse events

The incidence of adverse events is described in CS section B.3.3.3. The company included the incidence of the most frequent adverse events (≥1%) for molnupiravir and the comparators: nausea, headache, diarrhoea, dysgeusia, and vomiting. It is unclear to the EAG whether grade 3 or more adverse events were considered as this is not mentioned in the CS.

These data were collected from the MOVe-OUT trial[91] for molnupiravir and no treatment, from the Summary of Product Characteristics[92] for nirmatrelvir plus ritonavir, and from the COMET-ICE trial[93] for sotrovimab, as confirmed by the company in Clarification Response B5.

CS Table 64 presents the incidence of each adverse event, and we note that the incidences are quite low (<5%) for all the adverse events and treatments. In Clarification Response B5 the company amended the incidence of headache for no treatment (0.1%) and diarrhoea for molnupiravir (2.3%) and no treatment (3.2**%**).

The model also includes COVID-19 pneumonia. In Clarification Response B7, the company confirmed that this was accidently omitted from the CS. The source of COVID-19 pneumonia is the UK MHRA Public Assessment Report Table 21.[94] The EAG's clinical experts suggested that COVID-19 pneumonia should be treated as a treatment failure rather than an adverse event of treatment, since molnupiravir, nirmatrelvir plus ritonavir and sotrovimab are intended to prevent COVID-19 pneumonia. Removing COVID-19 pneumonia has a minimal impact on the model results.

EAG conclusion on the adverse events

We consider that the most relevant adverse events have been included in the economic model.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review of HRQoL studies in patients with COVID-19 or analogous conditions (such as pneumonia or influenza) to identify utilities for the model health states. The methodology is described in CS Appendix H. The cut-off date of the searches was 23 January 2024. CS Appendix H Table 68 presents the inclusion and exclusion criteria.

We consider that the company searched an adequate range of appropriate sources, and the searches are adequately up to date. A published HRQoL or utilities search filter was not used, and although it was not a sensitive search compared to published filters, it included relevant quality of life and utility terms, including for EQ-5D and SF-6D.

The review identified 42 studies reporting utility outcomes for patients with COVID-19 (CS Appendix H.1.4.2). Of those, 14 studies were conducted in the UK setting and reported EQ-5D utilities potentially relevant for the current appraisal.[3, 95-107] CS Appendix H Tables 69 and 70 show the characteristics and results of these studies.

The study by Soare et al. 2024[3] aimed to capture HRQoL changes over time for patients with mild-to-moderate COVID-19 in the UK and reported EQ-5D-5L utilities for pre-COVID, acute COVID, post-COVID and long-COVID health states either for hospitalised or non-hospitalised patients. The remaining 13 studies report utilities for post-discharge or long COVID.[95-107] Table 23 presents the results of the Soare et al. study.[3] as we consider that this study reports utility values relevant for several health sates of the current economic model.

We consider that sufficient informative studies were identified by the company, and it is not likely that they have missed any relevant study.

Table 23 Results of the study by Soare et al. 2024[3]

	Soare et al. 2024 [3]
Respondents	Patients with COVID-19
Sample size	Adult non-hospitalised sample: 236 Adult hospitalised sample: 42

	Soare et al. 2024 [3]
Elicitation method tariff	EQ-5D-5L, UK
Utility value, mean (SD)	Pre-COVID (adult non-hospitalised): 0.82 (0.25) Pre-COVID (adult hospitalised): 0.81 (0.22) Acute COVID (adult non-hospitalised): 0.62 (0.35) Acute COVID (adult hospitalised): 0.38 (0.32) Long COVID (adult non-hospitalised): 0.70 (0.26) Long COVID (adult hospitalised): 0.54 (0.28) Post-COVID (adult non-hospitalised): 0.84 (0.22) Post-COVID (adult hospitalised): 0.86 (0.17)
Notes	Baseline age: 48.3 years[a] Proportion of females: 52.2%[a] Data were collected between January and April 2022; HRQoL data collected retrospectively for several timepoints: before having COVID-19, during the acute phase of COVID-19 and during long COVID.

Source: Partly reproduced from CS Appendix H Table 70; Soare et al.[3]
SD, standard deviation
[a] Weighted average of hospitalised and non-hospitalised adults

Table 24 presents the utility inputs used in the previous NICE appraisals TA878 and TA971. In TA878 and TA971, the EAG assumed that COVID-19 patients at high risk of severe illness in the community would experience a similar quality of life as the general age- and sex-matched population. They acknowledged it was a simplification, although with a minor impact given the short duration of the acute COVID episode. For hospitalised patients with severe illness, the utilities were based on a previous cost-effectiveness study reported by Rafia et al. 2022[68] which used utilities for clostridium difficile infection as a proxy for the utilities of patients not requiring supplemental oxygen and utilities of patients with influenza (H1N1) as a proxy for the utilities of patients requiring supplemental oxygen. For patients with long COVID, a decrement of 0.13 was applied for the duration of long COVID, sourced from Evans et al. 2021[108] which reported the impact on HRQoL after hospitalisation due to COVID-19.

Table 24 Utility inputs used in TA878 and TA971

Health states	Utility inputs	Source
Baseline utility value	General population utilities from Ara and Brazier	Ara and Brazier 2010[109]

Health states	Utility inputs	Source
Outpatient at high risk of severe COVID-19	Similar to general population	Ara and Brazier 2010[109]
Hospitalised no longer requiring ongoing medical care (decrement)	0.36	Rafia et al. 2022[68]
Hospitalised not requiring supplemental oxygen (decrement)	0.36	Rafia et al. 2022[68]
Hospitalised, low-flow oxygen (decrement)	0.58	Rafia et al. 2022[68]
Hospitalised, high-flow oxygen or non-invasive ventilation (decrement)	0.58	Rafia et al. 2022[68]
Hospitalised, invasive mechanical ventilation or extracorporeal membrane oxygenation	0	Assumption
Long COVID (decrement)	0.13	Evans et al. 2021[108]
Source: TA878 and TA971.[20, 22, 28]		

4.2.7.2 Study-based health related quality of life

The health-related quality of life data used in the model is described in CS section B.3.4.5. As explained in CS section B.3.4.1, no utility data were collected as part of the MOVe-OUT trial. The CS did not discuss whether utility data were reported by the RWE studies included in the systematic literature review that informed the clinical parameters. The utilities for patients with COVID-19 used in the company base case were derived from a vignette study conducted by the company in which around 500 members of the UK general public completed EQ-5D-5L questionnaires for each of the health states described in the vignettes.[110, 111]

4.2.7.2.1 Vignette study

The vignette study is described in CS section B.3.4.2.2 and Appendix H.2. The description of the vignettes was informed by a large UK COVID-19 infection survey from the Office for National Statistics, relevant clinical trials and observational studies and aimed to reflect the health states relevant for patients who would be eligible for molnupiravir in clinical practice.

The vignettes represent eight health states: baseline (pre-infection) (S1), outpatient (mild) (S2), outpatient (moderate) (S3), general hospital ward (severe) (S4), high dependency unit (severe) (S5), intensive care unit (critical) (S6), recovered with no long-term sequelae (S7) and recovered with long-term sequelae (S8). Medical experts were consulted by the company to ensure that the vignette descriptions were reflective of the health states.

Around 0.6% of participants were experiencing COVID-19 at the time of the study, 11.8% were reported to have had COVID-19 before and 67.8% reported that close friends or family have had COVID-19 before. Most participants were fully vaccinated (83.8%). The mean age of participants was 44.2 years and 51.2% were female.

EQ-5D-5L responses from the vignettes were converted to EQ-5D-3L scores using the Hernández Alava et al. 2022 algorithm,[112] in line with NICE guidance.[74] CS Appendix H Table 77 presents a summary of the utility values derived from the vignette study for each of the vignette health states (S1-S8). A sensitivity analysis conducted by the company did not show any statistically significant differences in the responses given by participants with or without prior exposure to COVID-19.

As discussed by the company in CS Appendix H.2.5, the vignette study has several limitations:

- The EQ-5D questionnaires were completed by the general public and not by patients experiencing the health states, which adds uncertainty to the generalisability of these utility values to the utilities experienced by patients in clinical practice.
- The vignette descriptions cannot include all aspects of the patient experience within a health state, which might affect the validity of the derived utilities.
- The health state descriptions might have been misinterpreted and participants could struggle to distinguish between similar vignettes.
- The study approach does not meet the NICE Reference Case, as the EQ-5D questionnaires were not completed by patients (or carers).

As part of Clarification Question B8, the EAG asked the company to clarify why they used a vignette study to inform utilities.[74] The company responded that this approach was suggested in the TA971 Final Appraisal Document, i.e., to use COVID-19 severity-specific vignettes with EQ-5D-3L questionnaires completed by the UK general population. Further, the vignette study was conducted by the company in the UK as it was designed to directly inform the economic modelling. It represents a large UK-based study, with a sample

generalisable to the UK population. The EAG notes that this approach was suggested in TA971 because appropriate data was limited, and the model was being informed by utilities for diseases other than COVID-19.

4.2.7.2.2 Health state utilities used in the economic model

Table 25 below shows the utility values used in the company's base case. The vignettes informed these utilities as follows:

- Symptomatic outpatients - pooled mean utility of S2 and S3 (applied for the duration of symptoms),
- Patients hospitalised on a general ward (S4),
- Patients in an intensive care unit with mechanical ventilation (S6), and
- Patients with long-term sequelae (S8) (applied for the duration of symptoms).

We note that the company's utilities for symptomatic outpatients and those with long-term sequelae are slightly different to the values shown in the poster that reports the results of the vignette study.[110, 111] A baseline utility value based on Hernández Alava et al. 2022.[112] was applied based on the age and sex of the model population. No utility value was included for readmission after long-term sequelae. In response to Clarification Question B9, the company stated that they did not include it as they did not use readmission as a separate outcome in the model (as readmission cost/utility is included in the cost and utility assumed for the long-term sequelae applied). We note that changing this assumption has a minor impact on the model results, as the rate of readmission is assumed not to differ between arms.

The EAG notes that the utility values from the vignette study are very low in general, but particularly for hospitalised patients, for whom negative values were used, meaning that patients were experiencing states worse than death. Although we acknowledge that hospitalised patients might have a huge decrement in their quality of life, the values from the vignette study seem to lack face validity. The lack of face validity combined with the limitations of the vignette study mentioned above as well as the fact that it does not meet the NICE Reference Case, makes us reluctant to use the company's utility estimates.

In Clarification Response B8-b, the company explored alternative utility values in a scenario analysis on utility values which included utility estimates from previous NICE appraisals TA878 and TA971 for the hospitalised heath states and from other sources for the remaining health states (Table 33 of the Clarification Response document and Table 25 below). This scenario increased the ICER for molnupiravir versus no treatment from [redacted] to [redacted] (for

further details on the results of this scenario analysis, see section 5.2.2), although the company considered this scenario less methodologically robust.

Table 25 below also presents the utility values from Soare et al. 2024.[3] Soare et al. 2024 reports the utility for acute COVID-19 for hospitalised patients but does not report any details on the hospitalisation setting or if patients had ventilation. Therefore, we assume that the utility of acute COVID-19 for hospitalised patients reported by Soare et al. 2024 is reflecting the experience of patients in a general ward (i.e., not in the intensive care unit with mechanical ventilation). The sources informing the utilities for TA878 and TA971 are older than the Soare et al. study and not specific for COVID-19. Therefore, we consider the utility values from Soare et al. 2024 to be more appropriate for the EAG base case.

First, EQ-5D-5L utilities from Soare et al. 2024 were converted to EQ-5D-3L scores using the Hernández Alava et al. 2022 algorithm.[112] Then, we adjusted the baseline overall population utility values (based on the model from Hernández Alava) by applying the relative utility decrements observed in Soare et al. 2024 (see Table 25 below). The utility for being in an intensive care unit with mechanical ventilation (not directly reported by Soare et al. 2024) was assumed to be zero, as in TA878 and TA971 (Table 25).

