Single Technology Appraisal

Molnupiravir for treating COVID-19 [ID6340]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Molnupiravir for treating COVID-19 [ID6340]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Merck, Sharp & Dohme**:
   a. Company submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Clinically Vulnerable Families
   b. Royal College of Pathologists
   c. UK Clinical Pharmacy Association

4. **Expert personal perspectives** from:
   a. Dr David Lowe – clinical expert, nominated by British Society for Immunology
   b. Robert Burns – patient expert, nominated by the Cardiothoracic Transplant Patient Group
   c. Susannah Thompson – patient expert, nominated by Long COVID SOS

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Molnupiravir for treating COVID-19 [ID6340]

Document B

Company evidence submission

18th June 2024

File name	Version	Contains confidential information	Date
ID6340_Molnupiravir_COVID-19_STA_Document B_v1.0_18-06-2024	FINAL	Yes	18/06/2024

Contents

Tables and figures

Abbreviations

Abbreviation/acronym	Definition
A&E	Accident and emergency
ACE-2	Acetylcholinesterase-2
AE	Adverse event
AEOSI	Adverse event of special interest
APaT	All-participants-as-treated
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPI	Consumer price index
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EOT	End-of-treatment
EQ-5D	EuroQoL-5D
EU	European Union
GW	General ward
HDU	High dependency unit
HSCT	Haematological stem cell transplant
HR	Hazard ratio
HRQoL	Health related quality of life
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ITT	Intention to Treat
IV	Intravenous
KM	Kaplan-Meier
LCLE	Lower cost lower effects
LFU	Late follow-up visit
LY	Life years

LYG	Life year gained
MHRA	Medicines and Healthcare products Regulatory Agency
MITT	Modified intent-to-treat
MV	Mechanical ventilation
N/A	Not applicable
NHB	Net health benefit
NHC	N-hydroxycytidine
NHC-TP	NHC triphosphate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
ONS	Office for National Statistics
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per protocol
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RR	Relative risk
RSV	Respiratory syncytial virus
RT-PCR	Reverse-transcription polymerase chain reaction
RWE	Real world evidence
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
STA	Single technology appraisal
TSD	Technical Support Document
TTO	Time trade-off
UK	United Kingdom
VAS	Visual analog scale
VL	Viral load
WHO	World Health Organisation
YLL	Years of life lost

B.1 Decision problem, description of the technology and clinical care pathway

Key summary points

Disease overview and burden

- Since the emergence of the novel coronavirus designated SARS-CoV-2 in 2020, the disease, also known as COVID-19 remains a concern, particularly for patients with risk factors for severe illness who remain vulnerable to infection.
- Between 3.9 and 5.3 million people in the UK may be at high risk of progression to severe COVID-19, based on the definition used.
- Severe COVID-19 often requires hospitalisation, where both the frequency and duration of stay increases with age and number of comorbidities.
- Hospitalisation for COVID-19 is notably detrimental to patient quality of life, mental health and an increased risk for nosocomial infections.
- Unnecessary hospitalisations are costly, place additional burden on the NHS while it continues to deal with impacts of the pandemic and may increase the risk of onward transmission within the health system and across vulnerable groups.

Clinical pathway of care

- There is a need for a simple to administer, cost-effective, treatment in patients with mild to moderate COVID-19 at risk of severe illness that can also be used safely in patients with severe renal and hepatic impairment or who are taking other medications.
- For patients at risk of developing severe COVID-19, nirmatrelvir plus ritonavir and sotrovimab are the only treatments currently recommended for high-risk non-hospitalised patients. However, both are associated with limitations; namely, contraindications and drug-drug interactions for nirmatrelvir plus ritonavir, and uncertain clinical effectiveness and specialised administration for sotrovimab.
- Molnupiravir can provide an alternative to current treatments and is already approved for patients with mild to moderate COVID-19 at risk of severe illness.
- Healthcare practitioners who provide antiviral treatment have highlighted an underserved group of patients at risk of severe disease who remain without care options early on for mild to moderate disease due to contraindications to nirmatrelvir plus ritonavir and either falling outside the sotrovimab recommendation or unable to attend a clinical service for sotrovimab infusion.
- Within the current clinical pathway, molnupiravir may be placed as an alternative treatment to current options for COVID-19 patients at high risk of severe illness

according to either of the two commonly accepted criteria. Molnupiravir is the only viable alternative for those patients that are currently unable to receive the recommended options due to clinical or other considerations.

B.1.1 Decision problem

The single technology appraisal that is the focus of the company submission evaluates the clinical and cost-effectiveness of molnupiravir in the treatment of patients with mild to moderate COVID-19 at risk of developing severe illness. Molnupiravir has a conditional marketing authorisation in Great Britain for adults with a positive SARS-CoV-2 diagnostic test[i] and who have at least one risk factor for developing severe illness.(1)

The final scope for molnupiravir was issued by the National Institute for Health and Care Excellence (NICE) in April 2024[ii]. The company submission (CS) deviates from the NICE scope to accommodate patients who, based on current recommendations from NICE, are not eligible for recommended treatment options. Clinical advice to MSD is that there remains a group of patients that would not meet the criteria for treatment with either nirmatrelvir plus ritonavir or sotrovimab, as outlined in Section B.1.3.2, and are therefore currently eligible for "no treatment".(2) As such "no treatment" has been included as a comparator to molnupiravir.(2) The key evidence in the CS is based on the results of the phase II/III randomised controlled trial, MOVe-OUT, which evaluated the safety and efficacy of molnupiravir versus placebo in non-hospitalised patients with a positive SARS-CoV-2 diagnostic test and at least one underlying medical condition associated with an increased risk of severe illness from COVID-19. In addition, real-world evidence is presented to support the clinical efficacy data derived from MOVe-OUT. The decision problem addressed in this submission is summarised in Table 1.

[i] N.B. no limitations have been made on the mode of diagnosis
[ii] Molnupiravir for treating COVID-19 [ID6340]: https://www.nice.org.uk/guidance/indevelopment/gid-ta11409

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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	As per final scope	N/A
Intervention	Molnupiravir	As per final scope	N/A
Comparator(s)	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 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). Clinical experts have fed back to MSD that remdesivir is occasionally used in the treatment of patients with incidental COVID-19 acquired whilst in hospital for reasons not related to COVID-19, as per the previous NHS-E clinical commissioning policy.[2, 3] MSD have included remdesivir as a comparator of interest in the networks of evidence for comparative clinical effectiveness in outpatients with COVID-19. However, as remdesivir can only be given to patients in hospital, the only situation in which the comparison with molnupiravir is relevant is in incidental COVID-19. Additionally, given the limitation to inpatient use only, MSD note that the impact of remdesivir on the key clinical outcome of rate of hospitalisation is not relevant to the pharmacoeconomic assessment of specified comparators. MSD take the view that the outpatient data for remdesivir may be used to infer the relative clinical effectiveness as to our knowledge there is no study reporting on

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			the effects of treatments for incidental COVID-19 acquired in hospital. 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 ritonavir and sotrovimab, and who thus do not currently receive treatment for mild/moderate disease unless they deteriorate and are subsequently hospitalised.
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) • Symptoms of post-COVID-19 syndrome • Adverse effects of treatment • Health-related quality of life	• 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

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope

Subgroups to be considered	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 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
		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
		• People with chronic kidney disease
			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.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. 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 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 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.	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 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.	N/A. While these aspects cannot be directly modelled, they remain particularly relevant for decision making in the endemic phase.

BMI = body mass index; COVID-19 = coronavirus disease 2019; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; RWE = real-world evidence; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

B.1.2 Description of the technology being evaluated

A description of molnupiravir, the technology being appraised, is presented in Table 2. The summary of product characteristics and UK public assessment report is provided in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Molnupiravir (Lagevrio™)
Mechanism of action	Molnupiravir is an antiviral that acts via a viral error catastrophe mechanism. The prodrug, molnupiravir, is metabolised to NHC, which is then phosphorylated in cells to the pharmacologically-active NHC-TP. Viral RNA polymerase incorporates NHC-TP into the viral RNA resulting in accumulation of errors in the viral genome and inhibition of replication.
Marketing authorisation/CE mark status	Molnupiravir has a conditional marketing authorisation in Great Britain, granted on 4th November 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Molnupiravir is indicated for the treatment of mild to moderate COVID-19 in adults with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness.
Method of administration and dosage	Molnupiravir is for oral use. Capsules of 200 mg should be taken with or without food. The dose is 800mg twice daily for 5 days.
Additional tests or investigations	Molnupiravir is indicated in patients with a positive SARS-CoV-2 diagnostic test.
List price and average cost of a course of treatment	[redacted] MSD ask that the EAG does not copy across documents the confidential list price and instead refers to this table within the main submission document.
Patient access scheme (if applicable)	[redacted]

COVID-19 = coronavirus disease 2019; NHC = N-hydroxycytidine; NHC-TP = NHC triphosphate; SmPC = summary of product characteristics
SOURCE: Lagevrio™ Summary of Product Characteristics(1)

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Background to COVID-19 infection

A novel coronavirus, named SARS-CoV-2, was isolated from patients in January 2020 after Chinese authorities reported a pneumonia outbreak of unknown cause to the World Health Organization (WHO) in December 2019.(4) The disease caused by this new virus was named coronavirus disease 2019 (COVID-19) by the WHO in February 2020 and by the following month the outbreak had become pandemic.(4, 5) Transmission of SARS-CoV-2 primarily occurs when people come into close contact with an infected person through direct

(respiratory secretions or droplets) or indirect transmission, with transmission more likely around the time of symptom onset.[6, 7]

Since the start of the pandemic, numerous variants of SARS-CoV-2 have appeared, including Alpha (B.1.1.7), Delta (B.1.617.2) and Omicron (B.1.1.529).[6] As SARS-CoV-2 continues to evolve and mutate,[6] effective treatments are required for those who contract the virus and become ill.

Vaccines against SARS-CoV-2 became available between December 2020 and January 2021, and they provide protection against symptomatic and asymptomatic infection, as well as hospitalisation and death.[8, 9] While the vaccination programme in the UK initially prioritised older individuals and those with comorbidities, vaccines were subsequently offered population-wide during the pandemic, with 85% of people in the UK over 18 years of age having received two COVID-19 vaccine doses by October 2021.[10] Vaccine effectiveness has been reported to be lower in older individuals and people with comorbidities.[11-13] Since autumn 2022, COVID-19 vaccinations have been offered in a regular booster programme for people aged over 65 years, residents in care homes, people in a clinical risk group, and health and social care staff.[8, 14] By the end of the autumn 2023 booster vaccination programme in February 2024, over 7.8 million people in England had received a 2023 autumn COVID-19 booster vaccination.[15] However, despite a successful vaccination programme, there is a proportion of people who are under vaccinated and are thus at increased risk of severe COVID-19.[16] Under-vaccination is defined as having received fewer doses than the number recommended by the Joint Committee on Vaccination and Immunisation and has been linked, via a whole UK population database analysis, to socioeconomic deprivation, non-white ethnicity and male sex.[16] Moreover, UK COVID-19 vaccine surveillance reports suggest that there have been some waning effects since the autumn 2023 seasonal vaccine booster campaign.[17] There are also people who continue to be clinically vulnerable despite receiving seasonal booster vaccinations.[18] COVID-19 continues to circulate; in the 2023/2024 season, recorded infections peaked at a 7-day rolling average of 2,392 cases in the seven days to 2nd October 2023 followed by weekly hospital admissions in England peaking at 4,312 cases (week ending 6th October 2023) (Section B.1.3.1.6),[19] consequently the impacts of the disease remain a concern.

On 5th May 2023, the WHO declared that COVID-19 was a well-established and ongoing disease and no longer a public health emergency.[20] The UK government has stated that the pandemic is ongoing, with COVID-19 cases observed year-round, but that the disease is shifting to a more endemic state. Seasonal spikes in the number of reported cases of COVID-19 suggest that the disease may become a predominantly winter seasonal illness,[21,

[22] risking overwhelming the NHS at a time when services are already stretched (see Section B.1.3.1.11). Regardless of the status of the epidemic, a proportion of the general population, including patients with risk factors for severe illness, remain vulnerable to infection and therefore subsequent risks associated with disease itself.

B.1.3.1.2 Pathophysiology and clinical presentation

SARS-CoV-2 transmission from an infected individual results in viral particles in the upper respiratory tract binding to acetylcholinesterase-2 (ACE-2) on nasal epithelia and subsequent cellular incubation.[7, 23] As the virus replicates, respiratory symptoms often develop, and, in cases where the immune response is unable to stop the infection, patients may progress to develop severe symptoms.[7] Infected cells release cytokines and inflammatory markers resulting in a cytokine storm, attracting immune cells.[7, 23] Inflammation leads to lung injury and, in some cases, diffuse alveolar damage that can result in acute respiratory distress syndrome (ARDS).[7]

The clinical presentation of COVID-19 ranges from asymptomatic to mild, moderate, severe or critical symptoms, as defined in Table 3.[7] The range of disease severity is thought to be linked to the host's immune response and presence of risk factors.[23, 24]

Table 3. Clinical presentation of COVID-19[6, 7, 25-27]

Severity of disease	Presentation
Asymptomatic	No clinical symptoms
Mild illness	Acute upper respiratory infection such as fever, sore throat, cough and fatigue. May also present with gastrointestinal symptoms
Moderate illness	Pneumonia without hypoxemia and significant lesions on high-resolution chest CT
Severe illness	Pneumonia with hypoxemia (SpO_2 < 92%)
Critical state	ARDS, shock, coagulation defects, encephalopathy, heart failure and acute kidney injury

ARDS = acute respiratory distress syndrome; CT = computed tomography
SOURCE: Parasher et al., 2021;[7] Yuki et al., 2020.[25]

B.1.3.1.3 Diagnosis

SARS-CoV-2 can be identified by molecular testing such as reverse-transcription polymerase chain reaction (RT-PCR) or lateral flow immunoassay.[6] Currently, for patients not in a healthcare setting, UK guidelines only recommend testing in symptomatic patients who are eligible for COVID-19 treatment, namely those at highest risk of severe COVID-19.[28] Testing should be conducted with a lateral flow device, but RT-PCR may also be used in NHS settings to support diagnosis.[28]

B.1.3.1.4 Disease progression

Depending on the circulating variant and vaccination status, approximately 80% of patients with COVID-19 experience mild illness and do not require treatment or hospitalisation.[6] However, some patients may progress to develop more severe symptoms (e.g. respiratory failure, dyspnoea and ARDS; Section B.1.3.1.2) and are at risk of rapid clinical decline without treatment.[6] Progression to severe illness is thought to be due to hyperinflammation, with high levels of proinflammatory cytokines associated with disease severity.[23, 25] A number of risk factors increase the likelihood of progressing to severe illness, which are detailed in Section B.1.3.1.5.

Long-term sequelae of COVID-19, also known as long-COVID-19, have been reported in patients regardless of initial disease severity.[29] The WHO have defined long-COVID-19 as the presence of COVID-19 symptoms (either persistent or new) three months after the initial SARS-CoV-2 infection, which last for at least two months and cannot be explained by an alternative diagnosis.[30] As a condition, long-COVID-19 is heterogenous in its presentation and severity. Similarly, symptoms of long-COVID-19 are varied but commonly include fatigue, dyspnoea, joint pain and chest pain, and may also include specific organ dysfunction.[29-31] While long-COVID-19 can occur in patients with any disease severity, it is observed more frequently in patients who are hospitalised (~50%) compared to outpatients (25%–38%) and is more common in older patients and patients with comorbidities.[31-33] Please see Section B.3.3.1.6 for details on long-COVID-19 in the pharmacoeconomic assessment for this submission.

B.1.3.1.5 Risk factors

It is not fully understood why some patients with COVID-19 develop severe illness while others do not, but several factors have been proposed as being associated with an increased risk of progression to severe disease. Systematic literature reviews and meta-analyses have reported that older age and male sex are associated with severe illness and mortality.[24, 34-38] It has been suggested that the association with older age could be linked to the presence of more chronic conditions or to age-related immunosenescence.[24, 35] The following comorbidities have also been reported to have an association with severe COVID-19 illness, hospitalisation and death:

- Acute kidney injury[24] and chronic renal disease[34, 35, 38-40]
- Cerebrovascular disease[24, 35, 37, 40]
- Chronic obstructive pulmonary disease (COPD)[24, 35, 37, 39] and chronic lung disease[34, 36, 37, 40]

- Cardiovascular disease (CVD)[24, 34-37, 39, 40] and cardiac damage[24]
- Diabetes[24, 34-37, 39, 40]
- Down's syndrome[39]
- History of cancer[24, 34, 37] and chemotherapy[39]
- HIV/AIDS[39]
- Hypertension[24, 34-37]
- Liver disease[35, 39, 40]
- Neurological conditions[38-40]

The definition in England for being high risk for severe COVID-19 was first outlined in the Independent Advisory Group report (also known as the McInnes report),[41] but additional risk factors have since been highlighted in a subsequent report by the Therapeutics Clinical Review Panel (also known as the Edmunds report).[42] Both definitions are summarised in Table 4. The McInnes definition of high risk was used for the TA878 multiple technology appraisal, which originally included molnupiravir and other therapeutics.[43] It should be noted that, although definitions of high risk used in observational studies and clinical trials do not always fully align, because understanding of and approaches to management of COVID-19 have evolved during the pandemic, the definitions usually overlap and studies typically encompass similar patient groups.[44]

It is estimated that there are 3.9 million people at high risk of progression to severe COVID-19 in the UK, according to the McInnes definition.[45] When the definition is expanded to include the additional risk factors specified in the Edmunds report, this high-risk population is increased by a further 1.4 million people, to a total of 5.3 million people[iii].[45]

[iii] Note that the population size of individuals at high risk of progression to severe COVID-19 varies in the published literature, with reported estimates of up to 18.5 million in the UK (defined as either aged ≥ 70 years, or younger with an underlying health condition) based on a study of Clinical Practice Research Datalink GOLD by Walker et al., 2021.

Table 4. Definitions of high risk of progression to severe COVID

McInnes report (as per May 2022; used for TA878)	Edmunds report (as per March 2023)
Adults with the following comorbidities • Down's syndrome and other genetic disorders • Solid cancer • Haematological diseases and HSCT recipients • Renal disease • Liver diseases • Solid organ transplant recipients • Immune-mediated inflammatory disorders[a] • Respiratory disease • Immune deficiencies • HIV/AIDS • Neurological disorders	In ***addition*** to the comorbidities identified by the McInnes report, adults with: • Age ≥ 70 years • Diabetes • Obesity (defined as BMI ≥35 kg/m^2) • Heart failure
Led to original recommendation: nirmatrelvir plus ritonavir and sotrovimab for those contraindicated	Led to population expansion for: nirmatrelvir plus ritonavir

[a] diseases in which autoimmune or autoinflammation-based pathways are implicated in disease, for example, inflammatory arthritis, connective tissue diseases, inflammatory skin diseases, inflammatory gastrointestinal disease
BMI = body mass index; HSCT = haematological stem cell transplant
SOURCE: Department of Health and Social Care 2023 McInnes report;[41, 43] Department of Health and Social Care 2023 Edmunds report[42]

B.1.3.1.6 Incidence

Since the start of the COVID-19 outbreak in March 2020,over 24.9 million cases of COVID-19 have been reported in the United Kingdom (as of 13th April 2024).[46]

The incidence in England for the seven days up to 21st May 2024 was 1,820 and the rolling 7-day case rate was 2.01 per 100,000 people as of 29th May 2024.[19] Given that testing is no longer recommended for the general population, these figures likely represent a significant underestimation of actual COVID-19 incidence.