We ran an additional scenario analysis (EAG scenario in Table 25 below) to test the impact of using utility values for all the health states (hospitalised and non-hospitalised) from the previous appraisals TA878 and TA971.

Table 25 Utility values used in the model

	Company base case (vignette study)	EAG base case (Soare et al. 2024)	TA878, TA971 and other sources (company scenario)	TA878 and TA971 (EAG scenario)	Soare et al. 2024 (EQ-5D-5L)	Soare et al. 2024 (EQ-5D-3L calculated by the EAG)
Baseline overall population (pre-COVID)	0.8508	0.8490	0.8508	0.8490	0.82[b]	0.71
Symptomatic outpatient	0.30	0.59	0.57	0.8490	0.62[b]	0.49
Hospitalised in general ward	-0.18	0.28	-0.586 (decrement)	0.3808[a] (-0.47)	0.38	0.23
Hospitalised in ICU with MV	-0.38	0	0	0	NR	NR
Long-term sequelae	0.21	0.67	0.49	0.7208[a] (-0.13)	0.68[c]	0.56

Source: Reproduced from CS Table 65 and Table 33 of the Clarification Response document; TA878 and TA971[20, 22]; Soare et al. 2024 [3]
ICU, intensive care unit; MV, mechanical ventilation.
[a] A utility decrement was applied to the baseline overall population utility. The utility decrement for patients hospitalised in a general ward was calculated as 50%*0.36 + 50%*0.58, as Rafia et al. 2022[68] report utility values by oxygen requirement and we adjusted those according to hospital location, by assuming that 50% of patients in general wards were not receiving oxygen and 50% were receiving oxygen, as in the company's scenario analysis presented in Table 33 of the Clarification Response document.
[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.

4.2.7.3 Adverse event utility decrements

The company did not include adverse event utility decrements due to the mild nature of the adverse events included in the model for both molnupiravir and the comparator arms (see CS section B.3.4.4).

The EAG's clinical experts explained that these drugs are unpleasant to take but this is similar for molnupiravir, nirmatrelvir plus ritonavir and sotrovimab.

The EAG agrees that the adverse events for the outpatient treatments are mostly mild and notes that adding utility decrements has a minimal impact on the model results.

EAG conclusion on HRQoL

In the company's base case, health state utilities were informed by EQ-5D data derived from a vignette study. We consider that the vignette study has limitations, including the use of members of the general population to complete the EQ-5D questionnaires instead of patients. We also consider that the utilities from the vignette study lack face validity as they are too low.

For the EAG base case, we adjusted the general population utility to reflect the utilities reported by Soare et al. 2024.[3] The utility values used in the model have a significant impact on the model results and, based on the disagreement between the company and EAG approaches, we consider this to be a Key Issue (see Key Issue 7).

4.2.8 Resources and costs

The following costs and resource use were included in the company analysis: drug acquisition and administration costs (CS section B.3.5.1), health state unit costs (CS section B.3.5.2) and adverse event costs (CS section B.3.5.3). The cost year for the company's analysis was 2024. Where necessary, the company inflated the costs using the Unit Costs of Health and Social Care 2023 Manual, Personal Social Services Research Unit (PSSRU). The EAG notes that the latest value for inflation in PSSRU is for 2022/23.

4.2.8.1 Literature review of costs and resource studies

The company conducted a systematic literature review of costs and resource use associated with COVID-19, with a date cut-off of 22 January 2024. Eligibility criteria are shown in CS Appendix I Table 83. Results are shown in CS Appendix I section I.1.4. The CS does not comment on which study is the most relevant or whether any studies informed the company model.

4.2.8.2 Drug acquisition and administration costs

CS section B.3.5.1 presents the drug acquisition and administration costs, which are summarised in Table 26 below. Acquisition costs were obtained from the British National Formulary (BNF),[113-115] Drugs and Pharmaceutical Electronic Market Information Tool (eMIT)[116] or previous NICE appraisals TA878 and TA971.[5] In response to Clarification Question B3, the company amended the cost of remdesivir to £2,550.

The price of nirmatrelvir plus ritonavir (£829) used in the company's base case was obtained from the study by Metry et al. 2023[5] used in TA878 and the company clarified that the results for nirmatrelvir plus ritonavir should be treated with caution. NICE confirmed that the list price of £829 should be used in the current appraisal for nirmatrelvir plus ritonavir.

Molnupiravir and nirmatrelvir plus ritonavir are oral treatments. The recommended dose of molnupiravir is 800 mg every 12 hours for 5 days, while nirmatrelvir plus ritonavir is 300 mg of nirmatrelvir with 100 mg of ritonavir all taken together every 12 hours for 5 days. The administration cost of nirmatrelvir plus ritonavir used in the company's base case was £117, based on TA878. The EAG notes that, according to the NICE guidance following the TA878 appraisal, the NICE committee concluded that the administration cost of nirmatrelvir plus ritonavir should lie between £117 and £410.

The administration cost of molnupiravir is based on the same survey of healthcare professionals that informed the administration cost of nirmatrelvir plus ritonavir in NICE TA878, but without the cost for the review of drug-drug interactions.[117] An administration cost of £31.85 was applied in the economic model, which was calculated as the average cost for simple and complex patients. We think this is a reasonable approach as no drug-drug interactions have been identified for molnupiravir.[118]

We acknowledge the uncertainty around the administration costs of oral antivirals as some changes are expected in the future delivery of these drugs (changes to primary care, for example), as discussed in previous appraisals TA878 and TA971.[20, 22, 28] We also note that the model results are very sensitive to changes in the administration costs for oral treatments. Therefore, we tested the impact of assuming that oral treatments have the same administration costs (£117) in a scenario analysis.

The recommended dose of sotrovimab is a single 500 mg intravenous infusion administered following dilution in an outpatient setting and an administration cost of £287 was assumed based on the NHS reference code SB12Z, as in TA878 and TA971.[20, 22, 28]

We note that no administration costs were included for tocilizumab, remdesivir and systemic steroids. As these are inpatient treatments, the cost of drug administration should be embedded in the total cost of hospitalisation.

Table 26 Acquisition and administration costs for outpatient and inpatient treatments

	Cost	Source
Molnupiravir		
Acquisition costs	See CS Table 66	
Administration costs	£31.85 [a]	Butfield et al. 2023 [117]
Total	See CS Table 66	
Nirmatrelvir plus ritonavir		
Acquisition costs	£829.00	Metry et al 2023.[5]
Administration costs	£117.00	TA878[20, 28]
Total	£1,298.49	
Sotrovimab		
Acquisition costs	£2,209.00	BNF[113]
Administration costs	£287.00	NHS reference cost SB12Z [119]
Total	£2,496.00	
Tocilizumab		
Acquisition costs	£798.72	BNF[115]
Administration costs	£0 (IV)	Assumption
Total	£798.72	
Remdesivir		
Acquisition costs	£2,550.00	BNF[114]
Administration costs	£0 (IV)	Assumption
Total	£2,550.00	
Systemic steroids		
Acquisition costs	£3.94	eMIT, HRG code: DJA304[116]
Administration costs	£0 (IV)	Assumption
Total	£3.94	

Source: Partly reproduced from CS Table 66 and 67, and model cell 'TreatmentCost'!E41.
BNF, British National Formulary; eMIT, Drugs and Pharmaceutical Electronic Market Information Tool; IV, intravenous.
[a] Calculated as the average of "overall clinical review, prescribing and dispensing for standard and complex patients" minus "costs associated for drug-drug interaction assessment for standard and complex patients" (£113.58-£85.88)+(£78.94-£42.94).

EAG conclusion on the treatment acquisition and administration costs

As discussed in TA878 and TA971, there is uncertainty around the true administration costs for oral antivirals for COVID-19. The company assumed an administration cost of £117 for nirmatrelvir plus ritonavir, based on the lower range for this cost considered in TA878 and the survey of healthcare professionals.[117] We find this assumption to be conservative (i.e., favours the comparator treatments) as assuming a higher cost favours molnupiravir. For molnupiravir, we agree with the company's approach for estimating the administration cost as no drug-drug interactions have been identified for this medicine. We explored a scenario analysis where molnupiravir and nirmatrelvir plus ritonavir have the same administration costs (£117).

4.2.8.3 Health state unit costs and resource use

CS section B.3.5.2 describes the costs associated with health states in the model, which are summarised in Table 27 below. The costs for outpatient management and accident and emergency visits were included for COVID-19 patients in the outpatient setting, but they have only a small effect on the model results. For hospitalised patients, the costs of hospitalisation by hospital care setting and the cost of one accident and emergency visit were applied. The outpatient and inpatient costs were obtained from NHS reference costs.[119] The costs of accident and emergency visit, general ward and intensive care unit with mechanical ventilation were informed by the HRG codes used in previous appraisals TA878 and TA971[5] and changing them has a minimal impact on the model results.

In response to Clarification Question B5, the company corrected the unit costs for outpatient management, accident and emergency visits and the cost of hospitalisation (both general ward and intensive care unit) and submitted a new economic model (revised company model). We note, however, that the unit cost for general ward and intensive care unit with mechanical ventilation were not updated in the revised company model, so we corrected these costs and created the EAG corrected version of the revised company model (see section 5.3.4). Also, we corrected the unit cost for outpatient management from £165 (simple average) to £179 (weighted average) (see section 5.3.4).

A one-off cost of £411 was applied for patients discharged from hospital, comprising two chest x-rays and six e-consultations with general practitioners. This was also assumed in TA878 and TA971.[5]

The company applied an annual cost for managing long-term sequelae for the duration of long-term sequelae, based on the data for chronic fatigue syndrome considered in TA878 and TA971, which includes the cost of readmission.

Table 27 Health state costs updated after clarification responses from the company

	Cost	Source
Outpatient management	£165	340 and 341 Respiratory Medicine Service and Respiratory Physiology Service unit cost; NHS reference cost 2022[119]
A&E visit, per visit	£1,640	XC07Z; NHS reference cost 2022[119]
General ward	£385.19	DZ11R to DZ11V; NHS reference cost 2022[119]
ICU with MV	£3,362.52	XC01Z to XC07Z and WC08; NHS reference cost 2022[119]
Monitoring following discharge	£411.00	Rafia et al. 2022[68]
Long-term sequelae, annual	£2,426.37	Vos-Vromans et al. 2017[120]

Source: Reproduced from CS Table 68 and Clarification Response B5.
A&E, accident and emergency; ICU, intensive care unit; MV, mechanical ventilation.

EAG conclusion on the health state unit costs and resource use

The costs for the model health states are reasonable and mainly based on the assumptions used in previous appraisals TA878 and TA971.

4.2.8.4 Adverse event costs

The costs of managing adverse events are summarised in CS section B.3.5.3 (CS Table 69). The company assumed that each adverse event would be treated with a specific drug. Drug costs were obtained from eMIT.[116]. The drugs considered by the company are mostly available over-the-counter. Although this might fall outside the NHS and PSS perspective of analysis, the company considered they were representative of the costs of managing these adverse events within the NHS in the absence of better data.

COVID-19 pneumonia was not costed separately, as the company assumed that the costs of managing this adverse event are captured by the hospitalisation costs already included in the model.

We note that some of the adverse events occurring in the outpatient setting would probably need a general practitioner visit. However, we did not add this cost to the EAG base case as the costs associated with the management of adverse events have a negligible impact on the cost-effectiveness analysis results.

In response to Clarification Question B6 the company changed the adverse event cost for headache, using the cost for paracetamol from eMIT of £0.27.

EAG conclusion on the adverse event costs

Costs for drugs available over-the-counter were used to estimate the costs of managing adverse events. We consider this approach to be reasonable and we note that the costs associated with the management of adverse events have a minimal impact on the model results.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company reports their base case incremental cost-effectiveness analysis results for molnupiravir versus no treatment, versus nirmatrelvir plus ritonavir, and versus sotrovimab in CS Table 72, using a confidential list price for molnupiravir and list prices for all other treatments, except for dexamethasone (the company use the eMIT price of £3.94 for their analyses). It is noteworthy that nirmatrelvir plus ritonavir, sotrovimab, remdesivir and tocilizumab are subject to PAS discounts. Results of the cost-effectiveness analyses including the confidential list price for molnupiravir and the PAS discounts for nirmatrelvir plus ritonavir, sotrovimab, remdesivir and tocilizumab are presented in a separate confidential addendum to this report.

In their response to the clarification questions, the company updated their model, which changed their original base case results. The revised model received as part of the clarification response (and referred to as 'the revised company model') includes changes to:

- Percentages of adverse events – diarrhoea associated with molnupiravir; headache and diarrhoea associated with no treatment.
- Costs associated with outpatient management, A&E cost per visit, and headache.
- Treatment cost for remdesivir.

We have reproduced the cost-effectiveness results from the revised company model in Table 28. The pairwise ICER for molnupiravir in comparison with no treatment is [redacted] per QALY. Nirmatrelvir plus ritonavir, and sotrovimab, have higher costs and QALYs than molnupiravir and the ICERs for these treatments versus molnupiravir are [redacted] and [redacted] per QALY, respectively.

Table 28 Base case results of the revised company model

Technologies	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs molnupiravir (£/QALY)	Incremental NHB
No treatment	£1,028	12.873	Reference	[redacted][a]	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	Reference	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs molnupiravir (£/QALY)	Incremental NHB
Source: Partly reproduced from Table 36 of the Clarification Response document. ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality adjusted life years. [a] shows ICER for molnupiravir vs. comparator					

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company reports deterministic sensitivity analysis results in the form of tornado diagrams, showing the top 10 most influential parameters. The comparisons versus no treatment, versus nirmatrelvir plus ritonavir and versus sotrovimab are shown in Figure 4, Figure 5 and Figure 6, respectively (see Appendix 9). CS Table 70 reports the input parameters used in the company's deterministic sensitivity analysis. The range of variation for the input parameters was based on 95% confidence intervals or standard errors where available, or a range of +/- 20% variation around the mean. The company reports the impact on incremental net monetary benefit in these diagrams, using a threshold of £30,000 per QALY gained. Across all the comparators, the two most influential parameters are the underlying hospitalisation rate and the treatment effect on hospitalisation (relative risk).

5.2.2 Scenario analyses

The company conducted the following scenarios:

- Scenario 1a: Using trial-based data (where available) with mortality by highest hospital care setting (for further details on inputs see CS section B.3.11.3)
- Scenario 1b: Using trial-based data (where available) with overall mortality (for further details on inputs see CS section B.3.11.3)
- Scenario 2: Using data from CS Table 51 for the hospitalisation rate of untreated patients, and expert opinion-based mortality by hospital care setting, combined with the treatment effect for COVID-19 specific hospitalisation from the RWE NMA (for further details on inputs see CS section B.3.11.3)
- Scenario 3: Using utility values from previous NICE appraisals TA878 and TA971 (for further details on inputs see company's Clarification Response B8 Table 33 and Table 25)
- Scenario 4: Using the same utility values from the previous NICE appraisals as in scenario 3 and low molnupiravir prescription costs of £9.35 as per Png et al. 2024.[69]

The EAG was able to replicate the results from all the scenarios, except for Scenario 3 where we obtain slightly different results to those reported by the company. The results from the scenario analyses are reproduced below in Table 29 to Table 33.

Table 29 Scenario 1a: Trial-based scenario results - mortality by highest hospital care setting

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	£2,058	16.106	12.703	Reference	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from Table 38 of the Clarification Response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life years.
[a] shows ICER for molnupiravir vs. comparator

Table 30 Scenario 1b: Trial-based scenario results - overall mortality

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	£1,021	16.236	12.858	Reference	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from Table 39 of the Clarification Response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life years.
[a] shows ICER for molnupiravir vs. comparator

Table 31 Scenario 2: Using hospitalisation rate from TA971, mortality by location in hospital based upon expert opinion, treatment effect for COVID-19-specific hospitalisation from RWE NMA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	£877	16.263	12.888	Reference	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from Table 40 of the Clarification Response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life years; RWE NMA, real-world evidence network meta-analysis
[a] shows ICER for molnupiravir vs. comparator

Table 32 Scenario 3: Using utility values from TA878 and TA971[a]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	£1,028	16.257	12.951	Reference	[redacted][b]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Results obtained by the EAG; these estimates vary from those reported in *C*larification Response document Table 41.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life years.
[a] symptomatic outpatient: 0.57, general ward: decrement of 0.586, ICU: 0, long-term sequelae: 0.49
[b] shows ICER for molnupiravir vs. comparator

Table 33 Scenario 4: Using utility values from TA878 and TA971[a] and low molnupiravir prescription costs from Png et al. 2024

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	£1,028	16.257	12.951	Reference	[redacted][b]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Reference

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from Table 42 of the Clarification Response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life years.
[a] symptomatic outpatient: 0.57, general ward: decrement of 0.586, ICU: 0, long-term sequelae: 0.49
[b] shows ICER for molnupiravir vs. comparator

5.2.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis results from 1000 iterations of a Monte-Carlo simulation, using the revised base case are given in Table 37 and Figure 31 of the company's Clarification Response document (shown below in Table 34). The pairwise ICER per QALY gained is reported as [redacted] for molnupiravir versus no treatment, [redacted] for nirmatrelvir plus ritonavir versus molnupiravir, and sotrovimab [redacted] by molnupiravir. Within the revised company model, the sheet named "Sheet!Parameters" reports the input parameters and the distributions used in the probabilistic sensitivity analysis. Uncertainty in the ICER calculation is demonstrated by the cost-effectiveness scatter plots for molnupiravir versus comparators (see Figure 3). At a willingness-to-pay threshold of £20,000 per QALY, the probabilities of each treatment to be cost-effective are 9.5% for molnupiravir, 13.10% for nirmatrelvir plus ritonavir, 2.8% for sotrovimab and 74.6% for no treatment, respectively.

Table 34 Probabilistic results for the revised company model base case

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	£938	16.262	12.903	Ref	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Ref
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from Table 37 of clarification response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; MOV, molnupiravir; QALYs, quality adjusted life years.
[a] shows ICER for molnupiravir vs. comparator

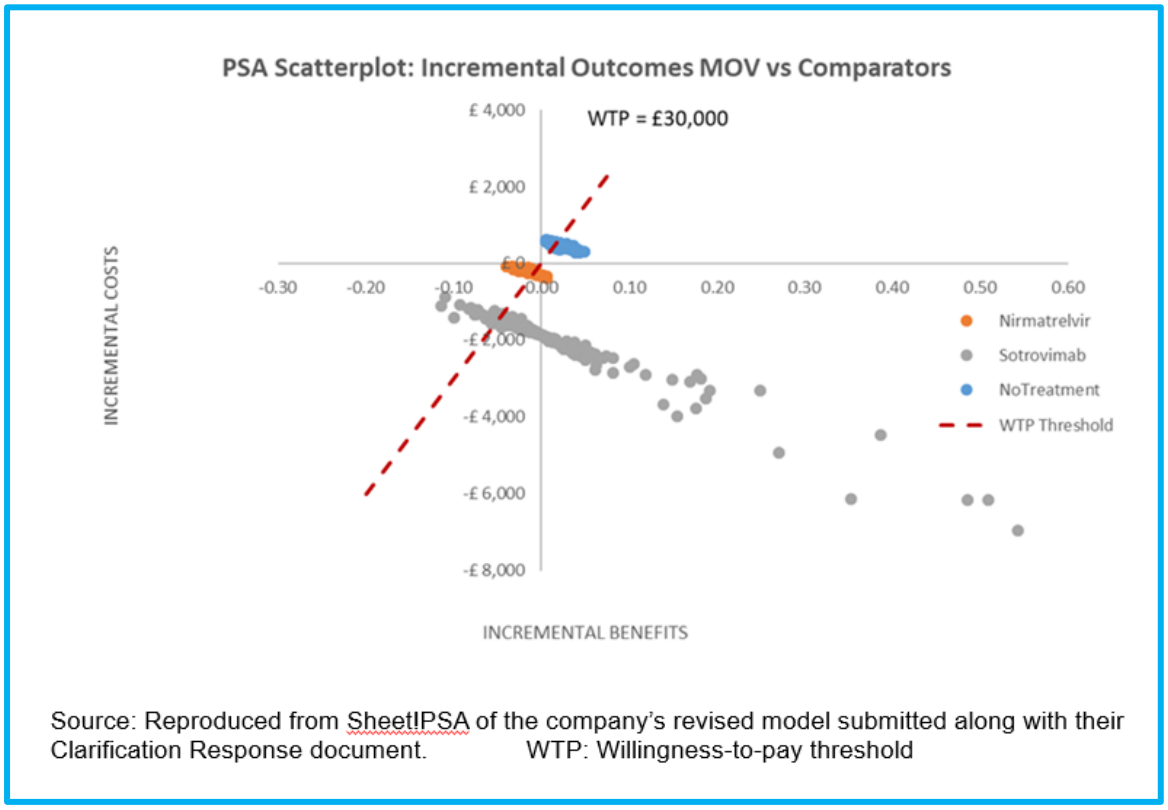

Figure 3 Scatter plot, revised company's model base case

EAG conclusions on the company's sensitivity analyses

The company conducted five scenario analyses, two of which used different utility values than the company's base case (Clarification Response B8). The EAG obtained slightly different cost effectiveness estimates for one of the utility scenarios that used values from TA878 and TA971 (scenario 3). We could replicate the company's results for all the remaining scenarios. The EAG consider that the company's choice of parameters and parameter distributions for the probabilistic sensitivity analysis is appropriate. We note that the revised company base case results and probabilistic ICERs for the comparisons of molnupiravir versus no treatment and versus nirmatrelvir plus ritonavir are similar. But this does not hold for the comparison between molnupiravir and sotrovimab: the base case deterministic ICER for sotrovimab versus molnupiravir is [redacted] per QALY while [redacted] in the PSA results. We note there are outliers in the probabilistic sensitivity analysis scatterplot for sotrovimab, which might explain the difference between the probabilistic and deterministic results.

5.2.4 Subgroup analysis

The company conducted subgroup analysis for the following population groups:

- Patients aged over 70 years;
- Patients contraindicated to nirmatrelvir plus ritonavir;
- Immunocompromised patients with mild to moderate COVID-19;
- Patients with chronic kidney disease.

The inputs for the subgroup analyses are presented in CS Appendix E. Results of the scenario analyses are presented in tables below.

For the subgroup of patients aged over 70 years, the pairwise ICER for molnupiravir in comparison with no treatment is [redacted] per QALY. The ICER for nirmatrelvir plus ritonavir versus molnupiravir is [redacted] per QALY (see Table 35).

Table 35 Company base case results for patients aged over 70 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	£2,313	8.011	5.721	Reference	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from Table 42 of the Clarification Response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life years.
[a]shows ICER for molnupiravir vs. comparator

For the subgroup of patients contraindicated to nirmatrelvir plus ritonavir, the pairwise ICER for molnupiravir in comparison with no treatment is [redacted] per QALY. The ICER for sotrovimab versus molnupiravir is [redacted] per QALY (see Table 36).