B.1.3.1.7 Mortality

As of 13th April 2024, 232,112 deaths due to COVID-19 have been reported in the United Kingdom.[46] The number of weekly deaths due to COVID-19 was 156 as of 17th May 2024.[47] An analysis of excess mortality in England reported 171,383 excess deaths in the period from 27th March 2020 to 29th December 2023.[48]

Risk of mortality from COVID-19 increases with age, male sex and the presence of comorbidities (see Section B.1.3.1.5).[24, 34-37, 39] However, there are mixed reports regarding the mortality risk by ethnicity. An analysis of GP practice records in England showed an increased risk of death for people with black, Asian/Asian British and mixed ethnicities compared to white ethnicity,[49] while a study aiming to develop a new COVID-19 risk algorithm showed no increased risk of COVID-19-related death for other ethnicities

compared to white ethnicity (but did report an increase in hospital admissions for Asian men, Asian women and black women).[39]

Vaccinated individuals have reduced COVID-19 mortality, with a greater risk reduction with increasing number of vaccine doses.[39] In addition, previous COVID-19 infection has also been associated with a lower risk of death.[39]

B.1.3.1.8 Clinical burden

Severe COVID-19 is associated with clinical complications and often requires hospitalisation for appropriate management.[27] The daily number of COVID-19 patients admitted to hospital in England was 264 as of 28th April 2024 and the daily count of confirmed COVID-19 patients in hospital was 1,780 as of 30th April 2024,[19] placing a substantial burden on healthcare systems and healthcare workers.[50]

In the recent winter (2023/24), weekly hospital admissions in England peaked at 4,312 cases (week ending 6th October 2023), and the number of patients in critical care beds at any one time reached 140 (2nd January 2024).[19, 51]

In a study (Yang et al., 2023) of 1.7 million patients with COVID-19 between August 2020 and March 2021 in England, 13,105 patients were hospitalised, and 1,934 (14.8%) were admitted to critical care.[52] The median total length of stay was 6.0 days (including general ward and critical care stay) and median length of stay in critical care was 8.0 days.[53] In another study (Kirwin et al., 2020) of 259,727 patients hospitalised with COVID-19 in England between March 2020 and September 2021, median length of stay prior to discharge peaked at 5.9 days (March 2020).[54] The median length of stay prior to discharge decreased overall during the pandemic to 3.6 days (September 2021).[54] Conversely, median length of stay prior to death increased, peaking at 10.4 days in July 2020 and June 2021.[54]

Older patients, particularly those over 65 years of age, have a higher number of general hospital admissions and a longer length of stay.[19, 53] There is also an association between age and critical care (intensive care unit [ICU] and high-dependency unit) admissions, with hospitalised patients aged over 50 years having higher rates of critical care admissions than younger patients.[19, 53] Patients with comorbidities also have more hospital and ICU admissions than those without comorbidities.[37, 39, 50]

B.1.3.1.9 Humanistic burden

COVID-19 has a significant humanistic burden on patients, caregivers and family members. In the UK, COVID-19 resulted in 543.2 years of life lost (YLL) per 100,000 population as of

14th July 2020, accounting for 4.0% of total YLL and 2.0% of total disability-adjusted life years (DALYs), a substantial proportion of total disease burden in the UK.[55]

Quality of life is significantly reduced in patients who have been hospitalised with COVID-19. A 2021 study (Halpin et al., 2021) conducted in the Leeds Teaching Hospitals NHS Trust reported that 68.8% of patients with COVID-19 who received treatment in the ICU had a decrease in EQ-5D of at least 0.05 (minimally clinically important difference [MCID] as validated in respiratory disease) at follow-up (at least 4 weeks after being discharged) compared to pre-COVID scores.[56] Similarly, 45.6% of COVID-19 patients who were treated on the general ward reported a decrease in EQ-5D of at least 0.05 after hospitalisation.[56]

The same study reported that 35% of patients experienced anxiety and depression after COVID-19 illness, of whom 74% had no previous mental health diagnoses.[56] In addition, 46.9% and 23.5% of patients experienced PTSD symptoms related to illness after treatment in the ICU or on the general ward, respectively.[56]

In non-hospitalised patients (N=548), followed-up prospectively in England for 6 months, it was shown that 27% of the study cohort reported a worsened health state after completion of the EQ-5D survey.[57] Moreover, a 6-month cross-sectional snapshot from this study revealed that COVID-19-affected individuals in England were more likely to report extreme tiredness, headache, loss of taste and/or smell, shortness of breath and cough than control cases.[57] Similarly, an online EQ-5D-based survey was retrospectively completed by 406 patients with mild to moderate COVID-19 in the UK who reported a positive test within the previous year (55.7% at high risk for severe disease). Multivariable analysis showed that EQ-5D scores were statistically significantly lower during both 'acute' and 'long'[iv] phases of COVID-19 infection versus pre-COVID-19 ($p < 0.001$ for both).[58]

B.1.3.1.10 Economic burden

The cost of COVID-19 has been substantial, with an estimated £310 billion to £410 billion spent by the UK government on COVID-19 measures according to a research briefing published 12th September 2023.[59] These costs include spending on public services and support for businesses and individuals during the height of the pandemic.[59]

There are limited published data on the direct health-related economic burden in the UK. One study of 1.7 million patients infected with SARS-CoV-2 reported direct costs of COVID-19 in England.[52] Mean healthcare cost per hospitalisation was £13,059, which increased to

[iv] Long COVID was defined according to the NICE criteria as symptoms which cannot be explained by an alternative diagnosis or condition, and which lasted or developed 12 weeks beyond the initial COVID-19 infection

£30,352 for critical care admissions and £51,103 for patients requiring mechanical ventilation (NHS cost data 2020/2021).[53] Costs were similar for patients at risk of developing severe illness, using three different definitions of high risk (McInnes[43], PANORAMIC[60] and Green Book[8]; see also Section B.1.3.1.5).[53] The economic implications are wider if the societal perspective is to be considered, which falls outside the strict NICE reference case definition.

B.1.3.1.11 Healthcare burden

The NHS faced considerable challenges with hospital capacity during the pandemic, with beds being reorganised and repurposed to meet requirements.[61] Approximately 90% of general and acute beds were occupied during the pandemic, of which 30% were occupied by COVID-19 patients at the peak in January 2021.[51, 62] During this same peak, 66% of ICU beds with mechanical ventilation were occupied by COVID-19 patients.[51] COVID-19 remains a burden that necessitates treatment, with higher rates of hospitalisation and ICU admissions compared to other respiratory diseases such as influenza and respiratory syncytial virus (RSV).[63]

With the increasing pressure on the NHS, hospital trusts were advised on 17th March 2020 to postpone all non-urgent elective operations.[61] Waiting times for patients increased throughout the pandemic, and the number of patients on waiting lists increased by 13% between October 2020 and April 2021.[61] Analyses conducted by the British Medical Association estimated that 4.44 million fewer elective procedures and 30.79 million fewer outpatient attendances took place between April 2020 and January 2022 compared to pre-COVID-19 averages.[61]

The NHS have put a plan in place to tackle the COVID-19 backlog. However, it highlights that ongoing uncertainties about COVID-19, such as infection numbers, long-COVID-19 and evolving viral variants, in addition to the response required by the health service, will impact the delivery of the plan. The median waiting time for treatment is still more than double the pre-COVID median waiting time (14.9 weeks in March 2024 vs 6.9 weeks in March 2019).[64, 65] The use of treatments such as molnupiravir that are designed for use in outpatient settings, and, thus, reduce the need for hospital care, can be reasonably expected to contribute to reducing the demand for services, especially for those groups that may currently be precluded from receiving any other treatments for mild to moderate COVID-19 infection (unless there is explicit progression to severe disease and therefore the need for hospitalisation and/or oxygenation in parallel).

Staff absences have also added to the pressures faced by the NHS. In addition to SARS-CoV-2 infection and illness, staff were absent for reasons including self-isolation, long-

COVID-19, short notice childcare demands and burnout.[61] The highest daily NHS staff absence was 108,000 cases, reported in January 2021, 52% of which were related to COVID-19.[61] COVID-19 related staff absences remain high, with 27,563 absences due to sickness or self-isolation reported in April 2024, accounting for 1.6% of total absences in April 2024.[51]

B.1.3.2 Clinical pathway of care and molnupiravir place in therapy

B.1.3.2.1 Current treatment options

As discussed in Section B.1.3.1.5, certain groups of patients are considered to be at elevated risk of progression to severe COVID-19, a situation which is likely to require respiratory support in a hospital setting, supplemented with antivirals, corticosteroids and/or anti-inflammatory drugs.[27] For these at-risk patients, mild to moderate COVID-19 can generally be treated at home and in the community setting with the aim of managing symptoms and reducing the risk of progression to severe disease and hospitalisation.[27] Nirmatrelvir plus ritonavir (Paxlovid™) and sotrovimab (Xevudy®) are the only treatments currently recommended by NICE (TA878) for these high-risk non-hospitalised patients (see Figure 1).[43] However, nirmatrelvir plus ritonavir and sotrovimab can also be used for mild to moderate COVID-19 that is acquired in hospital when a patient has been admitted for a medical reason unrelated to COVID-19 (i.e., 'incidental COVID-19'; see further discussion below). Healthcare professionals who treat these patients with incidental COVID-19 indicate that the treatment pathway for those on a general ward *not* requiring supplemental oxygen is the same as in the outpatient setting (i.e. nirmatrelvir plus ritonavir or sotrovimab). [2] However, the experts indicate that on occasion, remdesivir, which was recently recommended by NICE for COVID-19 treatment *in-hospital* only (TA971), *may be* used for these patients with incidental COVID-19, if deemed by the clinician to be the most appropriate treatment.[2] Thus, despite a small hypothetical crossover, remdesivir is not considered a strict and direct comparator of interest in this submission, which focuses on the community/outpatient setting (see further discussion below).

Molnupiravir is an alternative option available for use in the NHS, which was originally part of the TA878 multiple technology appraisal, but is now under a single technology appraisal for evaluation for routine use in patients with mild to moderate COVID-19 at risk of developing severe illness.[3, 27, 43] Molnupiravir can currently be accessed through an NHS England Interim Clinical Commissioning Policy. According to the most recent data from NHS Secondary Care Medicines Data, the current average monthly usage of molnupiravir stands at 500 units, with each unit representing a five-day treatment course. Data from Blueteq

shows that a total of 17,785 courses of molnupiravir were prescribed in 2022. Between January and the end of June 2023, 7,150 treatment courses of molnupiravir were prescribed.

Nirmatrelvir plus ritonavir

Nirmatrelvir plus ritonavir is an antiviral that is recommended by NICE as the first-line treatment for adult patients with mild to moderate COVID-19 at risk of developing severe illness (Figure 1).[3, 43] The clinical effectiveness of nirmatrelvir plus ritonavir is based on the phase II/III EPIC-HR trial and the OpenSAFELY real-world cohort study.[66] The EPIC-HR trial showed reductions in hospitalisations and death in patients receiving nirmatrelvir plus ritonavir compared with placebo.[67]

While nirmatrelvir plus ritonavir is considered cost-effective,[43] its use is associated with a number of limitations.[68]

- Treatment with nirmatrelvir plus ritonavir is contraindicated for up to 36% of patients.[69] These patients include individuals with severe hepatic or renal impairment,[68] which are comorbidities associated with increased risk of severe COVID-19 (Section B.1.3.1.5).[41, 43]
- Additionally, patients taking certain medications including, but not limited to, antiarrhythmics, anticoagulants, anticonvulsants, antiretrovirals, anxiolytics, cancer drugs or immunosuppressants, are at risk of serious drug-drug interactions with nirmatrelvir plus ritonavir treatment[v].[68, 70] Coadministration of nirmatrelvir plus ritonavir with these medicines may lead to serious or life-threatening side effects.[71] Significant specialist resources are required to conduct thorough drug interaction checks, which need to be completed by specialist pharmacists and/or clinicians who are familiar with the complexity of the pharmacokinetics of ritonavir. It is estimated that up to 27% of high-risk patients may be taking medications that would prevent them from receiving nirmatrelvir plus ritonavir and, as such, contraindications to other medicines should form part of the assessment when nirmatrelvir plus ritonavir is considered as a potential treatment for patients.[69]

Sotrovimab

Sotrovimab is an antiviral monoclonal antibody recommended by NICE for the treatment of patients with mild to moderate COVID-19 at risk of developing severe illness and who are contraindicated to, or unsuitable for treatment with, nirmatrelvir plus ritonavir (Figure 1).[43, 72]

[v] An overview of drug-drug interactions for COVID-19 therapies can be found at https://www.covid19-druginteractions.org/prescribing_resources [accessed 21 February 2024]

Sotrovimab can be used in adults and young people aged 12 years and over who weigh at least 40 kg.[43, 72] Clinical effectiveness is based on the phase II/III COMET-ICE trial, *in vitro* studies and the OpenSAFELY study.[43, 66, 72, 73] COMET-ICE showed a significantly lower risk of hospitalisation or death in patients treated with sotrovimab compared to placebo.[73] However, NICE have commented that clinical effectiveness is uncertain, with conflicting *in vitro* and real-world data for different variants.[43]

- Clinical effectiveness may also be limited in the future as new SARS-CoV-2 variants emerge. Sotrovimab is a neutralising monoclonal antibody that binds the SARS-CoV-2 spike protein, which can change over time as the virus evolves and mutates, thus making sotrovimab particularly susceptible to the emergence of new variants.[43]
- Other limitations of sotrovimab include being administered by intravenous (IV) injection, which requires patients to attend hospital or a clinic.[72] This raises concerns about accessibility to treatment in remote regions and with NHS capacity to deliver this treatment.

Remdesivir

Some patients may contract COVID-19 while in hospital or are diagnosed with COVID-19 when admitted for other medical reasons aside from COVID-19; these cases are referred to as 'incidental COVID-19'.

Remdesivir is an antiviral recommended by NICE for in-hospital treatment of COVID-19 in patients at high risk of severe illness, regardless of oxygenation needs (TA971).[74] Clinical experts indicate that the treatment pathway for patients with incidental COVID-19 on a general ward *not* requiring supplemental oxygen is the same as in the outpatient setting (i.e. nirmatrelvir plus ritonavir or sotrovimab).

Remdesivir, recently recommended by NICE for in hospital treatment of COVID-19 (TA971), may be used for these patients with incidental COVID-19 if deemed to be the most appropriate treatment option by the clinician.[2] Remdesivir may also be used for patients admitted to the hospital with high risk of developing severe COVID-19 having 'failed' treatment with an outpatient/community therapeutic per TA878.

For these reasons, remdesivir is not considered a strict and direct comparator of interest in this submission which focusses on treatment in the community/outpatient setting (see further discussion below).

However, remdesivir may at times be a comparator for the target population of molnupiravir in the context of incidental COVID-19.

- This patient group is not included in the cost-effectiveness model as there is no available trial evidence on the use of treatments for incidental COVID-19 (see Section B3 for further details on the model).
- Remdesivir is included in the network meta-analyses (NMA) of real-world evidence (RWE) and randomised controlled trial (RCT) data in the outpatient setting only (due to a lack of evidence for patients with incidental COVID-19), and evidence informing the relative effectiveness of molnupiravir versus remdesivir in outpatients in the real-world clinical practice is provided by the RWE NMA (Section B.2.9.2).

While the evidence for the effectiveness of remdesivir in outpatients with COVID-19 is limited and not fully aligned with NICE recommendations for remdesivir use in the NHS as per TA971, the clinical analyses presented may inform the decision making process enabling the committee to discuss the clinical effectiveness more holistically. Patients with incidental COVID-19 in hospital, regardless of therapeutic options received, are likely to benefit from treatment directly. Further, it is reasonable to assume that their treatment would also benefit other patients by resolving infection sooner and preventing subsequent onward transmission within the hospital. Thus, MSD is supportive of incidental COVID-19 being treated with the best available option based on clinical consideration and local health system constraints.

B.1.3.2.2 Molnupiravir place in therapy

Molnupiravir can provide an alternative to current treatments and is already approved for patients with mild to moderate COVID-19 at risk of severe illness.[1] The phase III MOVE-OUT trial and real-world studies (Section B.2.6) demonstrate that molnupiravir is clinically effective compared with placebo or usual care.[75, 76]

Nirmatrelvir plus ritonavir and sotrovimab, which are currently the only outpatient treatments recommended by NICE for those with mild to moderate COVID-19 at risk of developing severe illness,[43] are not always viable treatment options:

- Patients at risk of developing severe COVID-19 are likely to have multiple comorbidities and be taking several medications. Note that polypharmacy is common, with an estimated 18.9 million patients in England taking more than one unique medication.[77] Nirmatrelvir plus ritonavir may be unsuitable for these patients due to contraindications or risk of drug-drug interactions.[68, 70] Unlike nirmatrelvir plus ritonavir, molnupiravir can be used in patients with severe renal or hepatic impairment and in patients taking medications such as anticoagulants, anticonvulsants or antiarrhythmics who would be at risk of drug-drug interactions with

nirmatrelvir plus ritonavir, or when there is no capacity for a comprehensive review of drug-drug interactions.[1, 78]

- In contrast to the IV administration of sotrovimab, which is the current alternative to nirmatrelvir plus ritonavir, molnupiravir is an oral medication. Thus, compared with sotrovimab, molnupiravir would be expected to reduce hospital resourcing and cost, and ease the patient experience as molnupiravir enables at home administration.[1, 72]

Healthcare professionals who operate COVID-19 antiviral services have confirmed the occurrence of scenarios in which patients with mild to moderate COVID-19 at high risk of developing severe disease are not offered therapy due to presence of contraindications to nirmatrelvir plus ritonavir, and either falling outside the sotrovimab recommendation or being unable to attend a clinical service for sotrovimab infusion, leaving these patients without a suitable treatment option.[2]

Due to the limitations of nirmatrelvir plus ritonavir and sotrovimab, there is a need for a simple, cost-effective treatment in patients with mild to moderate COVID-19 at risk of severe illness that can decrease the risk of hospitalisation and death, can also be used safely in patients with severe renal and hepatic impairment or taking other medications, and can be given in a community setting for self-administration at home. Based on clinical and emerging RWE, molnupiravir is an effective treatment option comparable with nirmatrelvir plus ritonavir, but with fewer prescribing limitations, and, in contrast to sotrovimab, molnupiravir is administered orally allowing simpler access to treatment.[1, 68, 72] Additionally, treatment at home with molnupiravir removes potentially infectious patients from the hospital setting where they could cause infection in other patients who may themselves have conditions putting them at risk of severe COVID-19.

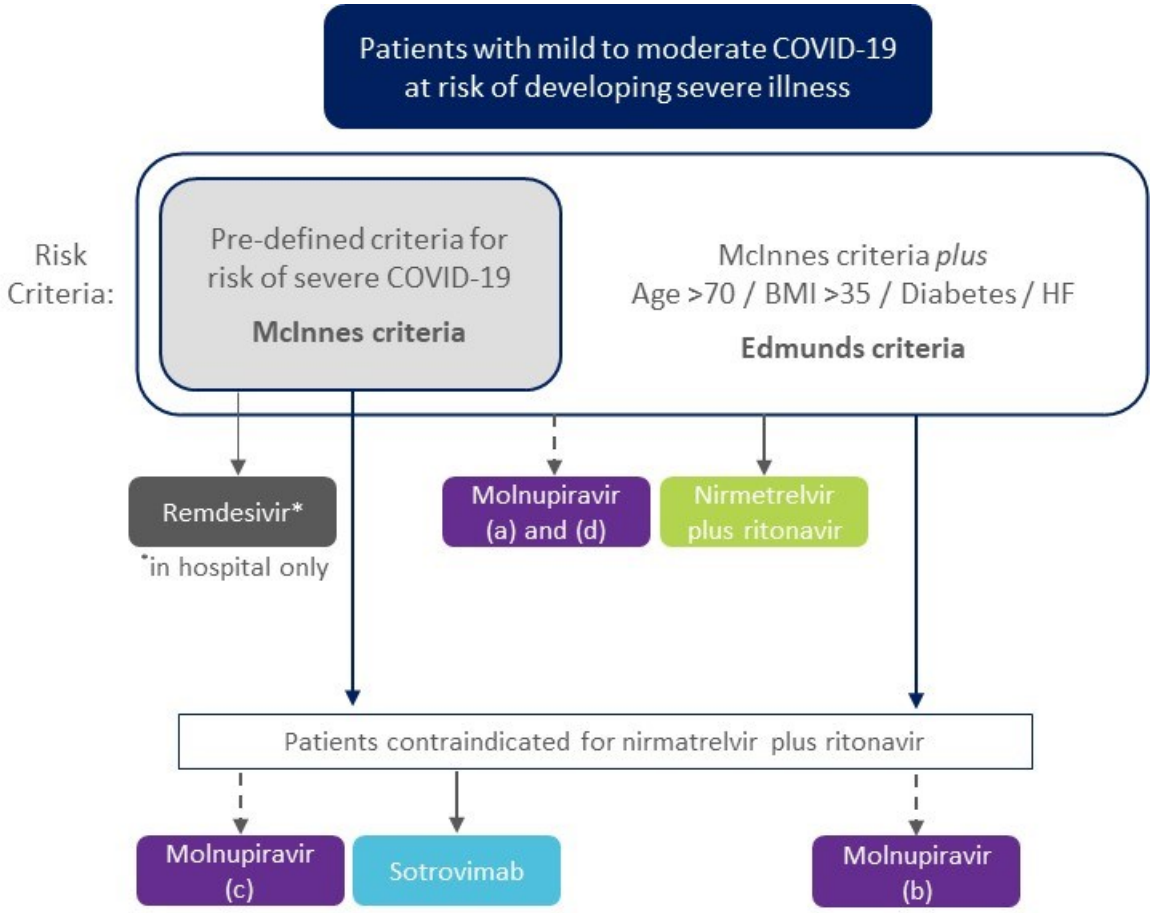
MSD propose the following positioning for molnupiravir (Figure 1):

- As an alternative to nirmatrelvir plus ritonavir in patients at risk of severe illness according to the McInnes and Edmunds definitions (i.e., position (a) in Figure 1);
- For patients at risk of severe illness according to the Edmunds definition, who are unsuitable for treatment with nirmatrelvir plus ritonavir (b);
- As an alternative to sotrovimab for patients at risk of severe illness according to the McInnes criteria, who are unsuitable for treatment with nirmatrelvir plus ritonavir (c).

Additionally, molnupiravir may be used as an alternative to nirmatrelvir plus ritonavir, sotrovimab or remdesivir in patients with incidental COVID-19 acquired in hospital (d).

MSD proposes the above positioning to enable clinicians to determine the most suitable treatment for each patient on an individual basis, accounting for personal and clinical considerations. MSD understands that molnupiravir may primarily continue to be used as per the current NHS-E commissioning policy if approved for routine use in the NHS – that is, within patients that fall in groups (b) and (c) alongside incidental COVID-19..

Figure 1. Clinical care pathway for patients with mild to moderate COVID-19 at risk of developing severe illness, as per NICE scope, with proposed positions for molnupiravir (i.e., positions (a) to (d))



BMI = body mass index; COVID-19 = coronavirus disease 2019; HF = heart failure

B.1.4 Equality considerations

Clinical experts have noted the residual unmet medical need remaining for patients with mild to moderate COVID-19 at high risk of developing severe disease are not currently offered a community/outpatient therapy or decline it out of necessity, leaving them exposed to the likelihood of onward hospital admission for severe disease if infection does not fully resolve on its own. As such, MSD considers that there are equity considerations to be taken into account for decision making and list specific examples below.