Table 36 Company base case results for patients contraindicated to nirmatrelvir plus ritonavir

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	£1,059	16.254	12.869	Reference	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from Table 44 of the Clarification Response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life years.
[a] shows ICER for molnupiravir vs. comparator

For the subgroup of immunocompromised patients, [redacted] no treatment and the pairwise ICERs for nirmatrelvir plus ritonavir and sotrovimab versus molnupiravir are [redacted] and [redacted] per QALY, respectively (see Table 37).

Table 37 Company base case results for immunocompromised patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
Molnupiravir	[redacted]	[redacted]	[redacted]	Reference	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment	£3,955	15.624	12.202	[redacted]	[redacted]

Source: Results obtained by the EAG as the EAG was unable to replicate the results reported by the company in Clarification Response Table 46.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; MOL, molnupiravir; QALYs, quality adjusted life years.

For the subgroup of patients with chronic kidney disease, the pairwise ICER for molnupiravir in comparison with no treatment is [redacted] per QALY. The ICER for nirmatrelvir plus ritonavir versus molnupiravir is [redacted] per QALY (see Table 38).

Table 38 Company base case results for patients with chronic kidney disease

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
No treatment	£1,125	18.737	15.278	Reference	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from Table 48 of the Clarification Response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life years.

The company conducted one scenario analysis on the subgroups using data from the MOVe-OUT trial (see Table 43, Table 45, Table 47, and Table 49 within Section D of the company's Clarification Response document). The company did not perform any other scenario analyses on the subgroups.

5.3 Model validation and face validity check

5.3.1 Company model validation

The company's approach to validating their model is described in CS section B.3.14. Quality control checks were performed by an internal peer reviewer not involved in the original model implementation. The checks included:

- Validating the structure of the model, mathematical formulas, sequences of calculations and the values of numbers supplied as model inputs.
- Extreme value tests to assess the model behaviour and ensuring the results were logical.
- Comparison of the cost-effectiveness estimates presented in "the MTA submitted to NICE in 2022" with the current model estimates. The company stated that while the incremental differences generated in the MTA and the current appraisal are similar, the QALY estimates in the current appraisal compared to those in the MTA are higher. They suggest this could be possibly due to a higher utility value used for long-term sequelae in the current model. We are unclear to what document the company is referring to with "the MTA submitted to NICE in 2022".

Additionally, in Clarification Response B10, the company explained that the comparison of the current model with that from the previous NICE appraisals TA878 and TA971 should be

interpreted with caution due to the differences in the model types between the submissions: the current submission uses a hybrid model including decision tree and Markov model structure whereas the previous TAs used a partitioned survival approach. Nonetheless, the company provided a comparison of the total discounted QALYs obtained across TA878, TA971 and the current appraisal (for further details, see Table 35 of the Clarification Response document).

Furthermore, the company provided a comparison of their model results with those published for PANORAMIC in-trial modelling,[69] although these are for a short-term time horizon of 6 months.

5.3.2 EAG model validation

The EAG conducted a range of tests to verify model inputs, calculations, and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources.
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses.
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses.
- Checking individual equations within the model ('white box' checks).
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks).

5.3.3 Company corrections to the model

The company's corrections to their original model are described in section 5.1 above. The EAG was able to replicate the results of the revised company model after applying the changes described in Clarification Responses B3, B5 and B6 to the original version of the model. For the subgroups, we could replicate the company's results except for the base case results of the immunocompromised patients (as shown in Table 37 above).

5.3.4 EAG corrections to the company model

Other than the issues raised by the EAG in the Clarification Questions, we did not identify any technical calculation errors in the company's economic model. However, we noted a few errors in the unit costs used by the company in the company revised model. These are summarised below in Table 39.

Table 39 EAG corrections to the revised company model

Parameters	Value used in the revised company model	EAG's estimates	Rationale for EAG estimate
Outpatient management cost	£165	£179	The correct weighted average cost for resource codes 340 and 341 (Respiratory Medicine Service cost and Respiratory Physiology Service unit cost) is £179; £165 is the simple average cost.
General ward cost	£438.20	£385	The company acknowledged their error in the value used in Clarification Response B5 but did not incorporate the correct cost of £385 in their revised model
Intensive care unit cost	£3623.29	£3362.52	The company acknowledged their error in the value used in Clarification Response B5 but did not incorporate the correct cost of £3362.52 in their revised model

We included these corrections in the EAG corrected version of the revised company model (referred to as "EAG corrected company revised model"). Incorporating the above corrections has a minimal impact on the overall cost-effectiveness results, as shown in Table 40.

Table 40 EAG corrected company revised model for the overall population and subgroups

Population	Treatments	Total cost	Total QALYs	Pairwise ICER vs. molnupiravir (£/QALY)
Overall population	No treatment	£1,000	12.873	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference

Population	Treatments	Total cost	Total QALYs	Pairwise ICER vs. molnupiravir (£/QALY)
	Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
Subgroup aged over 70 years	No treatment	£2,214	5.721	[redacted] [a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]
Subgroup contraindicated to nirmatrelvir plus ritonavir	No treatment	£1,028	12.869	[redacted] [a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Sotrovimab	[redacted]	[redacted]	[redacted]
Subgroup of immunocompromised patients	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
	No treatment	£3,770	12.202	[redacted]
Subgroup with CKD	No treatment	£1,091	15.278	[redacted] [a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Sotrovimab	[redacted]	[redacted]	[redacted]

Source: Corrections made by the EAG on the revised company's model
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years.
[a] shows ICER for molnupiravir vs. comparator

5.3.5 EAG summary of Key Issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model is presented in Table 41.

Table 41 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
Key model features			
Model structure	Decision tree and Markov model	We agree	No change
Population	Section 4.2.3	We are unclear on the generalisability of the model conclusions to the population with incidental COVID-19.	No change
Comparators	Section 4.2.4	We are unclear on the appropriateness of excluding remdesivir, while the characteristics of the no-treatment comparator are very uncertain.	No change
Perspective	NHS and PSS	We agree	No change
Time horizon	Lifetime	We agree	No change
Discounting	3.5% for costs and outcomes	We agree	No change
Model inputs			
Baseline characteristics	Section 4.2.3	We consider that the baseline characteristics (including age and proportion of female) of the population should be based on the same source where possible.	EAG base case: • Age: No change • Proportion of females: based on the PANORAMIC trial (59%)
Disease characteristics			

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
Hospitalisation rate (overall population)	All-cause hospitalisation rate from RWE NMA (3.79%)	We consider the use of COVID-19 related hospitalisation rate from OpenSAFELY more appropriate and aligned with NICE appraisals TA878 and TA971. Also, the only UK study included in RWE NMA uses the OpenSAFELY cohort.	EAG base case: • Hospitalisation rate: 2.41% (based on COVID-19 related hospitalisation rate from OpenSAFELY) EAG scenarios: • Hospitalisation rate: 2.93% (based on COVID-19 related hospitalisation rate from RWE NMA)
Hospitalisation rate (subgroups)	Section 4.2.6.1.1.2	We consider the hospitalisation rates for patients aged over 70 years and immunocompromised patients too high as these are not expected to be similar to the estimates from the MOVe-OUT trial reported for patients during the pandemic period.	EAG base case: • No change EAG scenarios for the subgroups: • >70 years: 8% (exploratory scenario) • Immunocompromised: 15.90% (from TA878 and TA971)
Distribution of patients by hospital care setting	Based on NHS data	We agree	No change
Length of stay	Based on Yang et al.	We agree	No change
Mortality (overall population and subgroups, except	Based on OpenSAFELY	We agree	No change

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
immunocompromised patients)			
Mortality (subgroup of immunocompromised patients)		According to the NICE committee for TA971, 24.98% is an overestimation of the mortality of immuno-compromised patients. The-TA971 committee considered the mortality rate to be between 10.39% and 14%, tending towards 10.39%.	EAG base case: • 10.39% (based on TA971) EAG scenario: • 14% (based on TA971)
Outpatient duration of symptoms	Based on PANORAMIC trial (9 days)	The EAG's clinical experts considered the duration of outpatient symptoms likely to be shorter for immunocompetent patients and longer for vulnerable groups, although it should be noted that the clinical experts were not experienced in the outpatient setting.	EAG base case: No change EAG scenarios: • Overall population: 5 days • Immunocompromised patients: 15 days • Other subgroups: 9 days (same as base case)
Outpatient visits	No outpatient or accident and emergency visits	We agree	No change
Long-term sequelae	Based on TA878 and TA971: 10% of non-hospitalised patients and	The EAG's clinical experts believe the proportion of patients with long-term sequelae is now quite low.	EAG base case: • No change

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
	100% of hospitalised patients for a duration of 113.60 weeks		EAG scenarios: • 1% of non-hospitalised patients and 10% of hospitalised patients (exploratory scenario) • 5% of non-hospitalised patients and 50% of hospitalised patients (exploratory scenario)
Treatment effectiveness			
RR of hospitalisation (overall population)	Section 4.2.6.2.1.1	The treatment effect on hospitalisation is very uncertain as the results from the RWE NMAs are not statistically significant for most comparisons. Also, the alternative values are not ideal. Therefore, we tested the impact of this assumption in scenario analyses.	EAG base case: • No change EAG scenarios: • Zheng et al. OPENSAFELY- all-cause hospitalisation • Zheng et al. OPENSAFELY - COVID-19 related hospitalisation • RWE NMA - COVID-19 related hospitalization • Direct meta-analysis - all-cause hospitalisation
RR of hospitalisation (subgroups)	Section 4.2.6.2.1.2	We agree	No change
HR for outpatient symptom duration	Section 4.2.6.2.2	There is limited evidence to inform the effect of outpatient treatments on symptom duration. Therefore, the values used for this input are very uncertain.	EAG base case: • No change EAG scenarios: • Varying HRs based on Table 21

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
Treatment effect of inpatient treatments (time to discharge)	HR for remdesivir: 1.27 HR for tocilizumab: 1.05	According to TA878 and TA971, not applying a treatment effect on time to discharge is a reasonable approach. The NICE committees in those appraisals also considered that not applying a treatment effect might underestimate the effects of drugs for the subgroup of immunocompromised patients.	EAG base case: Overall population and subgroups, except immunocompromised patients: • HR for remdesivir: 1 • HR for tocilizumab: 1
Treatment effect of inpatient treatments (mortality)	RR for remdesivir: 0.91 RR for tocilizumab: 0.88	In TA971, the NICE committee concluded there was no strong evidence to show a meaningful treatment effect of remdesivir on mortality. The committee considered that the relative risk should vary between 0.85 and 1, tending towards 1.	EAG base case • No change EAG scenario • a RR for mortality for remdesivir of 1.
Adverse events	Section 4.2.6.2.4	We agree	No change
Utilities			
Health state utilities	Utilities based on a vignette study	We consider that the company's utilities lack face validity as they are too low and some of them are negative (for states worse than death). Moreover, the vignette	EAG base case: • General population utilities adjusted for the relative decrements observed in Soare et al.[3] (see Table 25)

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
		study has several limitations including not meeting the NICE Reference Case.	EAG scenarios: • We test the utilities form previous appraisals TA878 and TA971 in scenario analysis (see Table 25)
Adverse event disutilities	Not applied	We agree	No change
Severity modifier	Not applied	We agree	No change
Resource use and costs			
Acquisition costs	Section 4.2.8.2	We agree	No change
Administration costs	Section 4.2.8.2	We agree with the company's base case although we acknowledge the uncertainty around the true administration costs of oral antivirals.	EAG base case: • No change EAG scenarios: • Same administration cost for oral antivirals – molnupiravir and nirmatrelvir plus ritonavir (£117)
Health state costs	Section 4.2.8.3	We agree	No change
Adverse event costs	Section 4.2.8.4	We agree	No change
HR, hazard ratio; NMA, network meta-analysis; PSS, Personal Social Services; RR, relative risk; RWE, real-world evidence;			

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

We ran the company's scenario analyses on the EAG corrected company revised model, along with some additional scenarios to explore the issues described in section 5.3.5 above. These analyses were conducted on the overall patient population (Table 42). Of the scenarios ran by the EAG, four assumptions relating to the (i) proportions of patients with the long-term sequelae, (ii) using trial-based data with mortality by hospital care setting, (iii) relative risk of hospitalisation, and (iv) health state utilities, had the most significant impact on the overall cost-effectiveness results.

Table 42 Additional analyses conducted by the EAG on the EAG corrected company revised model, pairwise ICERs for comparisons versus molnupiravir

Scenarios	No treatment	Nirmatrelvir plus ritonavir	Sotrovimab
EAG corrected company revised model base case	[redacted][a]	[redacted]	[redacted]
Scenarios conducted on the above model			
Company's Scenario 1a: Using trial-based data (where available) with mortality by hospital care setting	[redacted][a]	[redacted]	[redacted]
Company's Scenario 1b: Using trial-based data (where available) with overall mortality	[redacted][a]	[redacted]	[redacted]
Company Scenario 2: Using data from CS Table 51 for the hospitalisation rate and expert opinion-based mortality by hospital care setting, combined with the treatment effect for COVID-19 specific hospitalisation from the RWE NMA	[redacted][a]	[redacted]	[redacted]
Company Scenario 3: Using utility values from TA878 and TA971	[redacted][a]	[redacted]	[redacted]
Company Scenario 4: Using utility values from TA878 and TA971 and low molnupiravir prescription costs of £9.35 as per Png et al. 2024	[redacted][a]	[redacted]	[redacted]

Hospitalisation rate: 2.41% (based on COVID-19 related hospitalisation rate from OpenSAFELY)	[redacted][a]	[redacted]	[redacted]
Hospitalisation rate: 2.93% (based on COVID-19 related hospitalisation rate from RWE NMA)	[redacted][a]	[redacted]	[redacted]
Long term sequelae: 1% for non-hospitalised patients and 10% for hospitalised patients	[redacted][a]	[redacted]	[redacted]
RR of hospitalisation based on all-cause hospitalisation from Zheng et al. 2023 OpenSAFELY: • Molnupiravir versus nirmatrelvir plus ritonavir: 1.64	[redacted][a]	[redacted]	[redacted]
RR of hospitalisation based on COVID-19 related hospitalisation from Zheng et al. 2023 OpenSAFELY: • Molnupiravir versus nirmatrelvir plus ritonavir: 2.22	[redacted][a]	[redacted]	[redacted]
RR of hospitalisation based on RWE NMA: COVID-19 related hospitalisation: • Molnupiravir versus no treatment: 0.85 • Molnupiravir versus nirmatrelvir plus ritonavir: 1.58	[redacted][a]	[redacted]	[redacted]
RR of hospitalisation based on COVID-19 related hospitalisation or death from Tazare et al. 2023 OpenSAFELY:[2] • Molnupiravir versus no treatment: 1.0 [b]	[redacted][a]	[redacted]	[redacted]
RR of hospitalisation based on RWE direct meta-analysis: • Molnupiravir versus no treatment: 0.81 • Molnupiravir versus nirmatrelvir plus ritonavir: 0.88	[redacted][a]	[redacted]	[redacted]
Treatment effect of inpatient treatments (time to discharge)	[redacted][a]	[redacted]	[redacted]

• HR for remdesivir: 1.0 • HR for tocilizumab: 1.0			
Health state utilities: using general population utilities adjusted for the relative decrements observed in Soare et al. 2024[3] (see Table 28)	[redacted][a]	[redacted]	[redacted]
Same administration costs (£117) for oral antivirals (molnupiravir and nirmatrelvir plus ritonavir)	[redacted][a]	[redacted]	[redacted]
Source: Analyses conducted by the EAG ICER, incremental cost-effectiveness ratio. [a] shows the ICER for molnupiravir versus comparator. [b] a relative risk of 1.0 was used to reflect the hazard ratios reported by Tazare et al. 2023[2] which indicate no difference in the risk of COVID-19 related hospitalisation or death between molnupiravir and no treatment.			

6.2 EAG's preferred assumptions

Based on the EAG's critique of the company's model (discussed in section 5.3.5 above) and the scenarios described in section 6.1, we have identified several aspects of the EAG corrected company revised model with which we disagree. Our preferred assumptions for the overall population include:

- **Proportion of females at baseline**: 59% based on the PANORAMIC trial rather than 51.3% based on the MOVe-OUT trial (section 4.2.3).
- **Hospitalisation rate of untreated patients**: 2.41% based on COVID-19 related hospitalisation rate from the OpenSAFELY study rather than 3.79% based on the RWE NMA (section 4.2.6.1.1.1).
- **Treatment effect of inpatient treatments (time to discharge)**: HR of 1 for both remdesivir and tocilizumab based on previous appraisals TA878 and TA971 rather than a HR of 1.27 for remdesivir and 1.05 for tocilizumab (section 4.2.6.2.3).
- **Health state utilities**: utilities taken from Soare et al. 2024[3] rather than the company's vignettes (see Table 25).

Table 43 shows the cumulative effect of each of these changes to the EAG corrected company revised model base case, along with a breakdown of the total costs and the total QALYs. The EAG's preferred assumptions increase the ICER for molnupiravir versus no treatment from to [redacted] per QALY, and the ICERs for nirmatrelvir plus ritonavir versus

molnupiravir and sotrovimab versus molnupiravir from [redacted] to [redacted] per QALY and from [redacted] to [redacted] per QALY, respectively.

Table 43 EAG's cumulative model base case results with preferred assumptions, ICER versus molnupiravir (£/QALY)

Scenarios	Treatments	Total Costs	Total QALYs	Pairwise ICER vs molnupiravir
EAG corrected company revised model base case	No treatment	£1,000	12.873	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
+ Proportion of females based on PANORAMIC trial	No treatment	£1,000	12.901	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
+ Overall proportion hospitalised at baseline based on OpenSAFELY	No treatment	£797	12.928	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
+ Treatment effects of inpatient treatments (time to discharge): Using HRs for remdesivir and tocilizumab of 1 and 1 respectively	No treatment	£811	12.928	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
+ Using general population utilities adjusted for the relative decrements observed in Soare et al. 2024[3] (see Table 25)	No treatment	£811	13.042	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]
EAG preferred base case	No treatment	**£811**	**13.042**	[redacted][a]
	Molnupiravir	[redacted]	[redacted]	Reference
	Nirmatrelvir	[redacted]	[redacted]	[redacted]
	Sotrovimab	[redacted]	[redacted]	[redacted]

Source: Analyses conducted by the EAG
HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MOL, molnupiravir; QALYs, quality adjusted life years.
[a] shows the ICER for molnupiravir versus comparator

6.3 Scenarios conducted on the EAG's preferred base case

The EAG ran scenario analyses on our base case assumptions (see Table 44). The model is extremely sensitive to the proportion of patients with long-term sequelae: decreasing the proportion increases the ICER of molnupiravir versus no treatment, and substantially increases the ICERs of nirmatrelvir plus ritonavir versus molnupiravir and sotrovimab versus molnupiravir. Furthermore, the model is also sensitive to utility values obtained from the previous technology appraisals: using these estimates increases the ICER of molnupiravir versus no treatment and those of nirmatrelvir plus ritonavir and sotrovimab versus molnupiravir substantially. Assuming no effect on hospitalisation for molnupiravir versus no treatment increases the ICER from [redacted] to [redacted] per QALY. Using the relative risk of hospitalisation from Zheng et al. 2023 or using the relative risk of COVID-19 related hospitalisation from the RWE NMA decreases the ICER of nirmatrelvir plus ritonavir versus molnupiravir from [redacted] to less than [redacted] per QALY. We note that none of the scenarios change the direction of the results obtained in the EAG base case for molnupiravir versus no treatment and sotrovimab versus molnupiravir - the ICER is above £30,000 per QALY for all the scenarios.

Table 44 Additional analyses conducted on the EAG's preferred base case model, ICERs versus molnupiravir (£/QALY)

Scenarios	No treatment	Nirmatrelvir plus ritonavir	Sotrovimab
EAG preferred base case	[redacted][c]	[redacted]	[redacted]
Scenarios conducted on the above model			
Hospitalisation rate: 2.93% (based on COVID-19 related hospitalisation rate from RWE NMA)	[redacted][c]	[redacted]	[redacted]
Outpatient duration of symptoms: 5 days	[redacted][c]	[redacted]	[redacted]
Long term sequelae: 1% of non-hospitalised patients and 10% of hospitalised patients	[redacted][c]	[redacted]	[redacted]
Long term sequelae: 5% of non-hospitalised patients and 50% of hospitalised patients	[redacted][c]	[redacted]	[redacted]

Scenarios	No treatment	Nirmatrelvir plus ritonavir	Sotrovimab
RR of hospitalisation based on all-cause hospitalisation from Zheng et al. 2023 OpenSAFELY: • Molnupiravir versus nirmatrelvir plus ritonavir: 1.64	[redacted][c]	[redacted]	[redacted]
RR of hospitalisation based on COVID-19 related hospitalisation from Zheng et al. 2023 OpenSAFELY: • Molnupiravir versus nirmatrelvir plus ritonavir: 2.22	[redacted][c]	[redacted]	[redacted]
RR of hospitalisation based on RWE NMA for COVID-19 related hospitalisation: • Molnupiravir versus no treatment: 0.85 • Molnupiravir versus nirmatrelvir plus ritonavir: 1.58	[redacted][c]	[redacted]	[redacted]
RR of hospitalisation based on COVID-19 related hospitalisation from Tazare et al. 2023 OpenSAFELY:[2] • Molnupiravir versus no treatment: 1.0[d]	[redacted][c]	[redacted]	[redacted]
RR of hospitalisation based on RWE direct meta-analysis: • Molnupiravir versus no treatment: 0.81 • Molnupiravir versus nirmatrelvir plus ritonavir: 0.88	[redacted][c]	[redacted]	[redacted]
HR for outpatient symptom duration – lower bound (based on Table 21 above) • Molnupiravir versus no treatment:1.40[a]	[redacted][c]	[redacted]	[redacted]

Scenarios	No treatment	Nirmatrelvir plus ritonavir	Sotrovimab
• Nimatrelvir plus ritonavir versus molnupiravir: 0.7 • Sotrovimab versus molnupiravir: 0.7			
HR for outpatient symptom duration – higher bound (based on Table 21 above) • Molnupiravir versus no treatment:1.32[b] • Nimatrelvir plus ritonavir versus molnupiravir: 1.3 • Sotrovimab versus molnupiravir: 1.3	[redacted][c]	[redacted]	[redacted]
Effect of inpatient treatments (mortality): using a RR for remdesivir of 1.0	[redacted][c]	[redacted]	[redacted]
Utility from previous appraisals TA878 and TA971 (EAG scenario) (see Table 25 above) • Baseline overall population: 0.8490 • Symptomatic outpatient: 0.8490 • Hospitalisation in general ward: 0.3808 • Hospitalised in ICU with MV: 0 • Long-term sequelae: 0.7208	[redacted][c]	[redacted]	[redacted]
Administration costs of oral antivirals: same for molnupiravir and nirmatrelvir plus ritonavir (£117)	[redacted][c]	[redacted]	[redacted]

Source: Analyses conducted by the EAG
HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; MOL, molnupiravir; MV, mechanical ventilation; NMA, network meta-analysis; QALYs, quality adjusted life years; RR, relative risk; RWE, real world evidence.
[a] The HR of molnupiravir vs no treatment (1.40) is reciprocated to estimate the value of 0.71 for the HR of no treatment versus molnupiravir
[b] The HR of molnupiravir versus no treatment (1.32) is reciprocated to estimate the value of 0.76 for no treatment vs molnupiravir
[c] shows ICER for molnupiravir versus comparator.
[d] a relative risk of 1.0 was used to reflect the hazard ratios reported by Tazare et al. 2023[2] which indicate no difference in the risk of COVID-19 related hospitalisation or death between molnupiravir and no treatment.