Molnupiravir offers an option for patients with protected characteristics whose health status may limit the benefit of currently available treatments for COVID-19. It is likely that a number

of patients are contraindicated to or likely to have drug-drug interactions to the currently recommended first-line treatment, nirmatrelvir plus ritonavir. These are likely to be patients with protected characteristics, such as older individuals or those with long-term conditions and/or disabilities but could also include those of an ethnic minority background.

With current treatment recommendations, patients with protected characteristics may encounter additional burden from travelling to hospitals or clinics to receive IV treatment. Additionally, while at the hospital or clinic, these vulnerable patients risk exposure to other patients with communicable disease.[43, 72] As an oral medication, molnupiravir provides an alternative for these patients allowing self-administration at home, reducing travel burden and exposure.

Treatment for patients with multiple comorbidities and medications is also complicated as these patients are likely to be at risk of drug-drug interactions or require dose adjustments.[43, 68] Molnupiravir offers a simple, alternative treatment with no required dose adjustments. Moreover, no drug-drug interactions have been reported for molnupiravir.

Finally, patients with renal impairment are contraindicated to nirmatrelvir plus ritonavir and thus the only option with current treatment recommendations is sotrovimab.[43, 68] The prevalence of renal impairment is higher in black, Asian and other ethnic minority backgrounds,[79] and the risk of death and hospitalisation from COVID-19 is also higher in these groups.[39, 40] Thus, molnupiravir would provide a treatment option for these patients with protected characteristics at increased risk of developing severe COVID-19.

B.2 Clinical effectiveness

Key summary points

Overview of evidence

- Systematic literature reviews (SLRs) of randomised clinical trials (RCTs) and real-world evidence (RWE) were conducted to identify evidence of the efficacy and safety of molnupiravir versus placebo and other active treatments.
- Indirect evidence for the efficacy and safety of molnupiravir were generated by network meta-analyses (NMAs) of data identified from the RCT and RWE SLRs.
- The SLR of RWE was conducted on studies published from 2022 onward so the RWE NMA results specifically show effectiveness of active treatments versus Omicron variants to reflect the current endemic state.
    - This is opposed to the SLR of RCTs, as many of the trials were conducted in unvaccinated populations, before the emergence of the Omicron variants of SARS-CoV-2, so the relevance of their findings to the current situation is less clear.

Direct evidence for clinical effectiveness

- MOVe-OUT was the pivotal (registrational) phase II/III multicentre, randomised, double-blinded, placebo-controlled trial that demonstrated the efficacy and safety of molnupiravir against no treatment for mild to moderate COVID-19 in non-hospitalised adults who have at least one risk factor for developing severe illness.
- The primary efficacy endpoint of MOVe-OUT was successfully met. Fewer patients treated with molnupiravir were hospitalised for any cause or died from study initiation to Day 29 versus placebo (6.8% versus 9.7%), corresponding to a 3.0 percentage-point reduction (95% CI: -5.9, -0.1; one-sided p=0.0218; approximately 30% relative risk reduction).
- Results from the secondary efficacy endpoints of MOVe-OUT demonstrated that treatment with molnupiravir is associated with improved clinical outcomes through Day 29 compared to placebo, as assessed by self-reported COVID-19 signs/symptoms and the WHO 11-point ordinal scale.
- The safety profile of molnupiravir was comparable to placebo with no specific safety findings associated with molnupiravir observed.

Indirect evidence for clinical effectiveness

- NMAs of RCT data and RWE provided estimates of the clinical effectiveness of molnupiravir versus other active treatments or no treatment.

- NMAs indicated **molnupiravir to be statistically significantly better in comparison to no treatment** for improving:
    - All-cause hospitalisation or death (primary endpoint in the pivotal MOVe-OUT trial)
    - COVID-19 related hospitalisation or death
    - All-cause hospitalisation
    - COVID-19 related hospitalisation
    - All-cause death.
- Results from NMAs suggested **no significant difference for molnupiravir versus other active treatments** (nirmatrelvir plus ritonavir, sotrovimab and remdesivir) for all endpoints assessed.
- The clinical safety of molnupiravir versus other active treatments or no treatment was assessed in the RCT NMA only.
    - The results indicated **molnupiravir, in comparison to no treatment, to be associated with fewer of the following safety outcomes**:
        - Adverse events (AEs)
        - Serious adverse events (SAEs)
        - Treatment discontinuation due to AEs.
    - The resulted indicated **no significant difference for molnupiravir versus other active treatments** (nirmatrelvir plus ritonavir, sotrovimab and remdesivir) **for the safety outcomes assessed**.

B.2.1.1 Overview of the approach employed in this submission

Due to the rapidly evolving nature of COVID-19 disease and research, SLRs of both RCTs and RWE of COVID-19 in the community/outpatient setting were conducted for this submission and are introduced below.

While RCTs are the preferred source of evidence, RWE can be beneficial alongside RCT evidence to support conclusions, particularly when there are limitations with available RCT evidence or when there is a lack of RCT evidence.[80] This is the case with COVID-19, where RCT evidence does not reflect the most recent COVID-19 epidemiology, patient characteristics (such as vaccination status) and SARS-CoV-2 variants, and thus it is valuable to assess RWE alongside RCT data.

- **Direct RCT evidence** for the efficacy and safety of molnupiravir is presented from the MOVe-OUT study in Section B.2.2.1 versus placebo; no direct RCT evidence was identified for molnupiravir versus active treatment.

- **Indirect comparisons** for the efficacy and safety of molnupiravir versus comparator treatments is presented in the form of NMAs that utilise data identified from RCTs and RWE in Section B.2.9.1 and Section B.2.9.2, respectively.
    - As described in Section B.1.3.2, in addition to nirmatrelvir plus ritonavir and sotrovimab, the submission includes remdesivir as a comparator in the NMA for both RCT and RWE analyses (focusing explicitly in the outpatient setting for the remdesivir evidence base).
    - NICE only recommends the use of remdesivir for patients *in-hospital* (TA971),[74] and clinical experts have reported that remdesivir is occasionally used in patients with incidental mild to moderate COVID-19, thus overlapping with the indication in the current appraisal for molnupiravir (although for the majority of incidental COVID-19 cases, the treatment pathway follows that of the outpatient setting whereby nirmatrelvir plus ritonavir or sotrovimab is the treatment of choice).
    - The NMAs of RWE provide evidence on the relative effectiveness of molnupiravir versus remdesivir in outpatients in real-world clinical practice (Section B.2.9.2) and may be used as a proxy for incidental COVID-19, given the lack of data pertaining to the outcomes for incidental COVID-19 treated in hospital.

B.2.1.2 Identification and selection of relevant studies

B.2.1.2.1 SLR of RCTs

An SLR of clinical data was conducted to identify all relevant RCTs describing the efficacy and safety of treatments for mild to moderate COVID-19 in patients at risk of developing severe illness. Searches were conducted using the OVID platform and there was no lower limit on time horizon for database searches. The cut-off date for articles included in the SLR was 1st February 2024.

The SLR captured a total of 116 records including 76 full text publications, nine pre-print articles, 28 conference abstracts or posters and three press releases. Twenty-three RCTs included trials of molnupiravir and the comparators nirmatrelvir plus ritonavir, remdesivir, casirivimab + imdevimab, sotrovimab and tixagevimab + cilgavimab throughout the search period. The SLR of RCTs was carried out by MSD with a broader scope, as such several interventions were captured that are not relevant to the NICE decision problem. Of the

RCTs, with a focus on the interventions of interest to the decision problem for this single technology appraisal:

- Included literature on **molnupiravir** comprised 18 publications on nine RCTs (three phase II trials, one phase IIa trial, four phase III trials and one phase IV trial). [81-98]
    - Two phase III trials, conducted globally and in India, demonstrated a statistically-significant positive effect of molnupiravir on reducing risks of hospitalisation and/or death among outpatients versus placebo or standard of care, respectively.[84, 97, 98]
    - Included literature on molnupiravir encompasses trials conducted in unvaccinated patients, partially or predominantly vaccinated patients and in patients with unknown vaccination status.
- Included literature on **nirmatrelvir plus ritonavir** comprised five publications of two phase II/III RCTs.[99-103]
    - Nirmatrelvir plus ritonavir was shown to have statistically significant efficacy in reducing rates of hospitalisation or death in unvaccinated patients at high risk of progression to severe COVID-19 relative to placebo.
    - Nirmatrelvir plus ritonavir was also evaluated in a phase II/III trial that enrolled standard-risk outpatients with symptomatic COVID-19 who had not been vaccinated within the past 12 months.
- Included literature on **remdesivir** comprised six publications on two RCTs (one phase II and one phase III).[94-96, 104-107]
    - Phase III data on remdesivir suggest statistically significant efficacy in reducing risk of hospitalisation or death among high-risk outpatients versus placebo.[104]
- Included literature on **sotrovimab** comprised seven publications on two phase III RCTs.[108-114]
    - Phase III RCT data suggest that sotrovimab treatment is associated with a statistically significant reduction in the risk of hospitalisation or death among high-risk outpatients, and that its intramuscular formulation is associated with similar outcomes to the intravenous formulation.

In the context of the submission, the RCT data captured in the SLR may have limited generalisability; thus, the dossier primarily presents data from the MOVe-OUT trial as it is the pivotal study demonstrating the effectiveness and safety of molnupiravir in the community/outpatient setting and, therefore, aligns with the scope of the appraisal. PANORAMIC is another RCT of interest, pragmatic in nature, as stated by the authors, that

was identified by the SLR. Data from the study have been extracted to inform some of the cost-effectiveness model inputs (see Section B3), and the study, including its limitations are discussed in Section B.2.2.2.

B.2.1.2.2 SLR of RWE

Given the rapidly changing epidemiology of COVID-19, an SLR of RWE data was also conducted to provide supporting evidence of the comparative clinical effectiveness of molnupiravir versus other active treatments for adults with mild to moderate COVID-19 who are at increased risk of progressing to severe disease in the community/outpatient setting.

For the SLR of RWE, database and supplementary searches were conducted using the OVID platform to identify relevant RWE studies based on prespecified criteria of treatments for mild to moderate COVID-19 in patients at risk of developing severe illness. There was no lower limit on time horizon for database searches and the cut-off date for articles included in the SLR was 15th December 2023.

The SLR captured a total of 82 unique studies reported across 82 publications. Fifty studies were deemed unrepresentative of current UK practice or unsuitable for analysis due to futility or methodological concerns. Thirty studies were prioritised for inclusion, covering the SARS-CoV-2 Omicron variant time period and conducted in countries deemed comparable to the UK in terms of demography and relevant healthcare system factors such as vaccination. [66, 115-143] A topline summary includes:

- The population size of the studies ranged from 255 to 258,942 patients.
- The majority of studies were located in Italy and the USA, with other countries including the UK, Canada, France, Greece and Israel.
- Combined at-risk patients (defined as patients with any risk factor for severe disease) were investigated in 24 studies, while six studies included patients with a specific risk factor such as age or immunosuppression.

For the 24 studies in combined at-risk patients:[66, 121-143]

- The majority of studies included patients who were exposed to a SARS-CoV-2 Omicron variant with one study reporting numerous circulating variants of concern, including Omicron and its subvariants, and two studies not reporting details of the variants but were conducted during the time period when Omicron was the dominant variant.
- Fourteen studies evaluated molnupiravir, nineteen studies evaluated nirmatrelvir plus ritonavir, four studies evaluated sotrovimab and five studies evaluated remdesivir.

Of the six studies in specific at-risk populations:[115-120]

- Three studies focussed on older patients (≥ 65 years or > 70 years of age).[115-117]
- Two studies focussed on immunosuppressed populations; one with haematological malignancies and the other with autoimmune rheumatic disease.[118, 119]
- One study investigated patients with renal failure.[120]

Full details of the RWE SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix D.2.

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 MOVe-OUT

The RCT SLR described in Section B.2.1.2.1 identified several smaller investigator-initiated trials that evaluated the clinical effectiveness of molnupiravir versus placebo/no treatment. However, the submission provides direct evidence solely from the pivotal MOVe-OUT trial, which was sponsored by MSD.

MOVe-OUT (NCT04575597) is a phase II/III multicentre, randomised, double-blinded, placebo-controlled trial evaluating the efficacy and safety of molnupiravir for the treatment of mild to moderate COVID-19 in non-hospitalised adults with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness (Table 5).[84] The trial comprises two parts as follows; outcomes from Part 2 are presented in this dossier:[76, 84]

- Part 1 – Phase II; dose ranging
- Part 2 – Phase III; evaluation of selected dose.

The phase III portion of MOVe-OUT was initiated on May 6, 2021 and recruited 1,433 participants, including 775 participants enrolled at the time of the interim analyses[vi] and 658 patients enrolled after the interim analyses.[84] Participants were followed-up for 29 days for evaluation of efficacy, safety and virology, and up to 7 months for the evaluation of safety.[84]

Results from the final analysis are presented in this dossier. In the case of the primary efficacy endpoint, results from both the interim and final analyses are included (Section B.2.6.1).

[vi] 775 participants were enrolled in the interim analyses at which 50% of the planned enrolment had completed the Day 29 visit.

Table 5. Clinical effectiveness evidence - MOVe-OUT

Study	NCT04575597 (MOVe-OUT)	
Study design	Phase II/III multicentre, randomised, double-blinded, parallel assignment, interventional, placebo-controlled trial	
Population	Non-hospitalised participants ≥ 18 years of age with laboratory-confirmed SARS-CoV-2 infection with signs/symptoms attributable to COVID-19 and at least one risk factor for development of severe illness from COVID-19	
Intervention(s)	Molnupiravir	
Comparator(s)	Placebo	
Indicate if study supports application for marketing authorisation	Yes	
Indicate if study used in the economic model	Yes	
Rationale if study not used in model	Not applicable	
Reported outcomes specified in the decision problem	**Primary outcomes** • **All-cause hospitalisation or death** • AEs • AEs leading to discontinuation of study intervention	**Secondary outcomes** • COVID-19 signs/symptoms • WHO 11-point scale score
All other reported outcomes	• **Acute care visit** • **COVID-19 related acute care visit** (referred to as 'COVID-related hospitalisations' in the model) • Plasma PK concentration (e.g., C_{trough}) • SARS-CoV-2 RNA • Viral RNA sequences • Infectious SARS-CoV-2	

Outcomes marked in **bold** have been incorporated into the cost-effectiveness model
AE = adverse event; COVID-19 = coronavirus disease 2019; PK = pharmacokinetic; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization
SOURCE: MSD 2022 MOVe-OUT CSR;[76] Jayk Bernal et al., 2022.[84]

B.2.2.2 PANORAMIC

PANORAMIC is an ongoing UK multicentre, open-label, prospective, platform adaptive trial of treatments for COVID-19.[93] A platform trial allows for multiple treatments for the same disease to be tested simultaneously. PANORAMIC will provide results for both molnupiravir and nirmatrelvir plus ritonavir versus usual care for the treatment of COVID-19.[93] In the first phase of PANORAMIC, patients with COVID-19 who were either ≥ 50 years of age or ≥ 18 years of age with a comorbidity (see Table 6) were recruited within the community (i.e. non-hospitalised) and randomised 1:1 to usual care plus molnupiravir or usual care only.[93] Randomisation was stratified by age and vaccination status. Recruitment for PANORAMIC is now complete, with recruitment to the nirmatrelvir plus ritonavir arm ceasing in March 2024 and only overlapping with recruitment to the molnupiravir arm for a short period of time.[60] At the time of this submission, PANORAMIC is currently evaluating nirmatrelvir plus ritonavir for the treatment of COVID-19.[60] [93]

Between 8th December 2021 and 27th April 2022, 25,783 patients were recruited and followed for 28 days.[93] For final analysis, 12,774 were included in the molnupiravir plus usual care arm and 12,934 in the usual care only arm.[93] Outcomes of interest included all-cause hospitalisation or death and time to recovery.[93]

While PANORAMIC is well-designed and well-conducted, there are aspects of the study that should be considered in relation to the scope of the appraisal:

- The definition of being at high risk for severe COVID-19 in PANORAMIC was broader than the McInnes definition,[41] and the inclusion criteria for the MOVe-OUT trial,[84] allowing the inclusion of patients ≥ 50 years of age (without a comorbidity) and for clinical judgement in the assessment of clinically vulnerability.[44, 93] It is therefore likely that the baseline probability of events is lower than in the target population for this appraisal, which raises the Number Needed to Treat.
- A 2023 NICE report highlighted that patients at highest risk of severe COVID-19 disease were likely under-represented in the PANORAMIC population, as indicated by clinical experts.[44] Patients in PANORAMIC were triaged and those at highest risk would have received treatment via the established COVID Medicines Delivery Units (CMDUs).[44] Thus, PANORAMIC would not have included patients at highest risk who were eligible for treatment through UK interim clinical commissioning policies.[44]
- Additionally, as indicated in the same 2023 NICE report, the clinical experts agreed that the PANORAMIC baseline hospitalisation rate of 0.77% used for the population who have a high risk of progression to severe COVID-19 could be an underestimation due to the under-representation of the high-risk group in PANORAMIC.[44, 93] Patients enrolled in PANORAMIC were less likely to be hospitalised and do not reflect the patient population who would most likely benefit from treatment with molnupiravir.
- Patients randomised to usual care were able to obtain prescriptions of monoclonal antibodies and antivirals outside of the study.[93] Access to treatments outside of the trial is likely to confound the usual care treatment arm and limit any possible treatment effects in the study.
- At the time of writing, results for only molnupiravir have been reported from PANORAMIC. Although results for nirmatrelvir plus ritonavir will be published, there are no plans to evaluate other active interventions in PANORAMIC.

Given the factors listed above, the company consider the cohort enrolled in PANORAMIC is not as representative of the population that is the focus of this appraisal and MSD consider that the results from PANORAMIC may be biased against molnupiravir, the extent of which

cannot be quantified as data are not available for other active interventions generated under the same conditions. Therefore, the results from PANORAMIC are not presented here. However, the study has been included in the RCT NMA for completeness (see Section B.2.9.1) and in the absence of alternative inputs, data on time to recovery from PANORAMIC have been included in the cost-effectiveness analysis.

Table 6. Clinical effectiveness evidence - PANORAMIC

Study	PANORAMIC	
Study design	Multicentre, primary care, open-label, multigroup, prospective, platform adaptive trial	
Population	People in the community ≥ 50 years of age or ≥18 years of age with comorbidities who had COVID-19 symptoms with a positive SARS-CoV-2 test. Comorbidities included: • Chronic respiratory disease • Chronic heart or vascular disease • Chronic kidney disease • Chronic liver disease • Chronic neurological disease • Down's syndrome • Diabetes mellitus (Type or Type II) • Immunosuppression: primary or secondary • Solid organ, bone marrow and stem cell transplant recipients • Morbid obesity (BMI > 35) • Severe mental illness • Care home resident • Judged to be clinically vulnerable	
Intervention(s)	• Molnupiravir plus usual care (recruitment from December 2021 to April 2022) • Nirmatrelvir plus ritonavir plus usual care (recruitment from April 2022 to March 2024) **Note:** Recruitment to either treatment arm was between 8th December 2021 to 28th March 2024	
Comparator(s)	Usual care	
Indicate if study supports application for marketing authorisation	No	
Indicate if study used in the economic model	Yes	
Rationale if study not used in model	Not applicable	
Reported outcomes specified in the decision problem	**Primary outcomes** • All-cause hospitalisation or death	**Secondary outcomes** • **Time to self-reported/early sustained/sustained recovery** • Oxygen administration • Safety outcomes
All other reported outcomes	• Self-reported wellness • Time to initial/sustained alleviation of symptoms	

Study	PANORAMIC
	• Time to initial reduction of symptom severity • Contact with health or social services • Hospital assessment without admission • New household COVID-19 infections

Outcomes marked in **bold** have been incorporated into the cost-effectiveness model
BMI = body mass index; COVID-19 = coronavirus disease 2019; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SOURCE: Butler 2023;[93] PANORAMIC trial. Participant Information 2024.[60]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 MOVe-OUT: Trial design

MOVe-OUT is a randomised, double-blinded, parallel assignment, interventional, placebo-controlled trial designed to evaluate the efficacy and safety (up to 7 months' follow-up) of molnupiravir for the treatment of mild to moderate COVID-19 in non-hospitalised adults with a positive SARS-CoV-2 diagnostic test and with symptom onset within five days prior to randomisation, who have at least one risk factor for developing severe illness.[84]

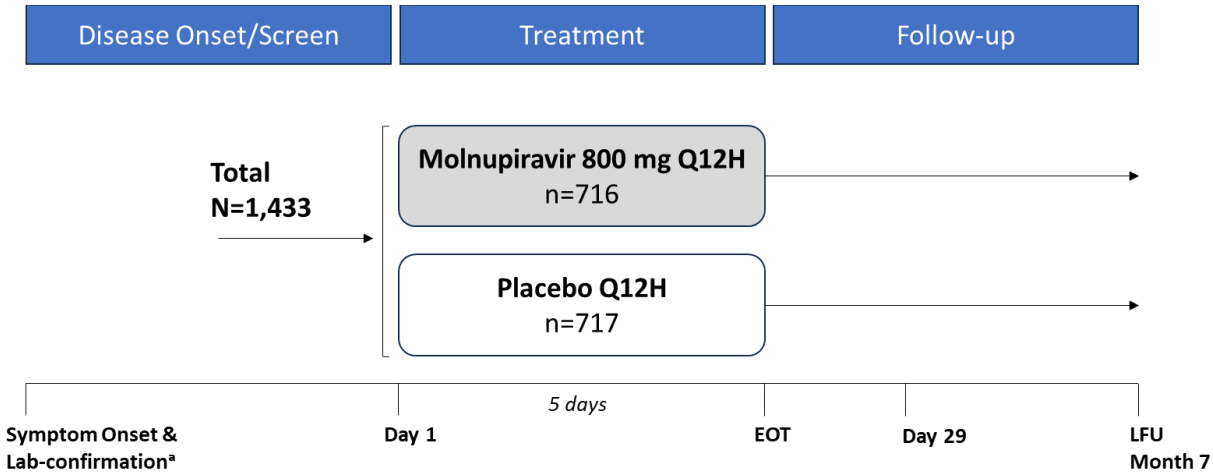
The MOVe-OUT trial was conducted in 107 sites in 20 countries across the US, Europe and Asia, including six sites in the UK.[76]

The primary efficacy objective of MOVe-OUT was to evaluate the efficacy of molnupiravir compared to placebo in reducing the proportion of participants who were hospitalised for any cause or who died from study initiation to Day 29.[84]

The primary safety objective of MOVe-OUT was to evaluate the safety and tolerability of molnupiravir compared to placebo as assessed by the number of adverse events (AEs) and AEs leading to discontinuation of study intervention from study initiation to Month 7.[84]

In the phase III component of MOVe-OUT, 1,433 participants were randomised 1:1 to receive either molnupiravir 800 mg (n=716) or placebo (n=717) every 12 hours (Q12H) for 5 days with 29-day and 7-month follow-up periods (Figure 2).[84] Interim analyses were conducted after 50% of the total planned population had been enrolled and had follow-up data at Day 29 (n=775).[84]

Figure 2. Study design for Part 2 of the phase III MOVe-OUT trial



[a] Eligible participants had laboratory-confirmed SARS-CoV-2 infection with signs/symptoms attributable to COVID-19 for ≤ 7 days in Part 1 and ≤ 5 days in Part 2 prior to randomisation. Calculation of the 7-day/5-day symptom onset window did not include the date of randomisation.
COVID-19 = coronavirus disease 2019; EOT = end-of-treatment; LFU = late follow-up visit; N= total number of participants in each study part; n = number of participants per group; Q12H = administered once every 12 hours; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
SOURCE: Jayk Bernal et al., 2022. (84)

B.2.3.2 MOVe-OUT: Inclusion/exclusion criteria

Eligible patients enrolled in MOVe-OUT were male or female participants ≥ 18 years of age with laboratory-confirmed SARS-CoV-2 infection with a sample that had been collected at least 5 days prior to randomisation.(84) Patients were required to have mild or moderate COVID-19 with at least one underlying medical condition associated with an increased risk of severe illness from COVID-19.(84) The MOVe-OUT definition for risk factors for progression to severe COVID-19 was most closely aligned with the wider population defined in the Edmunds report including age ≥ 70 years, diabetes, obesity and heart failure (see Table 4 in Section B.1.3.1.5). SARS-CoV-2 vaccines were prohibited at any time prior to randomisation and through Day 29.(75, 76, 84) Key inclusion and exclusion criteria used in MOVe-OUT are summarised in Table 7.