6.4 EAG analyses conducted for the subgroups

We ran our preferred model assumptions (discussed in section 5.3.5 above) on the subgroups, as follows.

The EAG base case assumptions for the following subgroups: i) aged over 70 years; ii) contraindicated to nirmatrelvir plus ritonavir and iii) with chronic kidney disease are:

- **Proportion of females at baseline**: 59% based on the PANORAMIC trial rather than 51.3% based on the MOVe-OUT trial (section 4.2.3).
- **Effect of inpatient treatments (time to discharge)**: HR of 1 for both remdesivir and tocilizumab based on previous appraisals TA878 and TA971 rather than a HR of 1.27 for remdesivir and 1.05 for tocilizumab (section 4.2.6.2.3).
- **Health state utilities**: utilities taken from Soare et al. 2024[3] rather than the company's vignettes (see Table 25).

The results for these three subgroups (presented in Table 45, Table 46 and Table 47 below) show that the ICERs of molnupiravir versus no treatment and those of nirmatrelvir plus ritonavir and sotrovimab versus molnupiravir increased compared to the EAG corrected company revised model results. Molnupiravir versus no treatment and nirmatrelvir plus ritonavir versus molnupiravir have an ICER below £30,000 per QALY in all the subgroups while sotrovimab has an ICER above £30,000 per QALY versus molnupiravir in all the subgroups.

Table 45 EAG base case assumptions applied to the subgroup: aged over 70 years

Technologies	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER MOL versus comparators (£/QALY)
No treatment	£2,293	5.930	Reference	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]

Source: Cumulative changes made by the EAG on the EAG-corrected revised company base case. ICER, incremental cost-effectiveness ratio; MOL, molnupiravir; QALYs, quality adjusted life years.
[a] shows the ICER for molnupiravir versus comparator

Table 46 EAG base case assumptions applied to the subgroup: contraindicated to nirmatrelvir plus ritonavir

Technologies	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER versus molnupiravir (£/QALY)
No treatment	£1,052	13.023	Reference	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	Reference
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]

Source: Cumulative changes made by the EAG on the EAG-corrected revised company base case.
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years.
[a] shows the ICER for molnupiravir versus comparator

Table 47 EAG base case assumptions applied to the subgroup: chronic kidney disease

Technologies	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER versus molnupiravir (£/QALY)
No treatment	£1,117	15.442	Reference	[redacted][a]
Molnupiravir	[redacted]	[redacted]	[redacted]	Reference
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]

Source: Cumulative changes made by the EAG on the EAG corrected revised company base case.
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years.
[a] shows the ICER for molnupiravir versus comparator

For the immunocompromised subgroup, the EAG preferred assumptions are as follows:

- **Proportion of females at baseline**: 59% based on the PANORAMIC trial rather than 51.3% based on the MOVe-OUT trial (section 4.2.3).
- **Mortality**: 10.39% based on TA971 rather than 24.98% based on the INFORM study (section 4.2.6.1.4.2).
- **Health state utilities**: utilities taken from Soare et al.2024 [3] rather than the company's vignettes (see Table 25).

The results of the EAG base case for the immunocompromised subgroup are shown in Table 48. The direction of the cost-effectiveness results follows a similar pattern to those of

the subgroups reported above. The only exception is that sotrovimab versus molnupiravir has an ICER below £30,000 per QALY.

Table 48 EAG base case assumptions applied to the subgroup: immunocompromised patients

Technologies	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs. molnupiravir (£/QALY)
Molnupiravir	[redacted]	[redacted]	Reference	Reference
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]
No treatment	£3,853	12.683	[redacted]	[redacted]

Source: Cumulative changes made by the EAG on the EAG corrected revised company base case
ICER, incremental cost-effectiveness ratio; MOL, molnupiravir; QALYs, quality adjusted life years.

In addition to the above, we also conducted several scenarios on the EAG preferred base case for the subgroups, as shown in Table 49 below. We note that the assumption for the proportion of patients with long-term sequelae had the most substantial impact on the cost-effectiveness results. This is consistent with the pattern observed in the results for the scenarios conducted on the overall population.

Table 49 Additional scenarios on EAG base case assumptions for the subgroups, ICER versus molnupiravir (£/QALY)

Scenarios	No treatment	Nirmatrelvir plus ritonavir	Sotrovimab
Aged over 70 years			
EAG preferred base case	[redacted][a]	[redacted]	N/A
Overall proportion hospitalised based on OpenSAFELY (8%)	[redacted][a]	[redacted]	N/A
For long term sequelae, proportion of non-hospitalised patients is 1% and that of hospitalised patients is 10%	[redacted][a]	[redacted]	N/A
Utility from previous appraisals TA878 and TA971 (EAG scenario) (see Table 25 above) • Baseline overall population: 0.8490	[redacted][a]	[redacted]	N/A

Scenarios	No treatment	Nirmatrelvir plus ritonavir	Sotrovimab
• Symptomatic outpatient: 0.8490 • Hospitalisation in general ward: 0.3808 • Hospitalised in ICU with MV: 0 • Long-term sequelae: 0.7208			
Contraindicated to nirmatrelvir plus ritonavir			
EAG preferred base case	[redacted][a]	N/A	[redacted]
For long term sequelae, proportion of non-hospitalised patients is 1% and that of hospitalised patients is 10%	[redacted][a]	N/A	[redacted]
Utility from previous appraisals TA878 and TA971 (EAG scenario) (see Table 25 above) • Baseline overall population: 0.8490 • Symptomatic outpatient: 0.8490 • Hospitalisation in general ward: 0.3808 • Hospitalised in ICU with MV: 0 • Long-term sequelae: 0.7208	[redacted][a]	N/A	[redacted]
Chronic Kidney Disease			
EAG preferred base case	[redacted][a]	N/A	[redacted]
For long term sequelae, proportion of non-hospitalised patients is 1% and that of hospitalised patients is 10%	[redacted][a]	N/A	[redacted]
Utility from previous appraisals TA878 and TA971 (EAG scenario) (see Table 25 above) • Baseline overall population: 0.8490 • Symptomatic outpatient: 0.8490 • Hospitalisation in general ward: 0.3808 • Hospitalised in ICU with MV: 0 • Long-term sequelae: 0.7208	[redacted][a]	N/A	[redacted]
Immunocompromised			
EAG preferred base case	[redacted]	[redacted]	[redacted]
Overall proportion hospitalised based on OpenSAFELY (15.90%)	[redacted]	[redacted]	[redacted]
Mortality: 14%	[redacted]	[redacted]	[redacted]

Scenarios	No treatment	Nirmatrelvir plus ritonavir	Sotrovimab
Outpatient symptom duration: 15 days	[redacted]	[redacted]	[redacted]
For long term sequelae, proportion of non-hospitalised patients is 1% and that of hospitalised patients is 10%	[redacted]	[redacted]	[redacted]
Utility from previous appraisals TA878 and TA971 (EAG scenario) (see Table 25 above) • Baseline overall population: 0.8490 • Symptomatic outpatient: 0.8490 • Hospitalisation in general ward: 0.3808 • Hospitalised in ICU with MV: 0 • Long-term sequelae: 0.7208	[redacted]	[redacted]	[redacted]
Source: Scenario analyses made by the EAG on the EAG base case model. ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; MOL, molnupiravir; MV, mechanical ventilation, N/A, not applicable; QALYs, quality adjusted life years. [a] shows the ICER for molnupiravir versus comparator			

6.5 Conclusions on the cost effectiveness evidence

The EAG considers the structure of the company's economic model to be appropriate and consistent with previous cost-effectiveness models of molnupiravir and other outpatient antivirals for COVID-19. Health state utilities were derived from a vignette study using an EQ-5D-5L questionnaire answered by the general public and therefore the company model did not meet the requirements of NICE's reference case for the estimation of health state utilities (see Table 11 above). The results of the revised company model show a pairwise ICER for molnupiravir in comparison with no treatment of [redacted] per QALY for the overall population. Nirmatrelvir plus ritonavir, and sotrovimab, have higher costs and QALYs than molnupiravir and the ICERs for these treatments versus molnupiravir are [redacted] and [redacted] per QALY, respectively, for the overall population.

The EAG disagrees with or is uncertain of several assumptions in the company's model and considers that further discussion and clinical expert opinion would be valuable to help address these uncertainties. These are: the hospitalisation rate of untreated patients (Key Issue 4), the effect of outpatient treatments on hospitalisation (Key Issue 5), the proportion of patients with long-term sequelae (Key Issue 6), and the health state utilities (Key Issue 7).

Incorporating the EAG's preferred assumptions for the overall population (see section 6.2), the pairwise ICER for molnupiravir versus no treatment increases to [redacted] per QALY, for

nirmatrelvir plus ritonavir versus molnupiravir increases to [redacted] per QALY and for sotrovimab versus molnupiravir increases to [redacted] per QALY.

For the subgroups, incorporating the EAG's preferred assumptions (see section 6.4) leads to an increase in the ICER for all the subgroups and comparisons. Molnupiravir has an ICER below £30,000 per QALY versus no treatment in all the subgroups, as well as nirmatrelvir plus ritonavir versus molnupiravir. The ICER of sotrovimab versus molnupiravir are above 30,000 per QALY for all the subgroups, except for the subgroup of immunocompromised patients.

For the overall population, the model results are most sensitive to changing assumptions for the proportions of patients with long-term sequelae, relative risks of hospitalisation and health state utilities. For the subgroups, the model results are most sensitive to changing assumptions on the proportion of patients with long-term sequelae.

7 SEVERITY

In CS section B.3.6, the company explain that a severity weighting was not considered appropriate for the COVID-19 disease area and therefore a severity modifier was not applied. Even for the most vulnerable subgroups of patients (immunocompromised or with chronic kidney disease), a severity modifier was not applied in line with the approach taken in TA971. The EAG agrees with the company's approach.

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9 APPENDICES

Appendix 1 Critique of the RCT SLR and the RWE SLR

Table 50 EAG critique of RCT SLR

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	PICOTS criteria reported in CS Appendix Table 5, section D.1.1.3.
Were appropriate sources of literature searched?	Yes	Broad range of sources including MEDLINE, Embase, Cochrane, and supplementary searching.
What time period did the searches span and was this appropriate?	Yes	Database inception up to 1st February 2024, incorporating several update searches. Only five months old.
Were appropriate search terms used and combined correctly?	Mostly	Used published RCT filters. However, the virus term instead of the disease term for COVID-19 was used. It is unclear whether mapping functionality was used on the search platform, if not, no translation of the subject headings was carried out between databases.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes. The criteria are appropriate, but we cannot tell if they were applied appropriately due to incomplete reporting.	CS Appendix Table 5 outlines the eligibility criteria which are broader than the NICE scope, e.g. multiple interventions. CS Appendix D.1.1.4 outlines the characteristics of trials of high relevance for inclusion in this appraisal. Criteria are relevant to the Decision Problem focusing on outpatients, relevant comparators, and more recent study dates (results from update searches only) for generalisability. Some discrepancies were resolved in Clarification Response A3. However, the EAG is unable to tell if the criteria were applied correctly because we were unable to find a discrete list of the 23 RCTs screened as included prior to further screening for high relevance.
Were study selection criteria applied by two or more reviewers independently?	Yes	Screening was conducted by two reviewers independently and any disputes were discussed or referred to an additional senior reviewer (CS Appendix D.1.1.3).
Was data extraction performed by two or more reviewers independently?	Unclear	The number of reviewers performing data extraction is not reported. A pre-specified data extraction form is reported in CS Appendix Table 6.
Was a risk of bias assessment or a quality assessment of the included	Yes	Cochrane RoB2 was used to assess risk of bias. Overall assessments for RCTs included in the RCT NMA are in CS Appendix Table 25, with the assessments for each domain of bias included in

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
studies undertaken? If so, which tool was used?		CS Appendix Table 26. Justifications for the assessments are reported in Clarification Response A7a.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	Not reported.
Is sufficient detail on the individual studies presented?	Mostly	All trial publications were provided (except for supplementary material). Study characteristics and study outcomes are tabulated in CS Appendix D.1.1.4.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	A Bayesian NMA was carried out. Discussed in sections 3.4, 3.5 and 3.6.

Table 51 EAG critique of RWE SLR

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The review question outlined in CS section B.2.9 and the PICOTS criteria in CS Appendix Table 35, are both appropriate to the NICE scope.
Were appropriate sources of literature searched?	Yes	MEDLINE, Embase, and Cochrane were searched, plus a focus on recent material from four relevant conferences and several preprint servers. Supplementary searching is well documented.
What time period did the searches span and was this appropriate?	Yes	Database inception up to 15th December 2023. No updates were run. Conferences were searched from 2022 and two of the preprint servers had date limits applied.
Were appropriate search terms used and combined correctly?	Yes	The searches used appropriate terminology for both subject headings and free-text terms. The search was peer reviewed.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	The PICOTS criteria in CS Appendix Table 35, aligned with NICE scope. After initial screening, a prioritisation stage was carried out with reasons for not prioritising studies summarised in the PRISMA flow diagram in CS Appendix Figure 14, the EAG find these reasons appropriate to

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
		identifying studies that are more recent (and more generalisable) than the RCTs and go some way towards a feasibility assessment by assessing study methods. Although the feasibility assessment was the next step.
Were study selection criteria applied by two or more reviewers independently?	Yes	At both title and abstract screening and full-text screening stages two independent reviewers determined eligibility and any disagreements were resolved by a third independent reviewer (CS Appendix D.2.1.3).
Was data extraction performed by two or more reviewers independently?	No, but second and third reviewers had roles	All data were extracted by one reviewer, checked for accuracy and consistency by a second reviewer, with disagreements resolved by a third reviewer (CS Appendix D.2.1.3). The methods for data extraction were in two phases and reported transparently. The EAG find this appropriate.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The risk of bias assessment was performed using criteria "based on the NICE checklist" (CS section B.2.5.2). Assessments reported in CS Appendix D.2.3 and CS Appendix Table 40, and overall assessments for each study are summarised in CS Table 13. The EAG suggest that ROBINS-I is the most appropriate tool to use for this evidence, and other published systematic reviews assessing the same studies consistently provide different assessments to the company when using the ROBINS-I tool. The company was unable to provide ROBINS-I assessments within the clarification timelines (Clarification Response A8a). Discussion in section 3.4.4.2.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No, but second and third reviewers had roles	Not reported in the CS. Each assessment was conducted by one reviewer and validated by a second independent reviewer, with discrepancies resolved by a third more senior investigator (confidential company RWE SLR report).
Is sufficient detail on the individual studies presented?	Mostly	Study publications were provided for all studies (except for supplementary material). Study methods and study outcomes are tabulated in CS Appendix D.2.1.6. Further details such as patient characteristics are discussed in the confidential company RWE SLR report.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken,	Yes	A Bayesian NMA was carried out for an active treatment network and for an active treatment/control network that included two

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
were appropriate methods used?		further comparators relating to no treatment. The company also report results from a direct meta-analysis and a Bucher ITC but they were only provided for reference (Clarification Response A16). Discussion of the RWE NMA is in sections 3.4, 3.5 and 3.6.

Appendix 2 Risk of bias assessment for MOVe-OUT

Risk of bias domain	Company assessment (CS Table 26)	EAG assessment
Randomization process	Low risk	**Agree: low risk of bias.** Patients were randomly assigned in a 1:1 ratio using a centralised interactive-response technology system suggesting the allocation was adequately concealed; there were no significant imbalances in participant baseline characteristics between trial arms.
Deviation from intended intervention	Low risk	**Agree: low risk of bias.** Participants and investigators were blinded until all actively enrolled participants had undergone the 7-month follow-up visit, except for the unblinded statistician and the unblinded team performing the analyses at the interim analyses (study protocol 9.7). There is nothing to suggest deviation from the intended deviation other than those listed as not adherent to the assigned regimen were similar between groups: 8 and 7 participants for molnupiravir and placebo respectively. A modified intention-to-treat analysis was performed: all randomized participants who received at least one dose of study intervention.
Missing outcome data	Low risk	Missing data for the primary outcome was imputed as either hospitalised or dead which is conservative and appropriate. There is likely to be missing data for the WHO 11-point ordinal scale outcome, described as “sparse” (CS Table 11), however the study protocol reports using reasonable methods of handling missing data for all outcomes.(Study protocol Table 5).[23]
Measurement of outcome	Low risk	**Agree: low risk of bias.** All outcomes were measured in the same way for both trial arms, the trial was double-blinded therefore the patient symptom diaries as well as scheduled examinations,

Risk of bias domain	Company assessment (CS Table 26)	EAG assessment
		therefore assessment was not influence by knowledge of the intervention.
Result selection	Low risk	For the trial publications: **low risk of bias.** All primary and secondary outcomes, plus additional post-hoc analyses are reported in the various trial publications. For results presented in the CS: initially high risk of bias. The results of the exploratory outcomes for viral load/infectivity and of the post-hoc-analysis that includes respiratory support were not reported in the CS, despite being outcomes of interest in the NICE scope. Reduced to **low risk of bias** with provision of data in Clarification Responses A1 and A2.
Overall	Low risk	**Agree: low risk of bias.** All RoB2 domains assessed at low risk of bias.

Appendix 3 Summary overview of population characteristics of trials included in the RCT NMAs

Study	Age, years	Sex, male	Modal race / ethnicity	Vaccinated	Any risk factor	Immuno-compromised	Obese	Diabetes	CVD	Renal disease	Respiratory disease	Liver disease	Hyper-tension	Cancer
MOVe-OUT[23]	Mean 45	48.7%	White	0%	99%	NR	74%	16%	12%	6% CKD	4% COPD	NR	NR	2%
NCT04405570[121]	Median 39-42	45-51%	White	NR	60%	NR	26-27%	NR	NR	NR	NR	NR	NR	NR
AGILE-CST-2[34]	Median 43	43%	White	50%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PANORAMIC[33]	Mean 57	41-42%	White	99%	69%	8-9%	15%	12%	7-8%	2%	23-25%	1%	22%	NR
PINETREE[122]	Mean 50	52%	White	0%	NR	4%	55%	62%	8%	3%	24%	<1%	48%	5%
EPIC-HR[123, 124]	Median 46	51%	White	0%	≥2 factors 61%	NR	81%	NR	NR	NR	39% smoking	NR	33%	NR
EPIC-SR[124, 125]	Median 42; ≥65: 5%	46%	White	57%	49%	NR	18%	5%	NR	NR	13% smoking	NR	12%	NR
COMET-ICE[93]	Median 53	43-48%	White	NR	>99%	NR	63-64%	21-23%	<1%	<1-2%	17% asthma; 5-6% COPD	NR	NR	NR
MONET[126]	≥65: 40-49%	45-54%	Caucasian	92-96%	NR	14-18%	15-19%	10-17%	36-44%	4-6%	15-28% COPD	0-2%	NR	NR
CTRI/2021/05/033739[a127]	Mean 35	67-70%	Indian	NR	NR	NR	3%	0.3%	NR	NR	NR	NR	1%	NR
CTRI/2021/07/034588[a128]	Mean 36-37	61-63%	Asian-Indian	NR	7.3%	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; NR, not reported.
[a]These trials (Sinha 2022 and Tippabhotla 2022) were only included in the networks for viral clearance outcomes which were not reported in the CS; viral outcome NMAs were provided in Clarification Responses A1 and A11).

Appendix 4 Summary overview of population characteristics of RWE studies

Rounded data; ranges are across all study arms.

Study (all dated 2023)	Age, years	Sex, male	No prior vaccine	Immuno-compr	Obese	Diabetes	CVD	Renal disease	Respir disease	Liver disease	Hyper-tension	Cancer	Modal race/ethnicity
Aggarwal[35] (USA)	18- ≥65	41-42%	20-22%	16-25%	19-27%	10-15%	12-15%	5-6%	22-28%	6-9%	27-38%	NR	White
Arbel[36] (Israel)	Mean 69-73	66-72%	NR	17-26%	35-37%	41-47%	10-16% cardiac	12-23% CKD	10-16% COPD	7-9%	61-73%	11-19%	Jewish
Bajema[37] (USA)	Median 59-70	84-92%	14-28%	7-13% on IST	82-83%	26-44%	26-52%	9-23%	26-42%	8-11%	NR	14-25%	White
Basoulis[38] (Greece)	Mean 60-65	56-61%	10-12%	47-61%	NR	23-26%	7-11% CAD 5-7% CHF	~~NR~~ 1-38% CKD	6-13% COPD/ asthma	2-3%	39-50%	21-46%	NR
Cegolon[42] (Italy)	Median 66-71	48-63%	12-23%	15-32%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cowman[43] (USA)	Median 58-64	33-40%	15-19% (no vacc record)	1%	16-18%	19-27%	38-52% cardiac	6-21%	10-16%	4-6%	NR	7-12%	Hispanic
Dryden-Peterson[45] (USA)	≥50	39-42%	4-9%	36%	34%	18-20%	14-16% cardiac or stroke	NR	7-8%	NR	NR	27%	White
Gentry[46] (USA)	≥65 (mean 64)	96-97%	~~9-10~~ 19-20%	13% on IST 8-9% immunologic/rheumatic	30-34% >100 kg	NR 50% metabolic/ endocrine	48-51%	33-34% incl urinary	21-24%	4% incl biliary	NR	18-20	White
Kabore[47] (Canada)	Mostly >17 to <90	33-43%	8-77% 0 or 1 dose	6-29%	NR	NR	NR	NR	NR	NR	NR	6-24%	NR

Manciulli{Manciulli, 2023 #201 (Italy)	Median 65-69	42-58%	3-20%	13-51%	18-30%	16-22%	48-56% cardiac	3-15% CKD	21-30% COPD	NR	NR	13-30%	NR
Paraskevis[a55] (Greece)	≥65	47-50%	10-20%	8-9% mod-severe	10-16%	19-28%	46-70%	4-6% CKD?	5-8%	0.4%	NR	NR	NR
Schwartz[58] (Canada)	>17; mean 52-74	37-41%	5-6%	6-16% excl autoimmune	NR	17-34%	11-25% cardiac	6-13% CKD	24-35%	1-2%	32-68%	NR	NR
Tiseo[59] (Italy)	Median 65-72	50-58%	13-25% not adeq	18-28% excl autoimmune	21-33%	16-22%	26-47%	9-10% CKD	27-29%	1-7%	39-55%	18-22% solid	NR
Torti[62] (Italy)	Mean 66-74	48-52%	NR (13-14% not fully vacc)	15-22% immunodef	20-24%	11-15% uncontrolled	31-52% cardio-cerebro	4-9% CKD	18-20% severe	0.2% moderate	NR	14-20%	NR
Van Heer[61] (Australia)	≥70	43-50%	0%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Xie[63] (USA)	Mean 67-69	89-91%	14-18%	5-6% Imm dys-function	NR	40-45%	40-49%	NR	29-34%	1%	NR	21-24%	White
Zheng[1] (UK, OpenSAFELY)	≥18 Mean 52-56	32-37%	1-2%	10-12% on IST 39-42% 39-46% disease	NR	12-18%	5-10% cardiac	NR	16-23%	NR	22-35%	11-14% (solid tumours)	White

CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IST, immunosuppressant therapy; NR, not reported

[a] The Paraskevis study reported comorbidities for the treated participants only, not the untreated participants.