Table 7. MOVe-OUT study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

• Aged ≥ 18 years
• Positive SARS-CoV-2 test result
• Initial onset of signs/symptoms[a] attributable to COVID-19 at least 5 days prior to the day of randomisation and at least one sign/symptom attributable to COVID-19 on the day of randomisation
• Mild[b] or moderate[c] COVID-19 and at least one of the following characteristics or underlying medical conditions associated with an increased risk of severe illness from COVID-19:
	• Currently hospitalised or expected to need hospitalisation for COVID-19 within 48 hours of randomisation
	• On dialysis or reduced eGFR < 30 mL/min/1.73m^2
	• Any of the following conditions:
	  ○ HIV with a recent viral load > 50 copies/mL (regardless of CD4 count) or an AIDS-defining illness in the past 6 months
	  ○ A neutrophilic granulocyte absolute count < 500/mm^3

○ Age > 60 years (patients > 60 years of age are automatically eligible based on their age alone as a risk factor) ○ Active cancer (excluding minor cancers not associated with immunosuppression or significant morbidity/mortality [e.g., basal cell carcinomas]) ○ Chronic kidney disease (excluding participants on dialysis or with reduced eGFR < 30 mL/min/1.73m^2) ○ Chronic obstructive pulmonary disease ○ Obesity (body mass index of 30 or higher) ○ Serious heart conditions such as heart failure, coronary artery disease or cardiomyopathies ○ Diabetes mellitus	• History of HBV or HCV infection with (a) cirrhosis, (b) end-stage liver disease, (c) hepatocellular carcinoma OR (d) AST and/or ALT > 3X upper limit of normal at screening • Platelet count < 100,000/μL or received a platelet transfusion in the 5 days prior to randomisation

[a] Includes: fever > 38.0ºC, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhoea, loss of taste, loss of smell.
[b] Must have ALL of the following: (1) Respiratory rate < 20 breaths per minute; (2) Heart rate < 90 beats per minute; (3) SpO_2 > 93% on room air or on supplemental oxygen for a reason other than COVID-19 which HAS NOT increased since onset of COVID-19 signs/symptoms AND must NOT have shortness of breath at rest or with exertion as assessed by the investigator, respiratory failure, shock or multi-organ dysfunction/failure.
[c] Must have ONE or MORE of the following: (1) Shortness of breath with exertion as assessed by the investigator; (2) Respiratory rate ≥ 20 to < 30 breaths per minute; (3) Heart rate ≥ 90 to < 125 beats per minute AND must have SpO_2 > 93% on room air or on supplemental oxygen for a reason other than COVID-19 which HAS NOT increased since onset of COVID-19 signs/symptoms [or only on ≤ 4 litres/min supplemental oxygen for COVID-19 (but was not previously on supplemental oxygen), regardless of SpO_2] AND must NOT have shortness of breath at rest as assessed by the investigator, respiratory failure, shock or multi-organ dysfunction/failure.
AIDS = acquired immunodeficiency syndrome; ALT = alanine transaminase; AST = aspartate aminotransferase; COVID-19 = coronavirus disease 2019; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SOURCE: Jayk Bernal et al., 2022.[84]

B.2.3.3 MOVe-OUT: Interventions

Patients in MOVe-OUT were randomised 1:1 to receive either molnupiravir 800 mg or placebo Q12H for 5 days, both administered orally, with randomisation stratified by time from symptom onset to the day of randomisation (i.e. either ≤ 3 days or > 3 [4-5] days).[76]

Concomitant therapies or drugs that were permitted during MOVe-OUT included:[84]

- Sponsor-designated standard of care for treatment of COVID-19 (e.g., corticosteroids).
- Supportive therapies (e.g., anti-pyretic and anti-inflammatory drugs) to manage COVID-19 signs/symptoms.

The following therapies and drugs were prohibited during MOVe-OUT:[75, 84]

- COVID-19 vaccines.
- COVID-19 monoclonal antibodies.
- Non-COVID-19 investigations agents (including devices).

B.2.3.4 MOVe-OUT: Objectives and endpoints

Study objectives and endpoints for MOVe-OUT are summarised in Table 8.[84]

Prespecified subgroup analyses were performed for the primary efficacy endpoint based on baseline characteristics (including timing of symptom onset relative to randomisation, age, obesity, baseline COVID-19 severity, region, sex, race and baseline viral load status).[76]

Table 8. MOVe-OUT study objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of molnupiravir compared to placebo as assessed by the proportion of participants who are hospitalised for any cause and/or die from randomisation through Day 29	• All-cause hospitalisation or death
To evaluate the safety and tolerability of molnupiravir compared to placebo	• AEs • AEs leading to discontinuation of study intervention
Secondary	
To evaluate the efficacy of molnupiravir compared to placebo as assessed by time to sustained resolution or improvement and time to progression of each targeted self-reported sign/symptom of COVID-19 from randomisation through Day 29	• COVID-19 signs/symptoms
To evaluate the efficacy of molnupiravir compared to placebo as assessed by the odds of a more favourable response on the WHO 11-point ordinal scale[a] on Day 3, EOT, Day 10, Day 15 and Day 29	• WHO 11-point scale score[a]
Exploratory	
To evaluate the efficacy of molnupiravir compared to placebo as assessed by the proportion of participants who have any acute care visit from randomisation through Day 29	• Acute care visit
To evaluate the efficacy of molnupiravir compared to placebo as assessed by the proportion of participants who have any COVID-19 related acute care visit from randomisation through Day 29	• COVID-19 related acute care visit
To measure the pharmacokinetics of NHC (the parent nucleoside) in plasma and NHC-TP (the pharmacologically-active triphosphate form) in PBMC collected at various timepoints	• Plasma PK concentration (e.g., C_{trough})
To evaluate the antiviral activity of molnupiravir compared to placebo as assessed by the change from baseline in SARS-CoV-2 RNA titre and proportion of participants with undetectable SARS-CoV-2 RNA in nasopharyngeal swabs at various timepoints	• SARS-Cov-2-RNA
To evaluate the effect of molnupiravir on viral RNA mutation rate and detection of treatment-emergent sequence variants as assessed by comparison of gene sequencing in virus isolated at baseline and post-baseline in samples with evaluable SARS-CoV-2 RNA	• Viral RNA sequences
To evaluate the antiviral activity of molnupiravir compared to placebo as assessed by the proportion of participants with undetectable infectious SARS-CoV-2 in nasopharyngeal swabs at various timepoints	• Infectious SARS-CoV-2
Late follow-up	

To evaluate the efficacy of molnupiravir compared to placebo as assessed by the proportion of participants who are hospitalised for any cause and/or die from randomisation through Month 7 (LFU)	• All-cause hospitalisation or death

[a] The WHO 11-point ordinal scale scores are categorised as follows: 0: Uninfected; 1-3: Ambulatory, mild disease; 4-5: Hospitalised, moderate disease; 6-9: Hospitalised, severe disease; 10: Death.
AE = adverse event; COVID-19 = coronavirus disease 2019; C_{trough} = trough concentration; LFU = late follow-up visit; NHC = N-hydroxycytidine; NCH-TP = N-hydroxycytidine pharmacologically-active triphosphate; PK = pharmacokinetic; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization
SOURCE: Jayk Bernal et al., 2022.(84)

B.2.3.5 MOVe-OUT: Patient disposition

Full details of the participant flow in MOVe-OUT are presented in Appendix D.1.2.

A total of 775 randomised patients were included in the interim analyses[vii] (molnupiravir: n=387; placebo: n=388).(84) The majority of patients completed the 5-day treatment regimen (94.9%) and the Day 29 follow-up (95.0%).(76) The most common reason for discontinuation by Day 29 follow-up was withdrawal by the participant (2.7%).(76)

For the final analysis after full enrolment, a total of 1,433 patients had been randomised 1:1 to the two treatment groups (molnupiravir: n=716; placebo: n=717).(84) The majority of patients completed the 5-day treatment regimen (95.3%) and the Day 29 follow-up (95.8%).(84) The most common reason for discontinuation by Day 29 follow-up was withdrawal by the subject (2.6%).(84) There were a total of nine (1.3%) deaths in the placebo group and one (0.1%) death in the molnupiravir group at Day 29.(84)

Most patients also completed the late follow-up visit (LFU) at Month 7 (94.8%), with those who did not complete the LFU mostly discontinuing due to withdrawal by the subject (2.7%).(144) Additionally, there were a total of 13 (1.9%) deaths in the placebo group and three (0.4%) deaths in the molnupiravir group at Month 7.(144)

Refer to Section B.2.10 for further safety data in MOVe-OUT at Day 14 and Month 7 follow-up.

Table 9 summarises the patient disposition for the final analysis after full enrolment.

Table 9. Disposition of patients in MOVe-OUT (final analysis)

	Molnupiravir	Placebo	Total
N	716	717	1,433
Status for study intervention, n (%)			
Started	710	701	1,411
Completed	680 (95.8)	665 (94.9)	1,345 (95.3)

[vii] 775 participants were enrolled in the interim analyses at which 50% of the planned enrolment had completed the Day 29 visit.

	Molnupiravir	Placebo	Total
Discontinued	30 (4.2)	36 (5.1)	66 (4.7)
AE	10 (1.4)	20 (2.9)	30 (2.1)
Lost to follow-up	2 (0.3)	2 (0.3)	4 (0.3)
Non-compliance with study drug	8 (1.1)	7 (1.0)	15 (1.1)
Physician decision	1 (0.1)	0	1 (0.1)
Withdrawal by subject	8 (1.1)	5 (0.7)	13 (0.9)
Other	1 (0.1)	2(0.3)	3 (0.2)
Status at Day 29 follow-up[a], n (%)			
Started	710	701	1,411
Completed	680 (95.8)	672 (95.9)	1,352 (95.8)
Discontinued	30 (4.2)	29 (4.1)	59 (4.2)
Death	1 (0.1)	9 (1.3)	10 (0.7)
Lost to follow-up	7 (1.0)	4 (0.6)	11 (0.8)
Withdrawal by subject	22 (3.1)	15 (2.1)	37 (2.6)
Other	0	1 (0.1)	1 (0.1)
Status at Month 7 follow-up, n (%)			
Started	710	701	1,411
Completed	675 (95.1)	663 (94.6)	1,338 (94.8)
Discontinued	35 (4.9)	38 (5.4)	73 (5.2)
Death	3 (0.4)	13 (1.9)	16 (1.1)
Lost to follow-up	10 (1.4)	8 (1.1)	18 (1.3)
Withdrawal by subject	22 (3.1)	16 (2.3)	38 (2.7)
Other	0	1 (0.1)	1 (0.1)

[a] Only participants who received at least one dose are included.
AE = adverse event
SOURCE: Jayk Bernal et al., 2022;[84] MSD 2022 MOVe-OUT CSR 7-month data.[144]

B.2.3.6 MOVe-OUT: Demographics and baseline characteristics

Participant baseline characteristics were generally similar between treatment groups (Table 10).[84] The study enrolled a diverse global participant population representative of patients likely to receive treatment with molnupiravir for COVID-19.[84]

- More than half of participants were female (51.3%) and of White race[viii] (56.7%) and 49.6% were of Hispanic or Latino ethnicity.
- The median participant age for the overall study population was 43.0 years (range: 18 to 90 years), with 17.2% over 60 years of age.
- Approximately half (47.7%) of participants had COVID-19 symptom onset ≤ 3 days prior to randomisation.
- Most participants had mild (54.8%) versus moderate (44.5%) symptoms of COVID-19 at baseline.

[viii] Race and ethnicity were reported separately in the MOVe-OUT trial.

- Almost all participants (99.4%) had at least one risk factor for developing severe COVID-19 (see Table 7 for risk factors).
    - The most commonly reported risk factor was obesity (BMI ≥ 30; 73.7%) followed by > 60 years of age (17.2%), diabetes mellitus (15.9%) and serious heart condition (11.7%).

Table 10. Patient characteristics in the MOVe-OUT trial (final analysis)

	Molnupiravir	Placebo	Total
N	716	717	1,433
Male sex, n (%)	332 (46.4)	366 (51.0)	698 (48.7)
Age[a], years			
Mean (SD)	44.4 (14.6)	45.3 (15.0)	44.8 (14.8)
Median	42.0	44.0	43.0
Range	18, 90	18, 88	18, 90
Race[a], n (%)			
American Indian or Alaska Native	60 (8.4)	44 (6.1)	104 (7.3)
Asian	26 (3.6)	23 (3.2)	49 (3.4)
Black or African American	40 (5.6)	35 (4.9)	75 (5.2)
White	400 (55.9)	413 (57.6)	813 (56.7)
Multiple	190 (26.5)	202 (28.2)	392 (27.4)
Ethnicity, n (%)			
Hispanic/Latino	355 (49.6)	356 (49.7)	711 (49.6)
Not Hispanic/Latino	355 (49.6)	358 (49.9)	713 (49.8)
Not Reported	4 (0.6)	1 (0.1)	5 (0.3)
Unknown[b]	2 (0.3)	2 (0.3)	4 (0.3)
Region[a]			
North America	45 (6.3)	46 (6.4)	91 (6.4)
Latin America	331 (46.2)	330 (46.0)	661 (46.1)
Europe	230 (32.1)	239 (33.3)	469 (32.7)
Asia Pacific	20 (2.8)	17 (2.4)	37 (2.6)
Africa	90 (12.6)	85 (11.9)	175 (12.2)
Time from onset of symptoms[a], n (%)			
≤ 3 days	340 (47.5)	336 (46.9)	676 (47.2)
> 3 days	374 (52.2)	379 (52.9)	753 (52.5)
Unknown[b]	2 (0.3)	2 (0.3)	4 (0.3)
Mean (SD)	3.5 (1.0)	3.5 (1.0)	3.5 (1.0)
Risk factors for severe illness, n (%)			
At least one risk factor	712 (99.4)	712 (99.3)	1424 (99.4)
Age > 60 years	119 (16.6)	127 (17.7)	246 (17.2)
Active Cancer	13 (1.8)	16 (2.2)	29 (2.0)

	Molnupiravir	Placebo	Total
CKD	38 (5.3)	46 (6.4)	84 (5.9)
COPD	22 (3.1)	35 (4.9)	57 (4.0)
Obesity (BMI ≥ 30)[a]	538 (75.1)	518 (72.2)	1056 (73.7)
Serious Heart Condition	86 (12.0)	81 (11.3)	167 (11.7)
Diabetes Mellitus	107 (14.9)	121 (16.9)	228 (15.9)
Baseline COVID-19 severity[a], n (%)			
Mild	395 (55.2)	390 (54.4)	785 (54.8)
Moderate	315 (44.0)	323 (45.0)	638 (44.5)
Severe	3 (0.4)	1 (0.1)	4 (0.3)
Unknown[b]	3 (0.4)	3 (0.4)	6 (0.4)
SARS qualitative assay viral load at baseline[a]			
High VL (> 10^6 copies/mL)	389 (54.3)	383 (53.4)	772 (53.9)
Low VL (500 to ≤ 10^6 copies/mL)	162 (22.5)	163 (22.7)	324 (22.6)
Undetectable (< 500 copies/mL)	64 (8.9)	71 (9.9)	135 (9.4)
Unknown[b]	102 (14.2)	100 (13.9)	202 (14.1)

[a] Baseline characteristics in which subgroup analyses of the primary endpoint were conducted.
[b] Missing data, invalid sample, tests not completed or results reported as "Unknown" are categorised as Unknown.
BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; SARS = severe acute respiratory syndrome; SD = standard deviation; VL = viral load
SOURCE: Jayk Bernal et al., 2022.(84)

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 MOVe-OUT: Study populations

All efficacy endpoints were assessed in two study populations:(76, 84)

- The main assessment of efficacy endpoints was conducted on the modified intent-to-treat (MITT) population, which consisted of all randomised patients who received at least one dose of study intervention and who were not hospitalised prior to administration of the first dose of study intervention.
- The supportive assessment of efficacy endpoints was conducted on the per-protocol (PP) population, which excluded patients based on deviations from the protocol and, therefore, may have affected the results of the primary efficacy endpoint.

Results of efficacy analyses in the PP population were consistent with the findings in the MITT population, therefore, this submission presents efficacy endpoint results for only the MITT population.

At the interim analyses, 775 patients had been randomised, of which 762 patients were included in the MITT population (molnupiravir: n=385; placebo: n=377). The PP population included 722 randomised patients (molnupiravir: n=368; placebo: n=354).[76]

At final analysis, a total of 1,433 patients had been randomised, of which 1,408 were included in the MITT population (molnupiravir: n=709; placebo: n=699) and 1,344 were included in the PP population (molnupiravir: n=679; placebo: n=665).[76, 84]

Safety analyses were based on the all-participants-as-treated (APaT) population, which included all randomised patients in the study who received at least one dose of study intervention.[76] The interim APaT population included 765 randomised patients and the final APaT population included 1,411 randomised patients.[76]

B.2.4.2 MOVe-OUT: Statistical analyses

The interim efficacy analyses were conducted when 50% of the anticipated phase III enrolment population was followed-up to Day 29.[76] The analyses consisted of the interim analysis (IA) 3 and IA4, which were conducted simultaneously:[76]

- **IA3:** primary purpose of assessing the need for sample size re-estimation (conducted when 30% to 50% of the planned enrolment had completed the Day 29 visit)
- **IA4:** planned to assess futility and early efficacy of molnupiravir (conducted when approximately 50% of the planned enrolment population had completed the Day 29 visit).

The prespecified statistical criterion for the primary efficacy endpoint (hospitalisation or death at Day 29) was met at the interim analyses (p=0.0012; one-sided p-value boundary < 0.0092) and the study's formal evaluation of efficacy was considered complete.[76] Thus, assessment of the primary efficacy endpoint at the final analysis is supportive of the analyses reported at the interim analyses timepoint.[76] Refer to Section B.2.6.1 for primary efficacy endpoint results at both interim and final analyses.

See Table 11 for a summary of the statistical analyses performed in the MOVe-OUT trial.

Table 11. Summary of statistical analyses in the MOVe-OUT trial

Trial number (NCT04575597)	MOVe-OUT
Hypothesis objective	Molnupiravir is superior to placebo as assessed by the percentage of participants who are hospitalised and/or die through Day 29.
Statistical analysis	The Miettinen and Nurminen method, stratified by randomisation strata, was used for the primary efficacy endpoint. The Cox regression model with Efrons' method of tie handling, with treatment and randomisation stratification factor as covariates, was also employed. The secondary endpoints of time to sustained improvement or resolution and time to progression was analysed using the Cox regression model with Efrons' method of tie handling, with treatment and randomisation stratification factor as covariates. Analyses for the secondary endpoint of response on the WHO 11-point ordinal scale were based on the proportional odd model with WHO-11 score categories as the response variable. The final model only included treatment as covariate due to sparse data. P-values were based on the Wald Chi-quare test. For the exploratory endpoint of acute care visits, analyses of the one-sided p-values were based on the Miettinen & Nurminen method stratified by randomisation strata.