Appendix 5 Full results of the NMAs of randomised controlled trials

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 (NMA Report Table 43)	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 (NMA Report Table 47)	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 (NMA Report Table 32)	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 (NMA Report Table 36)	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 (NMA Report Tables 39 & 40)	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**
Viral clearance by Day 5 (NMA Report Table 51)	9.30 (7.35 to 11.81) **Favours molnupiravir**	No data for this comparison	No data for this comparison	12.09 (1.02 to 14.64) **Favours molnupiravir**
Viral clearance by Day 10 (NMA Report Table 55)	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**

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 14/15 (NMA Report Table 59)	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 (NMA Report Table 63)	No data for this comparison	2.20 (0.35 to 13.59) **Favours molnupiravir**	No data for this comparison	2.47 (0.84 to 8.33) **Favours molnupiravir**
Viral load change to Day 3 (NMA Report Table 67)	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 (NMA Report Table 70)	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
Requirement for respiratory support (NMA Report Table 73)	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 (NMA Report Table 77)	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 (NMA Report Table 81)	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 (NMA Report Table 85)	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
"NMA Report" refers to the company's report on NMAs of RCTs that was provided in response to Clarification Question A11				

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
Abbreviations: mol, molnupiravir; n+r, nirmatrelvir + ritonavir; rem, remdesivir; sot, sotrovimab				

Appendix 6 Full results of the NMAs of real-world evidence studies

Data are relative risks (95% credible intervals) and (where reported) posterior probabilities of molnupiravir being the most effective treatment. Results of the direct meta-analyses and the Zheng et al. 2023 study[1] (the only RWE study conducted in the UK) are included for comparison. Dashes ('-') indicate where no data are available for a given analysis/comparison. The 'active' network is based on active therapies only (excluding no treatment).

Comparator	Network	Bayesian NMA	Direct meta-analysis	Zheng et al. 2023 OpenSAFELY cohort[1]
All-cause hospitalisation or death (CS Figures 15 and 16) – random effects model				
Nirmatrelvir plus ritonavir	Active	1.22 (0.50 to 2.99) Nonsignificant. Probability: 27.4	1.22 (0.68 to 2.18) Nonsignificant	1.64 (1.09 to 2.47) Favours comparator
	Active/control	1.28 (0.91 to 1.79) Nonsignificant. Probability: 6.5	1.22 (0.68 to 2.18) Nonsignificant	
	EAG replication [a]	1.28 (0.82 to 1.93)	-	
	'Uncertain no-treatment' node removed [b]	1.28 (0.92 to 1.78) Nonsignificant	-	
	High risk of bias study [c] (Paraskevis) removed	1.23 (0.81 to 1.88)	-	
	Scenario results [d]	7 analyses: vaccinated, symptomatic, age ≥60 years & cancer subgroups consistent with base case NMA; CVD, kidney disease	-	

Comparator	Network	Bayesian NMA	Direct meta-analysis	Zheng et al. 2023 OpenSAFELY cohort[1]
		and diabetes subgroups (FE model [e]) favour comparator.		
Sotrovimab	Active	1.07 (0.33 to 3.55) Nonsignificant. Probability 43.7	-	-
	Active/control	1.10 (0.55 to 2.23) Nonsignificant. Probability: 37.3	-	
	'Uncertain no-treatment' node removed [b]	1.10 (0.56 to 2.17) Nonsignificant	-	
	Scenario results [d]	3 analyses: vaccinated & symptomatic subgroups consistent with base case NMA; kidney disease subgroup (FE model [e]) favours comparator.	-	
Remdesivir – no data				
No treatment	Active/control	0.61 (0.43 to 0.86) Favours molnupiravir. Probability: 99.5	0.62 (0.46 to 0.83) Favours molnupiravir	-
	EAG replication [a]	0.60 (0.41 to 0.86)		
	'Uncertain no-treatment' node removed [b]	0.61 (0.43 to 0.86) Favours molnupiravir	-	
	High risk of bias study [c] (Paraskevis) removed	0.71 (0.46 to 0.96)		

Comparator	Network	Bayesian NMA	Direct meta-analysis	Zheng et al. 2023 OpenSAFELY cohort[1]
	Scenario results [d]	7 analyses: vaccinated, symptomatic, age ≥60 years, cancer, CVD & diabetes subgroups consistent with base case NMA; kidney disease subgroup favours comparator (FE model for cancer, CVD, diabetes, kidney disease [e])	-	
COVID-19-related hospitalisation or death (Clarification Response Figures 23 and 24 – supersede CS Figures 18 and 19) – random effects model				
Nirmatrelvir plus ritonavir	Active	1.79 (0.61 to 4.49) Nonsignificant. Probability: 12.2	-	2.22 (1.08 to 4.59) Favours comparator
	Active/control	1.77 (0.63 to 4.50) Nonsignificant. Probability: 12.8	-	
	Scenario results [d]	1 analysis: obesity subgroup - treatment effect favours comparator (FE model [e])	-	
Sotrovimab	Active	2.40 (0.88 to 7.32) Nonsignificant. Probability: 4.1	-	-
	Active/control	2.38 (0.85 to 7.57) Nonsignificant. Probability: 4.6	-	

Comparator	Network	Bayesian NMA	Direct meta-analysis	Zheng et al. 2023 OpenSAFELY cohort[1]
	Scenario results [d]	2 analyses: kidney disease and obesity subgroups - treatment effect favours comparator (FE model [e])	-	
Remdesivir	Active	0.94 (0.26 to 3.46) Nonsignificant. Probability: 53.6	0.98 (0.16 to 5.85) Nonsignificant	-
	Active/control	0.95 (0.25 to 3.50) Nonsignificant. Probability: 53.1	0.98 (0.16 to 5.85) Nonsignificant	
	Scenario results [d]	Scenario analyses not feasible	-	
No treatment	Active/control	0.75 (0.22 to 2.60) Nonsignificant. Probability: 75.8	-	-
	Scenario results [d]	Scenario analyses not feasible	-	
All-cause hospitalisation (CS Figures 21 and 22) – random effects model				
Nirmatrelvir plus ritonavir	Active	1.01 (0.53 to 1.81) Nonsignificant. Probability 47.6	1.04 (0.80 to 1.35) Nonsignificant	-
	Active/control	1.19 (0.98 to 1.43) Nonsignificant. Probability: 3.6	0.88 (0.59 to 1.29) Nonsignificant	-
	EAG replication [a]	1.15 (0.89 to 1.45)		
	'Uncertain no-treatment' node removed [b]	1.19 (0.98 to 1.43) Nonsignificant	-	

Comparator	Network	Bayesian NMA	Direct meta-analysis	Zheng et al. 2023 OpenSAFELY cohort[1]
	High risk of bias study [c] (Van Heer) removed	1.15 (0.80 to 1.54)		
	Scenario results [d]	3 analyses: vaccinated, age ≥60 years, age ≥70 years - results consistent with NMA base case (FE model used for age ≥70 years [e]),	-	
Sotrovimab – no data				
Remdesivir	Active	1.40 (0.21 to 9.45) Nonsignificant. Probability: 35.8	-	-
	Active/control	1.65 (0.35 to 8.63) Nonsignificant. Probability: 27.3	-	
	'Uncertain no-treatment' node removed [b]	1.71 (0.33 to 8.12) Nonsignificant	-	
	Scenario results [d]	1 analysis: vaccinated subgroup – results consistent with NMA base case	-	
No treatment	Active/control	0.79 (0.66 to 0.92) Favours molnupiravir. Probability: 99.6	0.81 (0.69 to 0.94) Favours molnupiravir	-
	EAG replication [a]	0.78 (0.63 to 0.91)		
	'Uncertain no-treatment' node removed [b]	0.79 (0.65 to 0.93) Favours molnupiravir	-	

Comparator	Network	Bayesian NMA	Direct meta-analysis	Zheng et al. 2023 OpenSAFELY cohort[1]
	High risk of bias study [c] (Van Heer) removed	0.80 (0.58 to 0.98)		
	Scenario results [d]	3 analyses: vaccinated & age ≥70 years subgroups consistent with NMA base case; age ≥60 years treatment difference non-significant (FE model for age ≥70 years [e])	-	
COVID-19-related hospitalization (CS Figures 24 and 25) – FIXED-EFFECT model				
Nirmatrelvir plus ritonavir	Active (FE model [e])	0.50 (0.11 to 2.26) Nonsignificant. Probability: 81.9	0.49 (0.11 to 2.28) Nonsignificant	-
	Active/control	1.58 (0.98 to 2.54) Nonsignificant. Probability: 2.9	-	
	'Uncertain no-treatment' node removed [b]	0.39 (0.10 to 1.57) Nonsignificant	-	
	Scenario results [d]	2 analyses: vaccinated & age ≥60 years subgroups - consistent with NMA base case (FE model [e])	-	
Sotrovimab	Active	0.43 (0.03 to 5.29) Nonsignificant. Probability: 74.5	-	-
	Active/control	1.64 (0.19 to 13.04) Nonsignificant. Probability: 33.4	-	

Comparator	Network	Bayesian NMA	Direct meta-analysis	Zheng et al. 2023 OpenSAFELY cohort[1]
	'Uncertain no-treatment' node removed [b]	0.51 (0.05 to 5.61) Nonsignificant	-	
	Scenario results [d]	1 analysis: vaccinated subgroup - consistent with NMA base case (FE model [e])	-	
Remdesivir – no data				
No treatment	Active/control	0.85 (0.49 to 1.53) Nonsignificant. Probability: 70.5	-	-
	'Uncertain no-treatment' node removed [b]	0.22 (0.05 to 0.87) Favours molnupiravir	-	
	Scenario results [d]	1 analysis: vaccinated subgroup – favours molnupiravir (FE model [e])	-	
All-cause death (CS Figure 27) – random effects model				
Nirmatrelvir plus ritonavir	Active (FE model [e])	1.48 (1.22 to 1.79) Favours comparator	-	-
	Active/control	1.44 (1.00 to 2.10) Nonsignificant. Probability: 2.5	1.48 (1.21 to 1.80) Favours comparator	
	'Uncertain no-treatment' node removed [b]	1.44 (0.99 to 2.12) Nonsignificant	-	
	Scenario results [d]	1 analysis: age ≥60 years subgroup - consistent with NMA base case (FE model [e])	-	

Comparator	Network	Bayesian NMA	Direct meta-analysis	Zheng et al. 2023 OpenSAFELY cohort[1]
Sotrovimab – no data				
Remdesivir – no data				
No treatment	Active/control	0.31 (0.21 to 0.46) Favours molnupiravir. Probability: 100	0.31 (0.23 to 0.42) Favours molnupiravir	-
	'Uncertain no-treatment' node removed [b]	0.31 (0.20 to 0.46) Favours molnupiravir	-	
	Scenario results [d]	1 analysis: age ≥60 years subgroup - consistent with NMA base case (FE model [e])	-	

[a] EAG replication of company's analysis prior to removing the high risk of bias study from the network (see section 3.4.4.2 above)

[b] From Clarification Response Table 25 (Clarification Response A15)

[c] EAG exploration of risk of bias – see section 3.4.4.2 above.

[d] From Clarification Response Tables 26 to 30 (Clarification Response A18).

[e] A fixed-effect model was used due to due to there being only one study per comparison, or only one instance of two studies for a comparison.

CVD, cardiovascular disease; FE, fixed-effect

Appendix 7 Tornado plots

Figure 4 Tornado diagram for molnupiravir versus no treatment, company revised base case

Figure 5 Tornado diagram for molnupiravir versus nirmatrelvir plus ritonavir, company revised base case

Figure 6 Tornado diagram for molnupiravir versus sotrovimab, company revised base case