WHO = World Health Organization
SOURCE: MSD 2022 MOVe-OUT CSR 7-month data.[144]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

B.2.5.1 Risk of bias assessment: RCT evidence base

The quality of unique trials included in the SLR was assessed using the Cochrane Risk of Bias assessment tool (RoB2) for RCTs[145] to confirm that trial publications were suitable for later use in the NMA. The quality assessment of the RCT studies rated seven out of the 14 included studies as 'low risk' with respect to bias, including MOVe-OUT, as shown in Table 12**.** Three studies were rated as being 'high risk'. One molnupiravir trial (DAWN; NCT04730206) was deemed not feasible for inclusion in the NMA due to early termination of the trial and small sample sizes in the treatment arms.

Further details of the risk of bias assessment can be found in Appendix D.1.

Table 12. Quality assessment of RCTs based on NICE checklist

Trial name and identifier	Overall assessment
MOVe-OUT (NCT04575597)	Low risk
(NCT04405570)	Low risk
AGILE CST-2 (NCT04746183)[81]	Low risk
CTRI/2021/05/033739	Some concerns
PANORAMIC (ISRCTN30448031)	Some concerns
(CTRI/2021/07/034588)	Some concerns
PLATCOV (NCT05041907)	Low risk
DAWN (NCT04730206)	High risk
PLATCOV (NCT05041907)	Some concerns
PINETREE (NCT04501952)	Low risk
EPIC-HR (NCT04960202)	Low risk
EPIC-SR (NCT05011513)	High risk[a]
COMET-ICE (NCT04545060)	Low risk
MONET (EudraCT:2021-004188-28)	High risk[a]

[a] Despite these studies being rated as high risk in the risk of bias assessment, they were still included in the NMA.
NICE = National Institute for Health and Care Excellence; RCT = randomised controlled trial
SOURCE: RCT SLR (see Appendix D.1)

B.2.5.2 Risk of bias assessment: RWE studies

The quality assessment of the RWE studies, based on the NICE checklist, rated 27 out of the 30 included studies as 'low concern' with respect to bias, as shown in Further details of the risk of bias assessment can be found in Appendix D.2.

Table 13. For three studies there were 'issues for concern' regarding the lack of adjustment for differences between cohorts or missing information on the criteria used to match study cohorts in terms of baseline risk. It was recommended that these three studies were excluded from the analyses.

Further details of the risk of bias assessment can be found in Appendix D.2.

Table 13. Quality assessment of RWE studies based on NICE checklist

Study Name	Overall Assessment
Aggarwal, 2023[136]	Low concern
Arbel, 2023[126]	Low concern
Bajema, 2023[137]	Low concern
Basoulis, 2023[124]	Low concern
Bruno 2022[146]	Issues for concern
Butt, 2023a[138]	Low concern
Butt, 2023b[139]	Low concern
Cegolon, 2023[130]	Low concern
Cowman, 2023[140]	Low concern
Del Borgo, 2023[131]	Low concern
Dryden-Peterson, 2023[141]	Low concern
Gentry, 2023[117]	Low concern
Kabore, 2023[121]	Low concern
Lin, 2023[142]	Low concern
Manciulli, 2023[132]	Low concern
Martin-Blondel, 2023[123]	Issues for concern
Mazzitelli, 2023[133]	Low concern
Minoia, 2023[118]	Low concern
Najjar-Debbiny, 2023[127]	Low concern
Najjar-Debbiny, 2023[128]	Low concern
Paraskevis, 2023[116]	Low concern
Petrakis, 2023[125]	Issues for concern
Qian 2023[119]	Low concern
Schwartz, 2023[122]	Low concern
Tiseo, 2023[134]	Low concern
Zheng, 2022[120]	Low concern
Zheng, 2023[66]	Low concern
Van Heer, 2023[115]	Low concern
Torti, 2023[135]	Low concern
Xie, 2023[143]	Low concern

NICE = National Institute for Health and Care Excellence; RWE = real-world evidence
SOURCE: RWE SLR (see Appendix D.2)

B.2.6 Clinical effectiveness results of the relevant studies

The primary efficacy outcomes from MOVe-OUT for all randomised patients support the hypothesis that treatment with molnupiravir is superior to placebo for reducing the incidence of all-cause hospitalisation or death through Day 29 for patients with SARS-CoV-2 infection with symptoms of COVID-19 and at risk of progressing to severe disease.[84] Treatment with molnupiravir was associated with a 3.0 percentage-point reduction (approximately a 30%

relative risk reduction) in the incidence of all-cause hospitalisation or death through Day 29 compared to placebo (Table 14).[84]

Results from the secondary efficacy endpoints of MOVe-OUT demonstrated that treatment with molnupiravir is associated with improved clinical outcomes through Day 29 compared to placebo, as assessed by self-reported COVID-19 signs/symptoms and the WHO 11-point ordinal scale (Figure 3; Figure 4; Table 17).[84]

B.2.6.1 MOVe-OUT: Primary efficacy endpoint: all-cause hospitalisation or death

B.2.6.1.1 Interim analyses through Day 29 (MITT population)

Molnupiravir met the protocol-defined criterion (one-sided p-value boundary < 0.0092) for superiority over placebo at the interim analyses for the primary efficacy endpoint through Day 29.[84]

- The proportion of patients who were hospitalised for any cause or died from study initiation to Day 29 was statistically significantly lower in the molnupiravir group (28 patients; 7.3%) versus placebo group (53 patients; 14.1%), corresponding to a 6.8 percentage-point reduction (95% CI: -11.3, -2.4; one-sided p=0.0012; approximately 50% relative risk reduction).
- All participants who died from study initiation to Day 29 were in the placebo group (8 patients; 2.1%).

B.2.6.1.2 Final analysis through Day 29 (MITT population)

Assessment of the primary efficacy endpoint at final analysis through Day 29 was supportive of the results at the interim analyses (Table 14).[76, 84] However, the differences in results between the interim and final analyses reflect that the trial could not be conducted under uniform conditions throughout the study duration.[147] Several factors such as shifts in circulating SARS-CoV-2 variants, changes in community/outpatient management and inclusion of trial sites from countries with different COVID-19 disease burdens could not be kept constant, despite a consistent trial design.[147]

- The proportion of patients who were hospitalised for any cause or died from study initiation to Day 29 was lower in the molnupiravir group (48 patients; 6.8%) versus placebo group (68 patients; 9.7%), corresponding to a 3.0 percentage-point reduction (95% CI: -5.9, -0.1; one-sided p=0.0218; approximately 30% relative risk reduction).

- Nine participants (1.3%) in the placebo group and one participant (0.1%) in the molnupiravir group died from study initiation to Day 29.

Table 14. Primary efficacy endpoint results: Hospitalisation or death at Day 29 (MITT population; final analysis)

MOVe-OUT outcome	Molnupiravir (n = 709), n (%)	Placebo (n = 699), n (%)	Molnupiravir versus placebo		
			Unadjusted difference	Adjusted difference in rates, % (95% CI)[a]	p-value
Proportion hospitalised for any cause and/or died from study initiation to Day 29					
Hospitalisation for any cause or death	48 (6.8)	68 (9.7)	-3.0	-3.0 (-5.9, -0.1)	0.0218
Hospitalisation for any cause	48 (6.8)	67 (9.6)	-	-	-
Death	1 (0.1)	9 (1.3)	-	-	-
Unknown Day 29 survival status[b]	0	1 (0.1)	-	-	-

[a] Adjusted differences, the corresponding confidence intervals and the one-sided p-values are based on Miettinen & Nurminen method stratified by randomisation strata.
[b] Unknown survival status at Day 29 was counted as having an outcome of hospitalisation or death in the primary efficacy analysis.
CI = confidence interval; COVID-19 = coronavirus disease 2019; MITT = modified intent-to-treat
SOURCE: MSD 2022 MOVe-OUT CSR;[76]; Jayk Bernal et al., 2022.[84]

B.2.6.1.3 Final Analysis Day 30 to Month 7 (MITT population)

Final analysis of the primary endpoint at Month 7 was consistent with analysis at Day 29, demonstrating improved efficacy of molnupiravir compared with placebo to treat mild to moderate COVID-19 in adults with a positive SARS-CoV-2 diagnostic test:[144]

- The proportion of patients who died from any cause from Day 30 to Month 7 was lower in the molnupiravir group (3 patients; 0.4%) versus the placebo group (6 patients; 0.6%).
    - One death in the molnupiravir group was considered to be COVID-19 related compared to two deaths in the placebo group.
- Fewer patients were hospitalised for any cause from Day 30 to Month 7 in the molnupiravir group (2 patients; 0.3%) versus the placebo group (3 patients; 0.4%).

B.2.6.2 MOVe-OUT: Secondary efficacy endpoint: sustained resolution or improvement of COVID-19 signs/symptoms through Day 29 (MITT population)

Results for the secondary efficacy endpoint of self-reported COVID-19 signs/symptoms from study initiation to Day 29 showed that sustained resolution or improvement was more likely for patients treated with molnupiravir versus placebo (hazard ratio [HR] > 1 favours the molnupiravir group; Table 15):[76, 84]

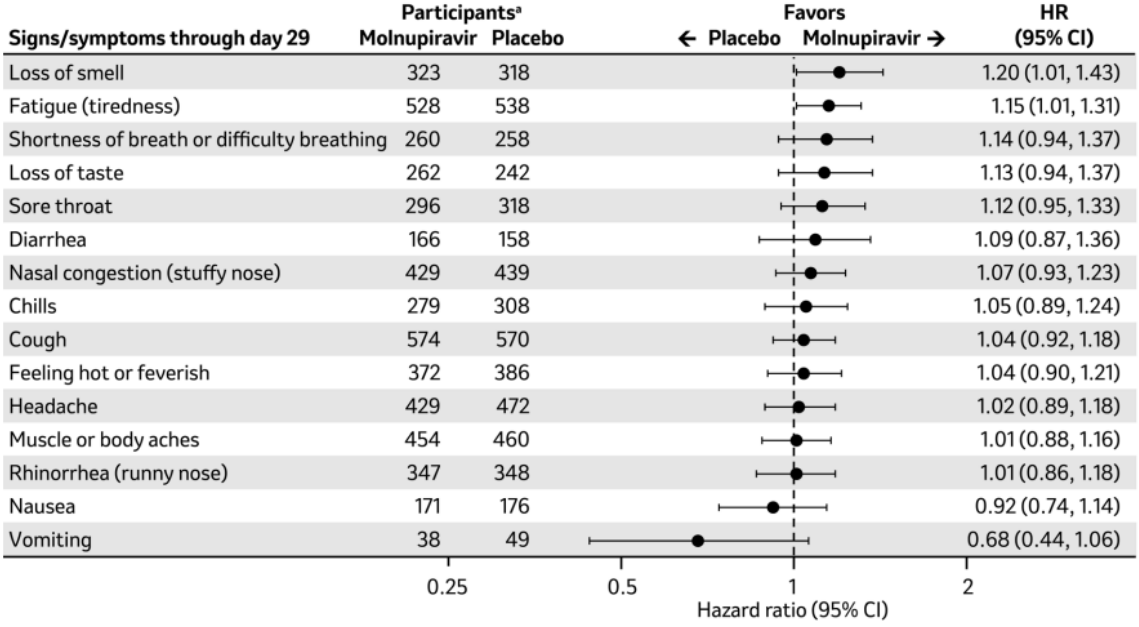
- The most notable difference between treatment groups was for loss of smell and fatigue (HR: 1.2 [95% CI: 1.01, 1.43] and HR: 1.15 [95% CI: 1.01, 1.31], respectively).
- A greater proportion of patients receiving molnupiravir reported sustained resolution or improvement versus placebo for any of the self-reported COVID-19 signs/symptoms at Day 29 (99.5% versus 99.0%).

Table 15. Time to sustained improvement or resolution of any sign or symptom through Day 29 (MITT population; final analysis)

	Molnupiravir (n = 706)	Placebo (n = 694)	Molnupiravir versus placebo	
			Hazard ratio (95% CI)[b]	p-value[c]
Number of events (%)	694 (98.3)	679 (97.8)	1.10 (0.99, 1.23)	0.0331
Person-day	2185.0	2388.0		
Event rate/100 person-days	31.8	28.4		
Median time to improvement or resolution (days, 95% CI)	2.0 (NA)	2.0 (NA)		
Improvement or resolution rate at Day 29, % (95% CI)[a]	99.5 (98.6, 99.9)	99.0 (98.0, 99.6)		

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on stratified Cox regression model with Efron's method of tie handling with treatment as covariates and randomisation stratum as the stratification factor. Hazard ratio > 1 favours the MK-4482 800 mg group.
[c] One-sided p-value based on log-rank test stratified by randomisation stratification stratum.
CI = confidence interval; NA = not applicable
SOURCE: MSD 2022 MOVe-OUT CSR.(76)

Figure 3. Secondary efficacy endpoint results: Time to sustained improvement or resolution of signs and symptoms through Day 29 (MITT population; final analysis)



Based on Cox regression model with Efron's method of tie handling with treatment and randomisation stratification factor as covariates. Hazard ratio > 1 favours the molnupiravir group.
[a] Number of participants eligible for sustained improvement or resolution (i.e., those who had the corresponding sign or symptom at baseline [at any severity]) in the MITT population.
CI = confidence interval; HR = hazard ratio; MITT = modified intent-to-treat
SOURCE: Jayk Bernal et al., 2022.(84)

B.2.6.3 MOVe-OUT: Secondary efficacy endpoint: progression of each targeted self-reported sign/symptom of COVID-19 through Day 29 (MITT population)

Results for the secondary efficacy endpoint of time to progression of self-reported COVID-19 signs/symptoms from study initiation to Day 29 showed that progression was less likely for patients treated with molnupiravir versus placebo (HR < 1 favours the molnupiravir group; Table 16; Figure 4), although the differences did not reach statistical significance:[76, 84]

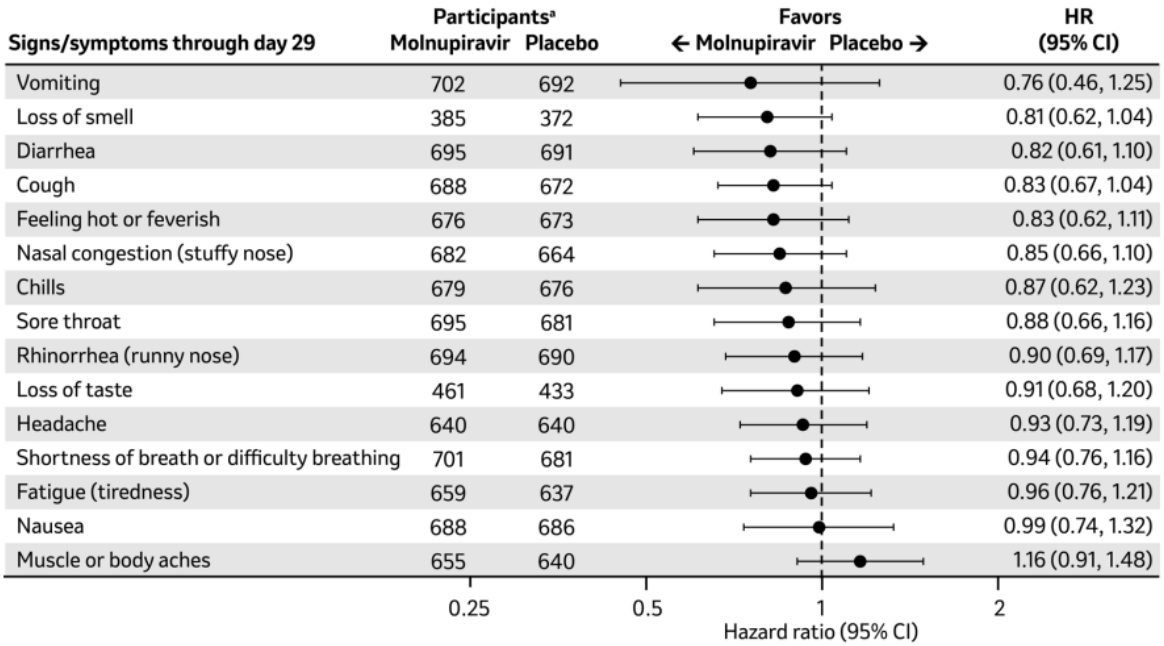
- The most notable difference between treatment groups was for vomiting and loss of smell (HR: 0.76 [95% CI: 0.46, 1.25] and HR: 0.81 [95% CI: 0.62, 1.04], respectively).
- A lower proportion of patients receiving molnupiravir reported progression versus placebo for any of the self-reported COVID-19 signs/symptoms at Day 29 (72.8% versus 75.3%).

Table 16. Time to progression of any sign or symptom through day 29 (MITT population; final analysis)

	Molnupiravir (n = 706)	**Placebo (n = 696)**	**Molnupiravir versus placebo**	
			Hazard ratio (95% CI)[b]	p-value[c]
Number of events (%)	512 (72.4)	520 (74.7)	0.92 (0.81, 1.04)	0.0955
Person-day	7238.0	6707.0		
Event rate/100 person-days	7.1	7.8		
Median time to progression (days, 95% CI)[a]	3.0 (NA)	3.0 (2.0, 3.0)		
Progression rate at Day 29, % (95% CI)[a]	72.8 (69.5, 76.1)	75.3 (72.0, 78.4)		

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on stratified Cox regression model with Efron's method of tie handling with treatment as covariates and randomisation stratum as the stratification factor. Hazard ratio < 1 favours the MK-4482 800 mg group.
[c] One-sided p-value based on log-rank test stratified by randomisation stratification stratum.
CI = confidence interval; NA = not applicable
SOURCE: MSD 2022 MOVe-OUT CSR.[76]

Figure 4. Secondary efficacy endpoint results: Time to progression of signs and symptoms through Day 29 in (MITT population)



Based on Cox regression model with Efron's method of tie handling with treatment and randomisation stratification factor as covariates. Hazard ratio < 1 favours the molnupiravir group.
[a] Number of participants at risk for progression (i.e., those without the sign or symptom at baseline or had the sign or symptom at baseline at mild or moderate severity) in the MITT population.
CI = confidence interval; HR = hazard ratio; MITT = modified intent-to-treat
SOURCE: Jayk Bernal et al., 2022.[84]

B.2.6.4 MOVe-OUT: Secondary efficacy endpoint: WHO 11-point ordinal scale on Day 3, EOT, Day 10, Day 15 and Day 29 (MITT population)

Results from the secondary efficacy endpoint of response on the WHO 11-point ordinal scale from study initiation to Day 29 showed that a lower proportion of patients treated with molnupiravir had poor outcomes on the scale versus placebo, with the largest observed differences by Days 10 and 15 (Table 17).[84]

- Prior to treatment, the majority of patients (> 98.0%) across treatment groups had a baseline WHO 11-point ordinal scale score of 2, indicating mild disease.
- When WHO 11-point ordinal scale scores were categorised (0 [Uninfected], 1-3 [ambulatory, mild disease], 4-5 [hospitalised, moderate disease], 6-9 [hospitalised, severe disease], 10 [death]), the odds of an improved outcome were 1.58 times higher for patients treated with molnupiravir compared to placebo at Day 10.

Table 17. Changes in WHO clinical progression scale (MITT population)

Visit	Score category	Molnupiravir (n=709)	Placebo (n=699)
		n/N (%)	n/N (%)
Baseline	0 1-3 4-5 6-9 10 Missing	0/706 (0) 706/706 (100) 0/706 (0) 0/706 (0) 0/706 (0) 3	0/695 (0) 695/695 (100) 0/695 (0) 0/695 (0) 0/695 (0) 4
Day 3	0 1-3 4-5 6-9 10 Missing	2/695 (0.3) 679/695 (97.7) 11/695 (1.6) 3/695 (0.4) 0/695 (0) 14	3/684 (0.4) 663/684 (96.9) 17/684 (2.5) 1/684 (0.1) 0/684 (0) 15
	Odds ratio (95% CI)	1.19 (0.62, 2.30)	
Day 5	0 1-3 4-5 6-9 10 Missing	11/697 (1.6) 663/697 (95.1) 17/697 (2.4) 6/697 (0.9) 0/697 (0) 12	10/684 (1.5) 636/684 (93.0) 34/684 (5.0) 4/684 (0.6) 0/684 (0) 15
	Odds ratio (95% CI)	1.52 (0.96, 2.39)	
Day 10	0 1-3 4-5 6-9 10 Missing	40/673 (5.9) 599/673 (89.0) 27/673 (4.0) 7/673 (1.0) 0/673 (0) 36	32/673 (4.8) 580/673 (86.2) 44/673 (6.5) 17/673 (2.5) 0/673 (0) 26
	Odds ratio (95% CI)	1.58 (1.14, 2.20)	
Day 15	0 1-3 4-5 6-9 10 Missing	102/669 (15.2) 548/669 (81.9) 15/669 (2.2) 4/669 (0.6) 0/669 (0) 40	94/667 (14.1) 525/667 (78.7) 33/667 (4.9) 10/667 (1.5) 5/667 (0.7) 32
	Odds ratio (95% CI)	1.36 (1.03,1.78)	
Day 29	0 1-3 4-5 6-9 10 Missing	312/645 (48.4) 324/645 (50.2) 6/645 (0.9) 2/645 (0.3) 1/645 (0.2) 64	314/650 (48.3) 314/650 (48.3) 12/650 (1.8) 1/650 (0.2) 9/650 (1.4) 49
	Odds ratio (95% CI)	1.04 (0.84, 1.29)	

Odds ratio > 1 favours molnupiravir over placebo.
CI = confidence interval
SOURCE: Jayk Bernal et al., 2022.[84]

B.2.7 Subgroup analysis

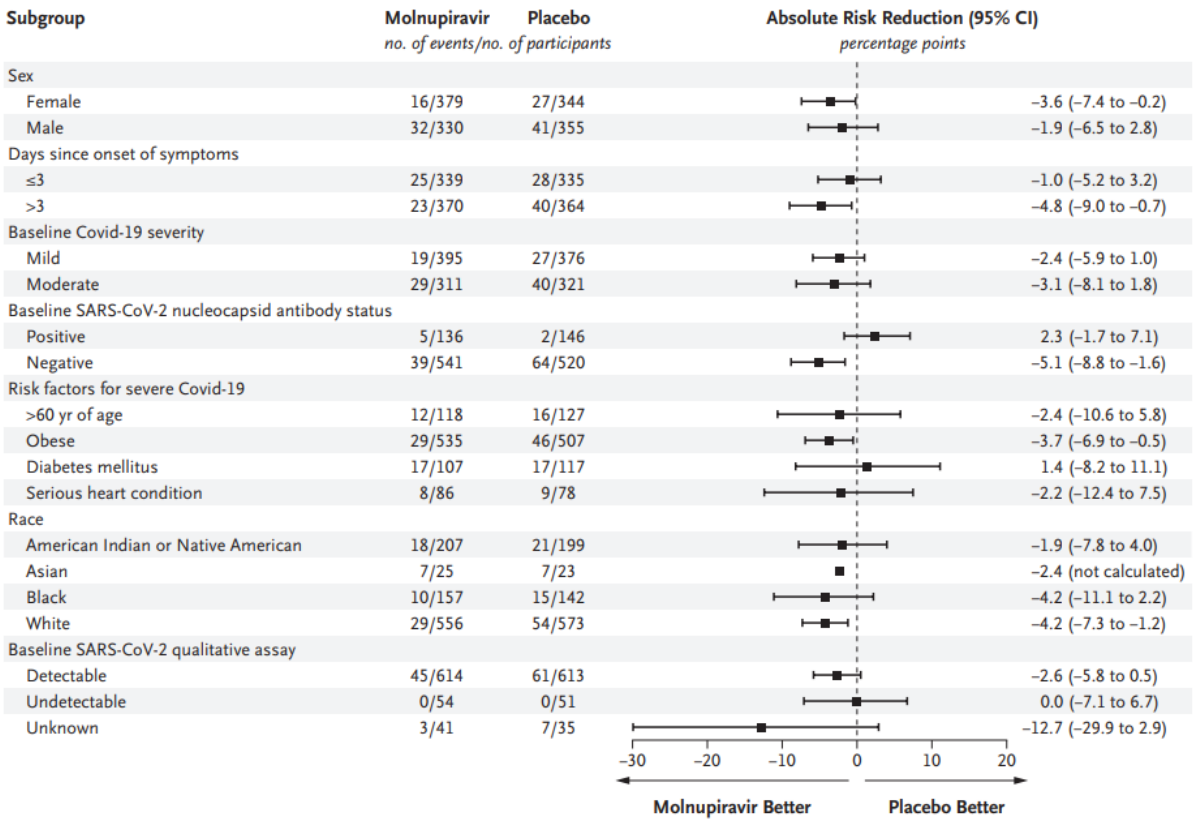
B.2.7.1 MOVe-OUT

Subgroup analyses of the primary efficacy endpoint were consistent with the primary analysis (Section B.2.6.1).[84] As described in Section B.1.1 , the subgroups of interest in the NICE scope were those: aged > 70 years; contraindicated to nirmatrelvir plus ritonavir; who were immunosuppressed; and those with chronic kidney disease.

Treatment with molnupiravir resulted in reduced risk of all-cause hospitalisation or death at Day 29 versus placebo for most subgroups assessed based on prespecified baseline characteristics. Subgroups for which molnupiravir was not associated with an improvement in hospitalisation or death were diabetes mellitus, baseline SARS-CoV-2 nucleocapsid antibody status and undetectable baseline SARS-CoV-2 qualitative assay subgroups (Figure 5).[84] The result reached statistical significance for the subgroup of obesity (3.7-point different [95% CI: -6.9, -0.5]) and favoured molnupiravir for those aged > 60 years (2.4-point difference [95% CI: -10.6, 5.8]) and with serious heart conditions (2.2-point difference [95% CI: -12.4, 7.5]), both of which are risk factors associated with progression to severe disease (see Appendix E).

MOVe-OUT was not powered to detect a difference in treatment effect in subgroups.

Figure 5. Primary efficacy endpoint results: Hospitalisation or death at Day 29 by subgroup (MITT population; final analysis)



The corresponding confidence interval is based on Miettinen & Nurminen method.
Time from symptom onset to randomisation is based on the value of the stratification factor collected at randomisation.
CI = confidence interval; COVID-19 = coronavirus disease 2019; MITT = modified intent-to-treat; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SOURCE: Jayk Bernal et al., 2022.[84]

B.2.8 Meta-analysis

Clinical effectiveness results from MOVe-OUT are presented in Section B.2.6

In the course of this submission, the SLR identified another RCT reporting the efficacy of molnupiravir in the treatment of mild to moderate COVID-19 in patients at risk of developing severe illness in the UK setting.

A formal pairwise meta-analysis was not conducted between studies comparing molnupiravir versus placebo due to the results of the feasibility assessment, study differences and the assumptions necessary as a result of inherent data limitations. Further, a single meta-analysis for molnupiravir versus placebo would not be sufficient to address the decision problem.

However, based on our current NMA of RCT evidence, molnupiravir is directly linked to placebo in all outcome networks. Therefore,estimates of molnupiravir versus placebo can be interpreted as a meta-analysed effect sizes. Given this, results comparing molnupiravir and

placebo in all pairwise comparison tables (see odds ratios and risk ratios presented in Section B.2.9.1) are considered direct evidence. As a result, MSD have not conducted a meta-analysis of molnupiravir studies.

B.2.9 Indirect and mixed treatment comparisons

As described in Section B.2.1.1 both RCT and RWE SLRs were conducted to identify evidence on the efficacy and safety of molnupiravir versus no treatment and existing treatments in COVID-19 (see Appendix D.1 for further details on methods and results). Due to the continual changes in COVID-19 epidemiology, it was deemed appropriate to conduct an RWE SLR in addition to an RCT SLR to identify efficacy and safety evidence of treatments for adults with mild to moderate COVID-19 and at increased risk of progressing to severe disease in the community/outpatient setting.

A feasibility assessment was conducted to establish the viability of a NMA for indirect comparison of efficacy and safety outcomes of interest between molnupiravir and other active treatments (nirmatrelvir plus ritonavir, sotrovimab and remdesivir) for mild to moderate COVID-19 in a community/outpatient setting. Results from the feasibility assessments deemed 11 of 14 studies from the RCT SLR and 22 of 30 studies from the RWE SLR to be suitable for inclusion in NMAs.

Following the feasibility assessment, NMAs of RCT and RWE data were used to estimate relative treatment effects between molnupiravir versus other treatments among adult patients with COVID-19. Bayesian NMAs were conducted to provide fixed effects and random effects models and these models were fitted to account for assumptions regarding heterogeneity of treatment effects. Since there was a considerable amount of clinical heterogeneity across studies, a random effects model was chosen *a priori* as the base case for the NMA of RWE data. Whereas in the NMA of RCT data, the random effects model was deemed unstable because most networks consisted of a limited number of studies, therefore, results reported in the base case corresponded to the fixed effects models given that these models provided more stable results (i.e., more reliable posterior distributions) and generally a better fit to the data.

MSD acknowledge that due to a relatively small number of trials included in the networks derived from RCTs, it was infeasible to conduct analyses using random effects models to account for between-trial heterogeneity of treatment effects, which could potentially contribute to the wider credible intervals (CrIs) presented in results below. See Section B.2.9.4 for further discussion of inherent limitations in the NMAs.

B.2.9.1 RCT network meta-analysis

The RCT SLR yielded a total of 14 studies that evaluated four community/outpatient COVID-19 treatments (molnupiravir, nirmatrelvir plus ritonavir, sotrovimab and remdesivir), of which 11 were deemed suitable for analysis in the NMA.

Results of the NMA demonstrated that across treatments, patients receiving molnupiravir had a comparable (non-significantly different) risk of all-cause hospitalisation, COVID-19 related hospitalisation or death than those receiving nirmatrelvir plus ritonavir, remdesivir or sotrovimab. However, molnupiravir was demonstrated to be a superior alternative to no treatment, associated with a lower risk of all-cause hospitalisation, COVID-19 related hospitalisation or death when compared with placebo. Limited RCT data reported across most studies precludes further statistical interrogation with more sophisticated methods to adjust for any residual differences in baseline risk for disease severity (or explore subgroup analyses specified within the final NICE scope).

B.2.9.1.1 Efficacy results: All-cause hospitalisation or death

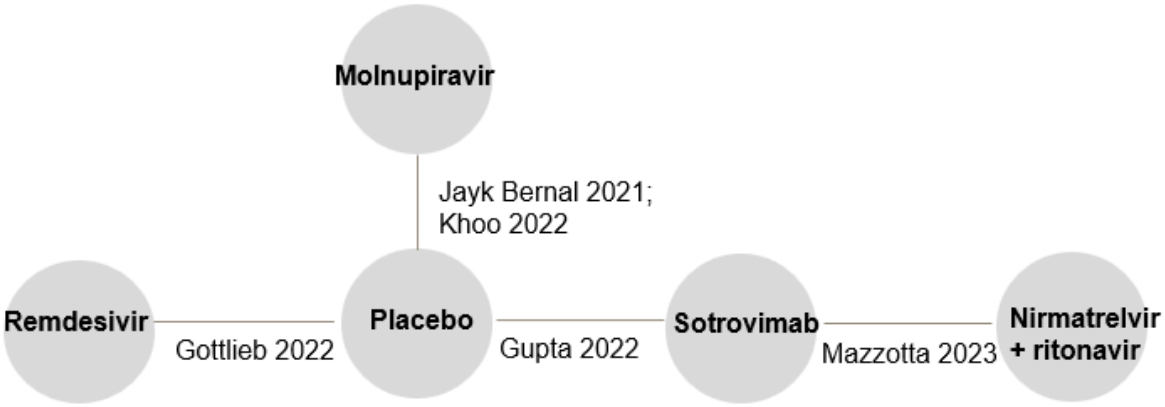
Four trials (two evaluating molnupiravir, one evaluating remdesivir, one evaluating sotrovimab) comparing an intervention with placebo or usual care and a fifth trial assessing nirmatrelvir plus ritonavir versus sotrovimab were included in the analysis of all-cause hospitalisation or death through Day 28 or Day 29 after randomisation (Table 18; Figure 6).

Table 18. Identified clinical trials and interventions of interest: All-cause hospitalisation or death

Intervention	Trial	Country	Publication (author/year)	Dosing
Studies that included molnupiravir as an intervention				
Molnupiravir versus placebo	MOVe-OUT (NCT04575597)	Global	Jayk Bernal 2021	• 800 mg orally every 12 hours for 5 days
	AGILE CST-2 (NCT04746183)	UK	Khoo 2022	
Studies that did not include molnupiravir as an intervention				
Remdesivir versus placebo	PINETREE (NCT04501952)	US, UK, Spain, Denmark	Gottlieb 2022	• 200 mg IV Day 1 and 100 mg IV Days 2-3
Sotrovimab versus placebo	COMET-ICE (NCT04545060)	US, Canada, Brazil, Peru, Spain	Gupta 2022	• 500 mg IV, single dose
Nirmatrelvir plus ritonavir versus sotrovimab	MONET (EudraCT:2021-004188-28)	Multinational	Mazzotta 2023	• 500 mg IV, single dose

IV = intravenous; UK = United Kingdom; US = United States
SOURCE: RCT SLR (see Appendix D.1)

Figure 6. Network for all-cause hospitalisation or death



SOURCE: RCT SLR (see Appendix D.1)

The total number of patients and the number/proportion of patients with all-cause hospitalisation or death in each trial arm are summarised in Table 19. Comparing across treatments, patients receiving molnupiravir had a higher risk of all-cause hospitalisation or death than those receiving nirmatrelvir plus ritonavir, sotrovimab or remdesivir. However, compared with placebo, proportions of patients with all-cause hospitalisation or death by Day 28 or Day 29 were lower for those receiving molnupiravir, nirmatrelvir plus ritonavir, sotrovimab or remdesivir (Table 20).

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.1.

See Section B.2.6.1 for all-cause hospitalisation or death results for patients treated with molnupiravir in the MOVe-OUT trial.

Table 19. Event rates for the analysis of all-cause hospitalisation or death

Trial name / Author and year	Treatment	Outcome	Sample size	Event rate (%)
Gottlieb 2022	Placebo	18	283	6.36
	Remdesivir	5	279	1.79
Gupta 2022	Placebo	30	529	5.67
	Sotrovimab	6	528	1.14
Jayk Bernal 2021	Placebo	68	699	9.73
	Molnupiravir	48	709	6.77
Khoo 2022	Placebo	4	90	4.44
	Molnupiravir	0	90	0.00
Mazzotta 2023[a]	Nirmatrelvir plus ritonavir	1	139	0.72
	Sotrovimab	2	135	1.48

[a] In Mazzotta 2023, 0 event was reported in the nirmatrelvir + ritonavir arm. To allow for estimation of this NMA, a correction was applied to Mazzotta 2023 by adding 1 to the number of event and 2 to the number of patients at risk (i.e., sample size) for both arms for this trial.

SOURCE: RCT SLR (see Appendix D.1)

Table 20. Odds ratio and risk ratio of all-cause hospitalisation or death of each treatment versus placebo

	Odds ratio versus placebo			Risk ratio versus placebo		
Treatment	**Mean**	**Median**	**95% CrI**	**Mean**	**Median**	**95% CrI**
Molnupiravir	0.64	0.63	(0.43, 0.92)	0.66	0.65	(0.45, 0.93)
Remdesivir	0.29	0.26	(0.08, 0.66)	0.30	0.27	(0.09, 0.68)
Sotrovimab	0.20	0.18	(0.07, 0.42)	0.21	0.20	(0.07, 0.44)
Nirmatrelvir plus ritonavir	0.19	0.07	(0.00, 1.07)	0.19	0.08	(0.00, 1.07)

CrI = credible interval
SOURCE: RCT SLR (see Appendix D.1)

B.2.9.1.2 Efficacy results: COVID-19 related hospitalisation or death

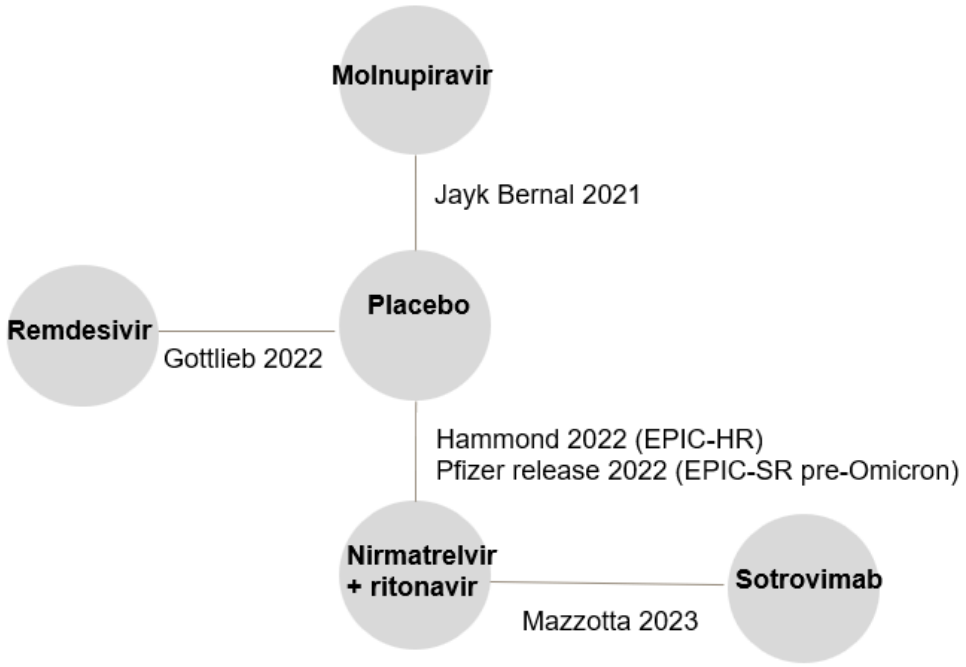
Four trials (one evaluating molnupiravir, two evaluating nirmatrelvir plus ritonavir and one evaluating remdesivir) comparing an intervention with placebo or usual care and a fifth trial assessing nirmatrelvir plus ritonavir versus sotrovimab were included in the analysis of COVID-19 related hospitalisation or death through Day 28 or 29 following randomisation (Table 21; Figure 7).

Table 21. Identified clinical trials and interventions of interest: COVID-19 related hospitalisation or death

Intervention	Trial	Country	Publication (author/year)	Dosing
Studies that included molnupiravir as an intervention				
Molnupiravir versus placebo	MOVe-OUT (NCT04575597)	Global	Jayk Bernal 2021	• 800 mg orally every 12 hours for 5 days
Studies that did not include molnupiravir as an intervention				
Nirmatrelvir plus ritonavir versus placebo	EPIC-HR (NCT04960202)	Global	Hammond 2022	• Two 150 mg nirmatrelvir tablets and one 100 mg ritonavir tablet, orally every 12 hours for 5 days
	EPIC-SR (NCT05011513)		Pfizer press release 2022	
Remdesivir versus placebo	PINETREE (NCT04501952)	US, UK, Spain, Denmark	Gottlieb 2022	• 200 mg IV Day 1 and 100 mg IV Days 2-3
Nirmatrelvir plus ritonavir versus sotrovimab	MONET (EudraCT:2021-004188-28)	Multinational	Mazzotta 2023	• 500 mg IV, single dose

COVID-19 = coronavirus disease 2019; IV = intravenous; UK = United Kingdom; US = United States
SOURCE: RCT SLR (see Appendix D.1)

Figure 7. Network for COVID-19 related hospitalisation or death



COVID-19 = coronavirus disease 2019
SOURCE: RCT SLR (see Appendix D.1)

The total number of patients and the number/proportion of patients with COVID-19 related hospitalisation or death in each trial arm are summarised in Table 22. Comparing across treatments, patients receiving remdesivir or nirmatrelvir plus ritonavir had similar risk of COVID-19 related hospitalisation or death, both of which were lower than those receiving sotrovimab and molnupiravir. However, compared with placebo, proportions of patients with COVID-19 related hospitalisation or death by Day 28 or Day 29 were lower for those receiving molnupiravir, remdesivir, nirmatrelvir plus ritonavir or sotrovimab (Table 23).

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.1.

See Section B.2.6.1 for COVID-19 related hospitalisation or death results for patients treated with molnupiravir in the MOVe-OUT trial.

Table 22. Event rates for the analysis of COVID-19 related hospitalisation or death

Trial name / Author and year	Treatment	Outcome	Sample size	Event rate (%)
Pfizer 2022 (EPIC-SR, pre-Omicron)	Placebo	10	426	2.35
	Nirmatrelvir plus ritonavir	3	428	0.70
Gottlieb 2022	Placebo	15	283	5.30
	Remdesivir	2	279	0.72
Hammond 2022 (EPIC-HR)	Placebo	44	682	6.45
	Nirmatrelvir plus ritonavir	5	697	0.72

Trial name / Author and year	Treatment	Outcome	Sample size	Event rate (%)
Jayk Bernal 2021	Placebo	64	699	9.16
	Molnupiravir	45	709	6.35
Mazzotta 2023[a]	Nirmatrelvir plus ritonavir	1	139	0.72
	Sotrovimab	2	135	1.48

[a] In Mazzotta 2023, 0 event was reported in the nirmatrelvir + ritonavir arm. To allow for estimation of this NMA, a correction was applied to Mazzotta 2023 by adding 1 to the number of event and 2 to the number of patients at risk (i.e., sample size) for both arms for this trial.
SOURCE: RCT SLR (see Appendix D.1)

Table 23. Odds ratio and risk ratio of COVID-19 related hospitalisation or death of each treatment versus placebo

	Odds ratio versus placebo			Risk ratio versus placebo		
Treatment	**Mean**	**Median**	**95% CrI**	**Mean**	**Median**	**95% CrI**
Molnupiravir	0.68	0.67	(0.45, 1.00)	0.70	0.68	(0.47, 1.00)
Nirmatrelvir plus ritonavir	0.14	0.13	(0.06, 0.27)	0.15	0.14	(0.06, 0.28)
Remdesivir	0.14	0.11	(0.02, 0.42)	0.15	0.12	(0.02, 0.44)
Sotrovimab[a]	2.96	0.33	(0.02, 11.62)	0.99	0.35	(0.02, 6.93)

[a] Due to wide CrIs, these results should be interpreted with caution.
COVID-19 = coronavirus disease 2019; CrI = credible interval
SOURCE: RCT SLR (see Appendix D.1)

B.2.9.1.3 Efficacy results: All-cause hospitalisation

Four trials (two evaluating molnupiravir, one evaluating remdesivir and one evaluating sotrovimab) comparing an intervention with placebo or usual care and a fifth trial assessing nirmatrelvir plus ritonavir versus sotrovimab were included in the analysis of all-cause hospitalisation through Day 28 or Day 29 following randomisation (Table 24; Figure 8).

Table 24. Identified clinical trials and interventions of interest: All-cause hospitalisation

Intervention	Trial	Country	Publication (author/year)	Dosing
Studies that included molnupiravir as an intervention				
Molnupiravir versus placebo	MOVe-OUT (NCT04575597)	Global	Jayk Bernal 2021	• 800 mg orally every 12 hours for 5 days
	AGILE CST-2 (NCT04746183)	UK	Khoo 2022	
Studies that did not include molnupiravir as an intervention				
Remdesivir versus placebo	PINETREE (NCT04501952)	US, UK, Spain, Denmark	Gottlieb 2022	• 200 mg IV Day 1 and 100 mg IV Days 2-3
Sotrovimab	COMET-ICE (NCT04545060)	US, Canada, Brazil, Peru, Spain	Gupta 2022	• 500 mg IV, single dose

Intervention	Trial	Country	Publication (author/year)	Dosing
Nirmatrelvir plus ritonavir versus sotrovimab	MONET (EudraCT:2021-004188-28)	Multinational	Mazzotta 2023	• 500 mg IV, single dose

IV = intravenous; UK = United Kingdom; US = United States
SOURCE: RCT SLR (see Appendix D.1)

Figure 8. Network for all-cause hospitalisation

The outcome of hospitalisation is not relevant for remdesivir as it can only be given while the patient is in hospital.
SOURCE: RCT SLR (see Appendix D.1)

The total number of patients and the number/proportion of patients with all-cause hospitalisation in each trial arm are summarised in Table 25. In the trial evaluating nirmatrelvir plus ritonavir versus sotrovimab (Mazzotta 2023), zero events were reported in the treatment arm of nirmatrelvir plus ritonavir, which is implausible. Therefore, to allow for estimation of this NMA, a zero-event correction was applied to this trial by adding one to the number of events and two to the number of patients at risk for both arms of this trial.

Comparing across treatments, patients receiving molnupiravir had a higher risk of all-cause hospitalisation than those receiving nirmatrelvir plus ritonavir, remdesivir or sotrovimab. However, compared with placebo, proportions of patients with all-cause hospitalisation by Day 28 or Day 29 were lower for those receiving molnupiravir, nirmatrelvir plus ritonavir, sotrovimab or remdesivir (Table 26).

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.1.

See Section B.2.6.1 for all-cause hospitalisation results for patients treated with molnupiravir in the MOVe-OUT trial.

Table 25. Event rates for the analysis of all-cause hospitalisation

Author and year	Treatment	Outcome	Sample size	Event rate (%)
Gottlieb 2022	Placebo	18	283	6.36

Author and year	Treatment	Outcome	Sample size	Event rate (%)
	Remdesivir	5	279	1.79
Gupta 2022	Placebo	29	529	5.48
	Sotrovimab	6	528	1.14
Jayk Bernal 2021	Placebo	68	699	9.73
	Molnupiravir	48	709	6.77
Khoo 2022	Placebo	4	90	4.44
	Molnupiravir	0	90	0.00
Mazzotta 2023[a]	Nirmatrelvir plus ritonavir	1	139	0.72
	Sotrovimab	2	135	1.48

[a] In Mazzotta 2023, 0 event was reported in the nirmatrelvir + ritonavir arm. To allow for estimation of this NMA, a correction was applied to Mazzotta 2023 by adding 1 to the number of event and 2 to the number of patients at risk (i.e., sample size) for both arms for this trial.
SOURCE: RCT SLR (see Appendix D.1)

Table 26. Odds ratio and risk ratio of all-cause hospitalisation of each treatment versus placebo

	Odds ratio versus placebo			Risk ratio versus placebo		
Treatment	**Mean**	**Median**	**95% CrI**	**Mean**	**Median**	**95% CrI**
Molnupiravir	0.64	0.63	(0.43, 0.92)	0.66	0.65	(0.45, 0.93)
Nirmatrelvir plus ritonavir	0.20	0.07	(0.00, 1.12)	0.20	0.08	(0.00, 1.11)
Sotrovimab	0.21	0.19	(0.07, 0.43)	0.22	0.20	(0.07, 0.45)
Remdesivir	0.29	0.25	(0.08, 0.66)	0.30	0.27	(0.09, 0.68)

CrI = credible interval
SOURCE: RCT SLR (see Appendix D.1)

B.2.9.1.4 Efficacy results: COVID-19 related hospitalisation

Three trials (one evaluating molnupiravir, one evaluating remdesivir and one evaluating nirmatrelvir plus ritonavir) comparing an intervention with placebo or usual care and a fourth trial assessing sotrovimab versus nirmatrelvir plus ritonavir were included in the analysis of COVID-19 related hospitalisation through Day 28 or Day 29 following randomisation (Table 27; Figure 9).

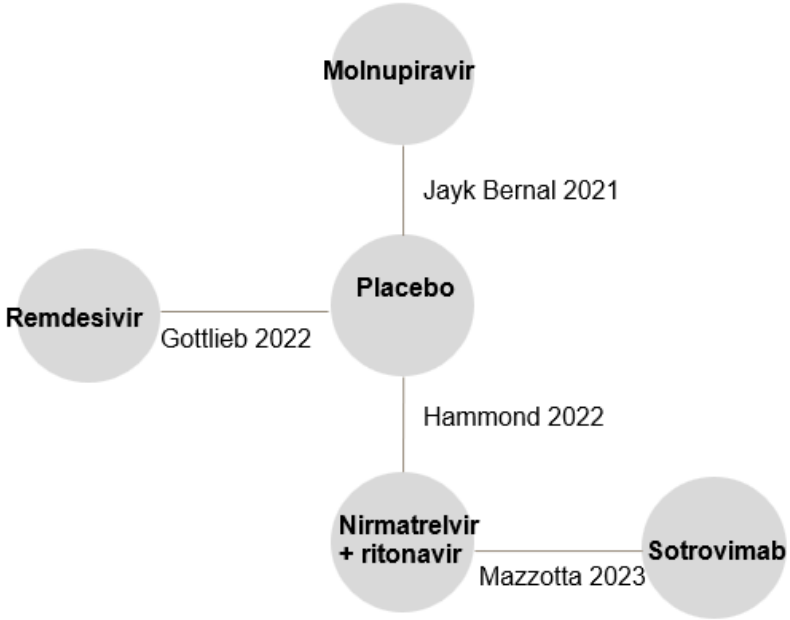
Table 27. Identified clinical trials and interventions of interest: COVID-19 related hospitalisation

Intervention	Trial	Country	Publication (author/year)	Dosing
Studies that included molnupiravir as an intervention				
Molnupiravir versus placebo	MOVe-OUT (NCT04575597)	Global	Jayk Bernal 2021	• 800 mg orally every 12 hours for 5 days
Studies that did not include molnupiravir as an intervention				
Nirmatrelvir plus ritonavir	EPIC-HR (NCT04960202)	Global	Hammond 2022	• Two 150 mg nirmatrelvir tablets and one 100 mg ritonavir tablet,

versus placebo				orally every 12 hours for 5 days
Remdesivir versus placebo	PINETREE (NCT04501952)	US, UK, Spain, Denmark	Gottlieb 2022	• 200 mg IV Day 1 and 100 mg IV Days 2-3
Sotrovimab versus nirmatrelvir plus ritonavir	MONET (EudraCT:2021-004188-28)	Multinational	Mazzotta 2023	• 500 mg IV, single dose

The outcome of hospitalisation is not relevant for remdesivir as it can only be given while the patient is in hospital.
COVID-19 = coronavirus disease 2019; IV = intravenous; UK = United Kingdom; US = United States
SOURCE: RCT SLR (see Appendix D.1)

Figure 9. Network for COVID-19 related hospitalisation



COVID-19 = coronavirus disease 2019
SOURCE: RCT SLR (see Appendix D.1)

The total number of patients and the number/proportion of patients with COVID-19 related hospitalisation in each trial arm are summarised in Table 28. In the trial evaluating nirmatrelvir plus ritonavir versus sotrovimab (Mazzotta 2023), zero number of events were reported in the treatment arm of nirmatrelvir plus ritonavir, which is implausible. Therefore, to allow for estimation of this NMA, a zero-event correction was applied to this trial by adding one to the number of events and two to the number of patients at risk for both arms of this trial.

Comparing across treatments, patients receiving remdesivir or nirmatrelvir plus ritonavir had a similar risk of COVID-19 related hospitalisation or death, both of which were lower than those receiving sotrovimab or molnupiravir. However, compared with placebo, proportions of patients with COVID-19 related hospitalisation by Day 28 or Day 29 were lower for molnupiravir, nirmatrelvir plus ritonavir, sotrovimab and remdesivir (Table 29).

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.1.

See Section B.2.6.1 for COVID-19 related hospitalisation results for patients treated with molnupiravir in the MOVe-OUT trial.

Table 28. Event rates for the analysis of COVID-19 related hospitalisation

Trial name / Author and year	Treatment	Outcome	Sample size	Event rate (%)
Gottlieb 2022	Placebo	15	283	5.30
	Remdesivir	2	279	0.72
Hammond 2022	Placebo	44	682	6.45
	Nirmatrelvir plus ritonavir	5	697	0.72
Jayk Bernal 2021	Placebo	64	699	9.16
	Molnupiravir	45	709	6.35
Mazzotta 2023[a]	Nirmatrelvir plus ritonavir	1	139	0.72
	Sotrovimab	2	135	1.48

[a] In Mazzotta 2023, 0 event was reported in the nirmatrelvir + ritonavir arm. To allow for estimation of this NMA, a correction was applied to Mazzotta 2023 by adding 1 to the number of event and 2 to the number of patients at risk (i.e., sample size) for both arms for this trial.
SOURCE: RCT SLR (see Appendix D.1)

Table 29. Odds ratio and risk ratio of COVID-19 related hospitalisation of each treatment versus placebo

	Odds ratio versus placebo			Risk ratio versus placebo		
Treatment	**Mean**	**Median**	**95% CrI**	**Mean**	**Median**	**95% CrI**
Molnupiravir	0.68	0.67	(0.45, 1.00)	0.70	0.69	(0.47, 1.00)
Nirmatrelvir plus ritonavir	0.11	0.10	(0.03, 0.23)	0.11	0.11	(0.04, 0.25)
Remdesivir	0.14	0.11	(0.01, 0.43)	0.15	0.12	(0.02, 0.45)
Sotrovimab[b]	2.51	0.25	(0.02, 8.83)	0.79	0.26	(0.02, 5.60)

[a] Due to wide CrIs, these results should be interpreted with caution.
[b] The posterior distribution of the effect of sotrovimab versus placebo is skewed, which contributes to the observed difference in the median and mean estimate of effect.
COVID-19 = coronavirus disease 2019; CrI = credible interval
SOURCE: RCT SLR (see Appendix D.1)

B.2.9.1.5 Efficacy results: All-cause death

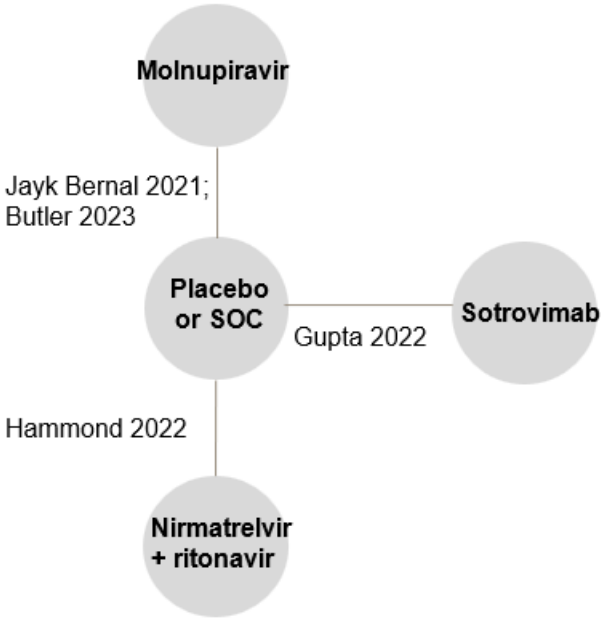
Four trials (two evaluating molnupiravir, one evaluating nirmatrelvir plus ritonavir and one evaluating sotrovimab) comparing an intervention with placebo or usual care were included in the analysis of all-cause death through Day 28 or Day 29 following randomisation (Table 30; Figure 10).

Table 30. Identified clinical trials and interventions of interest: All-cause death

Intervention	Trial	Country	Publication (author/year)	Dosing
Studies that included molnupiravir as an intervention				
Molnupiravir versus placebo	MOVe-OUT (NCT04575597)	Global	Jayk Bernal 2021	800 mg orally every 12 hours for 5 days
	PANORAMIC (ISRCTN30448031)	UK	Butler 2023	
Studies that did not include molnupiravir as an intervention				
Nirmatrelvir plus ritonavir versus placebo	EPIC-HR (NCT04960202)	Global	Hammond 2022	Two 150 mg nirmatrelvir tablets and one 100 mg ritonavir tablet, orally every 12 hours for 5 days
Sotrovimab versus placebo	COMET-ICE (NCT04545060)	UK, Canada, Brazil, Peru, Spain	Gupta 2022[108]	500 mg IV, single dose

IV = intravenous; UK = United Kingdom
SOURCE: RCT SLR (see Appendix D.1)

Figure 10. Network for all-cause death



SOURCE: RCT SLR (see Appendix D.1)

The total number of patients and the number/proportion of patients with all-cause mortality in each trial arm are summarised in Table 31. Comparing across treatments, patients receiving molnupiravir had a higher risk of all-cause death than those receiving nirmatrelvir plus ritonavir or sotrovimab. However, compared with placebo, proportions of patients with all-cause mortality by Day 28 or Day 29 were lower for those receiving molnupiravir, nirmatrelvir plus ritonavir and sotrovimab (Table 32).

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.1.

See Section B.2.6.1 for mortality results for patients treated with molnupiravir in the MOVe-OUT trial.

Table 31. Event rates for the analysis of all-cause mortality

Trial name / Author and year	Treatment	Outcome	Sample size	Event rate (%)
Butler 2022	Placebo	5	12,525	0.04
	Molnupiravir	3	12,529	0.02
Gupta 2022	Placebo	2	529	0.38
	Sotrovimab	0	528	0.00
Hammond 2022	Placebo	9	682	1.32
	Nirmatrelvir plus ritonavir	0	697	0.00
Jayk Bernal 2021	Placebo	9	699	1.29
	Molnupiravir	1	709	0.14

SOURCE: RCT SLR (see Appendix D.1)

Table 32. Odds ratio, risk ratio and risk difference of all-cause mortality of each treatment versus placebo

	Odds ratio versus placebo			Risk ratio versus placebo		
Treatment	**Mean**	**Median**	**95% CrI**	**Mean**	**Median**	**95% CrI**
Molnupiravir	0.30	0.27	(0.07, 0.76)	0.31	0.27	(0.07, 0.76)
Nirmatrelvir plus ritonavir	0.00	0.00	(0.00, 0.00)	0.00	0.00	(0.00, 0.00)
Sotrovimab	0.01	0.00	(0.00, 0.02)	0.01	0.00	(0.00, 0.02)

CrI = credible interval
SOURCE: RCT SLR (see Appendix D.1)

B.2.9.1.6 Safety results: Any adverse event

Four trials (two evaluating molnupiravir, one evaluating remdesivir and one evaluating sotrovimab) comparing an intervention with placebo or usual care were included in the analysis of patients with any AEs by Day 28 or Day 29 following randomisation (Table 33; Figure 11).

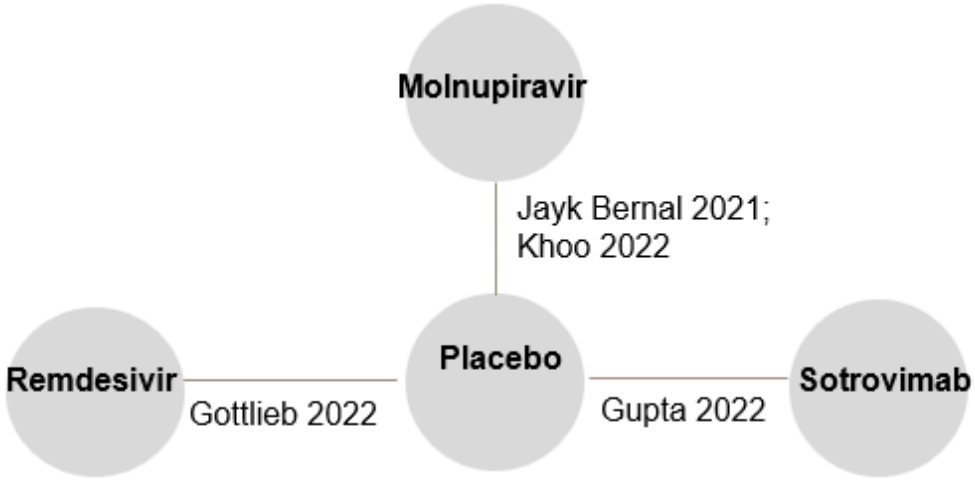
Table 33. Identified clinical trials and interventions of interest: Any adverse event

Intervention	Trial	Country	Publication (author/year)	Dosing
Studies that included molnupiravir as an intervention				
Molnupiravir versus placebo	MOVe-OUT (NCT04575597)	Global	Jayk Bernal 2021	• 800 mg orally every 12 hours for 5 days
	AGILE CST-2 (NCT04746183)	UK	Khoo 2022	

Intervention	Trial	Country	Publication (author/year)	Dosing
Studies that did not include molnupiravir as an intervention				
Remdesivir versus placebo	PINETREE (NCT04501952)	US, UK, Spain, Denmark	Gottlieb 2022	• 200 mg IV Day 1 and 100 mg IV Days 2-3
Sotrovimab versus placebo	COMET-ICE (NCT04545060)	US, Canada, Brazil, Peru, Spain	Gupta 2022	• 500 mg IV, single dose

IV = intravenous; UK = United Kingdom; US = United States
SOURCE: RCT SLR (see Appendix D.1)

Figure 11. Network for any adverse event



SOURCE: RCT SLR (see Appendix D.1)

The total number of patients and the number/proportion of patients with any AEs by Day 28 or Day 29 in each trial arm are summarised in Table 34. Comparing across treatments, patients receiving remdesivir had a slightly lower risk of developing any AEs than those receiving molnupiravir or sotrovimab. However, compared with placebo, proportions of patients with AEs by Day 28 or Day 29 were slightly lower for those receiving molnupiravir, sotrovimab or remdesivir (Table 35).

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.1.

See Section B.2.10.1.1 for AE results at Day 14 for patients treated with molnupiravir in the MOVe-OUT trial.

Table 34. Event rates for the analysis of any AEs

Trial name / Author and year	Treatment	Outcome	Sample size	Event rate (%)
Gottlieb 2022	Placebo	131	283	46.29
	Remdesivir	118	279	42.29
Gupta 2022	Placebo	123	526	23.38
	Sotrovimab	114	523	21.80
Jayk Bernal 2021	Placebo	231	701	32.95
	Molnupiravir	216	710	30.42
Khoo 2022	Placebo	68	90	75.56
	Molnupiravir	73	90	81.11

SOURCE: RCT SLR (see Appendix D.1)

Table 35. Odds ratio and risk ratio of any AEs of each treatment versus placebo

	Odds ratio versus placebo			Risk ratio versus placebo		
Treatment	**Mean**	**Median**	**95% CrI**	**Mean**	**Median**	**95% CrI**
Molnupiravir	0.93	0.93	(0.75, 1.15)	0.95	0.95	(0.82, 1.09)
Remdesivir	0.86	0.85	(0.61, 1.19)	0.90	0.90	(0.70, 1.12)
Sotrovimab	0.92	0.91	(0.68, 1.22)	0.94	0.94	(0.77, 1.13)

CrI = credible interval
SOURCE: RCT SLR (see Appendix D.1)

B.2.9.1.7 Safety results: Severe adverse events

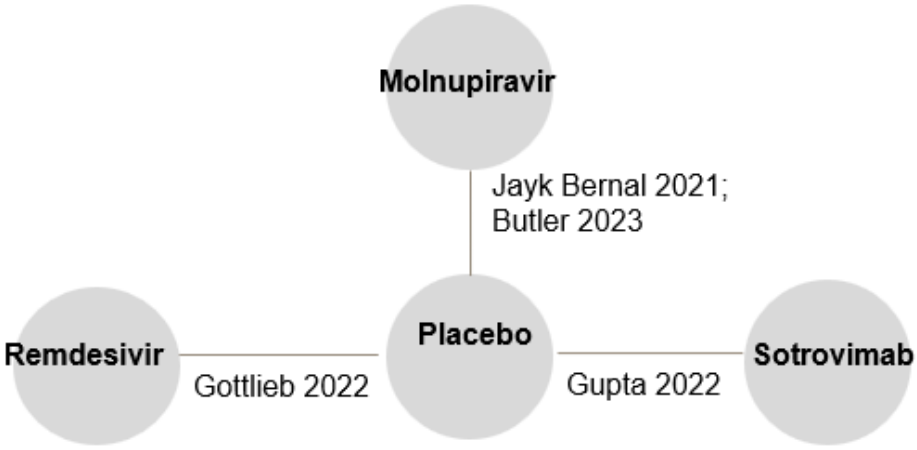
Four trials (two evaluating molnupiravir, one evaluating remdesivir and one evaluating sotrovimab) comparing an intervention with placebo or usual care were included in the analysis of patients with severe AEs by Day 28 or Day 29 following randomisation (Table 36; Figure 12).

Table 36. Identified clinical trials and interventions of interest: Severe AEs

Intervention	Trial	Country	Publication (author/year)	Dosing
Studies that included molnupiravir as an intervention				
Molnupiravir versus placebo	MOVe-OUT (NCT04575597)	Global	Jayk Bernal 2021	• 800 mg orally every 12 hours for 5 days
	PANORAMIC (ISRCTN30448031)	UK	Butler 2023	
Studies that did not include molnupiravir as an intervention				
Remdesivir versus placebo	PINETREE (NCT04501952)	US, UK, Spain, Denmark	Gottlieb 2022	• 200 mg IV Day 1 and 100 mg IV Days 2-3
Sotrovimab versus placebo	COMET-ICE (NCT04545060)	US, Canada, Brazil, Peru, Spain	Gupta 2022	• 500 mg IV, single dose

IV = intravenous; UK = United Kingdom; US = United States. SOURCE: RCT SLR (see Appendix D.1)

Figure 12. Network for severe AEs



SOURCE: RCT SLR (see Appendix D.1)

The total number of patients and the number/proportion of patients with SAEs by Day 28 or Day 29 in each trial arm were summarised in Table 37. Comparing across treatments, patients receiving remdesivir or sotrovimab had similar risk of developing SAEs, both of which were lower than those receiving molnupiravir. However, compared with placebo, proportions of patients with severe AEs by Day 28 or Day 29 were lower for those receiving molnupiravir, sotrovimab or remdesivir (Table 38).

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.1.

See Section B.2.10.1.1 for SAE results at Day 14 for patients treated with molnupiravir in the MOVe-OUT trial.

Table 37. Event rates for the analysis of severe AEs

Trial name / Author and year	Treatment	Outcome	Sample size	Event rate (%)
Butler 2022	Placebo	45	12,934	0.35
	Molnupiravir	50	12,774	0.39
Gottlieb 2022	Placebo	19	283	6.71
	Remdesivir	5	279	1.79
Gupta 2022	Placebo	32	526	6.08
	Sotrovimab	11	523	2.10
Jayk Bernal 2021	Placebo	67	701	9.56
	Molnupiravir	49	710	6.90

SOURCE: RCT SLR (see Appendix D.1)

Table 38. Odds ratio and risk ratio of severe AEs of each treatment versus placebo

	Odds ratio versus placebo			Risk ratio versus placebo		
Treatment	**Mean**	**Median**	**95% CrI**	**Mean**	**Median**	**95% CrI**
Molnupiravir	0.89	0.88	(0.66, 1.16)	0.89	0.88	(0.67, 1.16)
Remdesivir	0.27	0.24	(0.08, 0.62)	0.27	0.24	(0.08, 0.62)
Sotrovimab	0.34	0.32	(0.15, 0.64)	0.35	0.33	(0.16, 0.64)

CrI = credible interval
SOURCE: RCT SLR (see Appendix D.1)

B.2.9.1.8 Safety results: Treatment discontinuation due to adverse events

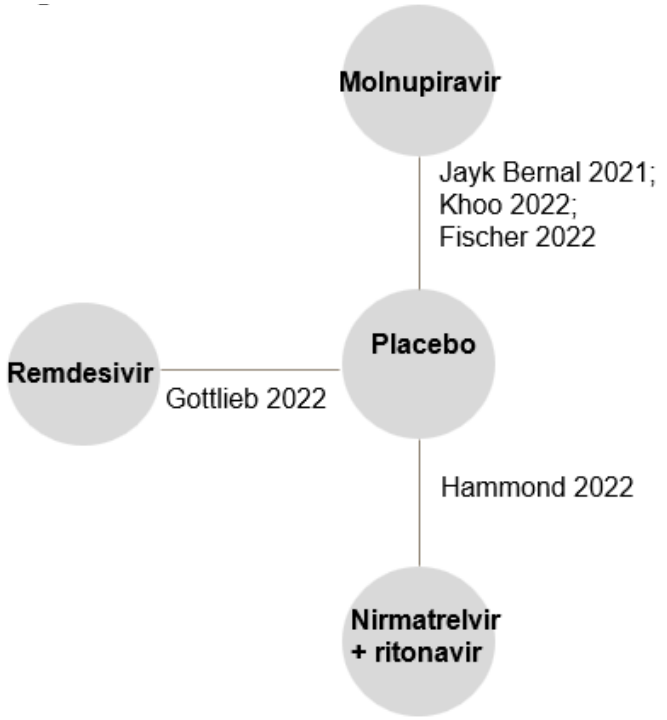
Five trials (three evaluating molnupiravir, one evaluating nirmatrelvir plus ritonavir and one evaluating remdesivir) comparing an intervention with placebo or usual care were included in the analysis of patients with treatment discontinuation due to AEs by Day 5 following randomisation (Table 39; Figure 13).

Table 39. Identified clinical trials and interventions of interest: Treatment discontinuation due to AEs

Intervention	Trial	Country	Publication (author/year)	Dosing
Studies that included molnupiravir as an intervention				
Molnupiravir versus placebo	MOVe-OUT (NCT04575597)	Global	Jayk Bernal 2021	• 800 mg orally every 12 hours for 5 days
	AGILE CST-2 (NCT04746183)	UK	Khoo 2022	
	NCT04405570	US	Fischer 2022	
Studies that did not include molnupiravir as an intervention				
Nirmatrelvir plus ritonavir versus placebo	EPIC-HR (NCT04960202)	Global	Hammond 2022	• Two 150 mg nirmatrelvir tablets and one 100 mg ritonavir tablet, orally every 12 hours for 5 days
Remdesivir versus placebo	PINETREE (NCT04501952)	US, UK, Spain, Denmark	Gottlieb 2022	• 200 mg IV Day 1 and 100 mg IV Days 2-3

IV = intravenous; UK = United Kingdom; US = United States
SOURCE: RCT SLR (see Appendix D.1)

Figure 13. Network for treatment discontinuation due to AEs



SOURCE: RCT SLR (see Appendix D.1)

The total number of patients and the number/proportion of patients with treatment discontinuation by Day 5 in each trial arm were summarised in Table 40. Comparing across treatments, patients receiving remdesivir had lower treatment discontinuation than those receiving nirmatrelvir plus ritonavir or receiving molnupiravir. However, compared with placebo, proportions of patients with treatment discontinuation were lower for those receiving molnupiravir, nirmatrelvir plus ritonavir or remdesivir (Table 41).

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.1.

See Section B.2.10.1.1 for Day 14 treatment discontinuation due to AE results for patients treated with molnupiravir in the MOVe-OUT trial.

Table 40. Event rates for the analysis of treatment discontinuation due to adverse event

Trial name / Author and year	Treatment	Outcome	Sample size	Event rate (%)
Fischer 2022	Placebo	1	62	1.61
	Molnupiravir	1	55	1.82
Gottlieb 2022	Placebo	5	283	1.77
	Remdesivir	2	279	0.72
Hammond 2022	Placebo	47	1,115	4.22
	Nirmatrelvir + ritonavir	23	1,109	2.07

Trial name / Author and year	Treatment	Outcome	Sample size	Event rate (%)
Jayk Bernal 2021	Placebo	20	701	2.85
	Molnupiravir	10	710	1.41
Khoo 2022	Placebo	2	90	2.22
	Molnupiravir	2	90	2.22

SOURCE: RCT SLR (see Appendix D.1)

Table 41. Odds ratio and risk ratio of treatment discontinuation due to AE of each treatment versus placebo

	Odds ratio versus placebo			Risk ratio versus placebo		
Treatment	**Mean**	**Median**	**95% CrI**	**Mean**	**Median**	**95% CrI**
Molnupiravir	0.58	0.55	(0.27, 1.08)	0.59	0.56	(0.28, 1.07)
Nirmatrelvir plus ritonavir	0.49	0.48	(0.28, 0.78)	0.50	0.49	(0.29, 0.79)
Remdesivir	0.50	0.36	(0.04, 1.83)	0.50	0.37	(0.05, 1.78)

AE = adverse event; CrI = credible interval
SOURCE: RCT SLR (see Appendix D.1)

B.2.9.2 RWE network meta-analysis

The RWE SLR yielded a total of 30 relevant studies prioritised for full extraction, of which 22 were deemed suitable by the feasibility assessment for analysis in the NMA.

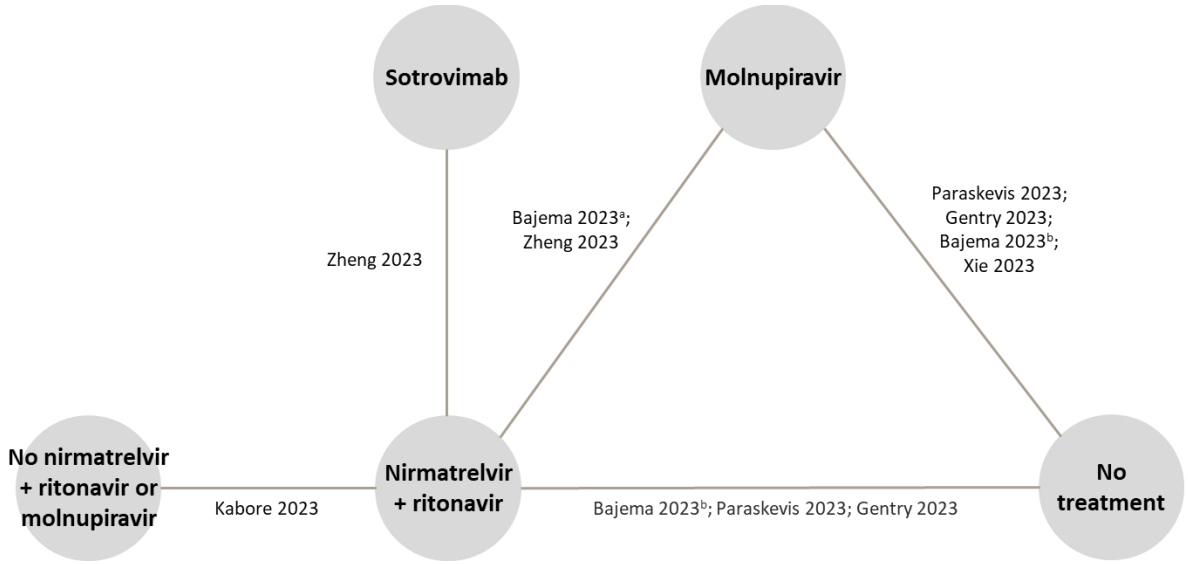
Aligned with the findings of the RCT NMA, molnupiravir was demonstrated to be a superior alternative to no treatment, associated with improved outcomes. Additionally, results from the RWE NMA suggested that molnupiravir has similar effectiveness in reducing the risk of all-cause hospitalisation or death relative to nirmatrelvir plus ritonavir and sotrovimab in outpatients with mild to moderate COVID-19, highlighting its suitability as an alternative treatment option.

To account for uncertainties resulting from the reporting of other potential treatments received by control patients, the NMA of RWE contains two control nodes, one labelled "no treatment" in which the patients in the control group were considered to be untreated, and one labelled "no nirmatrelvir + ritonavir or molnupiravir" in which control patients did not receive either of the oral antivirals but may have received other active interventions.

B.2.9.2.1 Efficacy results: All-cause hospitalisation or death

Six studies reporting the risk of all-cause hospitalisation or death in outpatients with mild to moderate COVID-19 were included in the NMA (Figure 14; Table 42).

Figure 14. Network for all-cause hospitalisation or death



SOURCE: RWE SLR (see Appendix D.2)

Table 42. Identified studies and interventions of interest: All-cause hospitalisation or death

Publication (author/year)	Intervention	Country	Study design	Population
Studies that included molnupiravir as an intervention				
Xie 2023	Molnupiravir *versus* no treatment	US	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection with at least one risk factor for progression to severe disease
Gentry 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir	US	Matched case control	US Veterans ≥ 65 years of age with mild to moderate COVID-19 considered to be at high risk of disease progression
Bajema 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir *versus* no treatment	US	Retrospective cohort	Non-hospitalised veterans in VHA care who are at risk for severe COVID-19 and tested positive for SARS-CoV-2
Paraskevis 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir *versus* no treatment	Greece		Non-hospitalised patients with COVID-19 ≥ 65 years of age
Zheng 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir *versus* sotrovimab	UK	Retrospective cohort	Non-hospitalised high-risk COVID-19 patients across England (OpenSAFELY study)
Studies that did not include molnupiravir as an intervention				
Kabore 2023	Nirmatrelvir plus ritonavir *versus* no nirmatrelvir plus ritonavir or no molnupiravir	Canada	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection with at least one risk factor for progression to severe disease

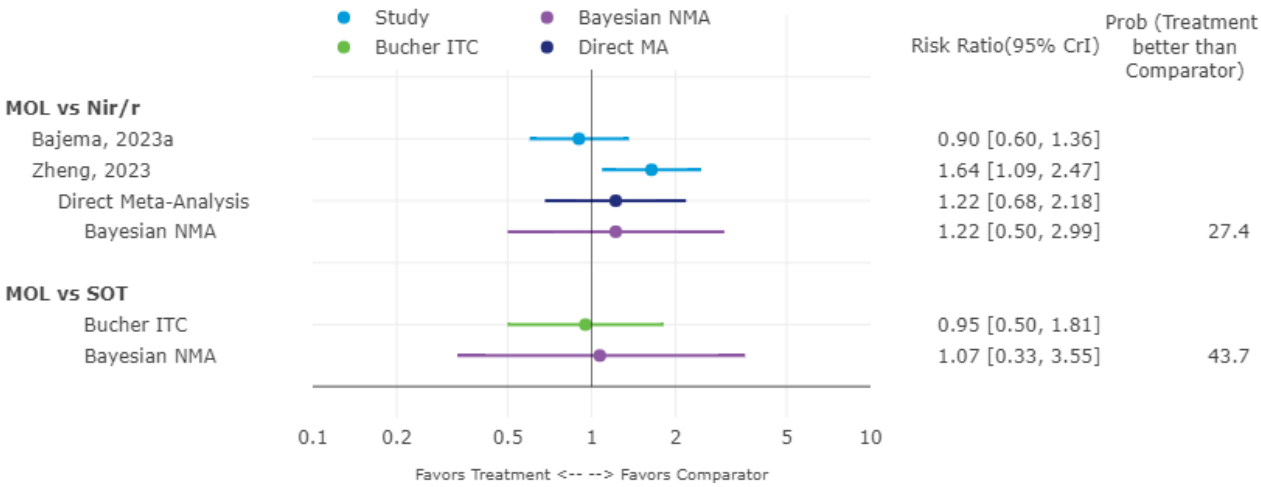
COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UK = United Kingdom; US = United States. SOURCE: RWE SLR (see Appendix D.2)

The base case NMA results derived from the active treatment network suggested similar effectiveness of molnupiravir relative to nirmatrelvir plus ritonavir and sotrovimab in reducing the risk of all-cause hospitalisation or death in outpatients with mild to moderate COVID-19 (Figure 15). Molnupiravir and sotrovimab were found to have similar clinical effectiveness with an estimated risk ratio (RR) of 1.07 (95% CrI: 0.33, 3.55) for the difference in treatment effect. Results also suggested little difference between molnupiravir and nirmatrelvir plus ritonavir (RR 1.22, 95% CrI: 0.50, 2.99) but indicate that molnupiravir is unlikely to be superior to nirmatrelvir plus ritonavir. There was insufficient evidence to assess the relative effectiveness of molnupiravir versus remdesivir.

The results derived from the active treatment/control network suggested that molnupiravir reduces the risk of hospitalisation or death relative to no treatment (RR 0.61, 95% CrI: 0.43, 0.86; Figure 16). Results showed even better treatment benefit when molnupiravir was compared against no molnupiravir or no nirmatrelvir plus ritonavir (RR 0.41, 95% CrI: 0.19, 0.89).

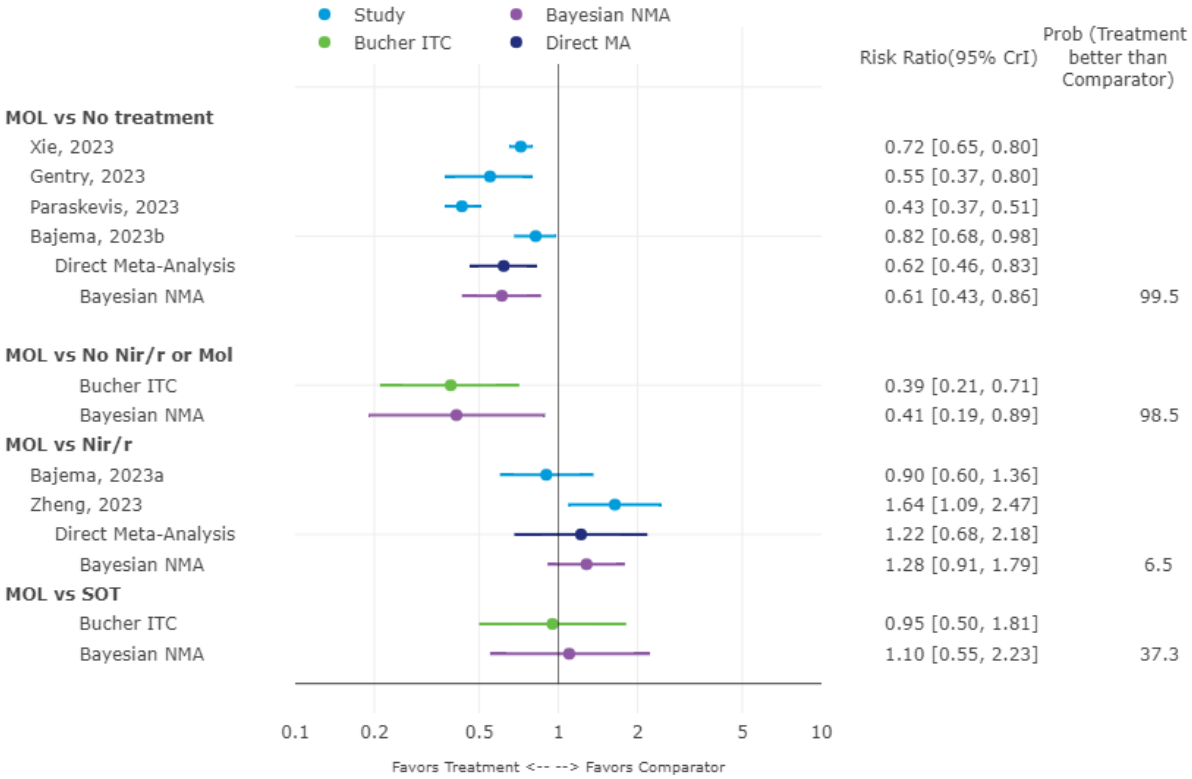
Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.2.

Figure 15. Active treatment evidence network NMA results all-cause hospitalisation or death (random effects)



Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; SOT = sotrovimab
SOURCE: RWE SLR (see Appendix D.2)

Figure 16. Active treatment/control evidence network NMA results all-cause hospitalisation or death (random effects)

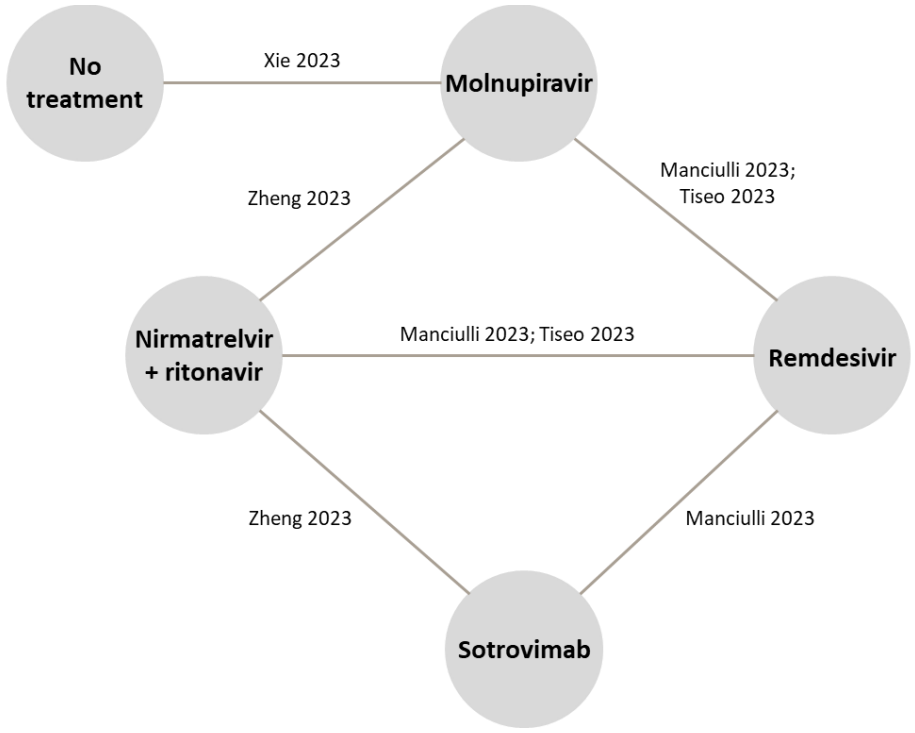


Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
Note: Zheng, 2022 specifically focussed on patients with renal failure and was therefore excluded from the base case and only included in the renal failure sensitivity analysis. Zheng, 2023 compared Nir/r vs. SOT and Nir/r vs. MOL - both data sets were included in the analysis, but the above figure only displays the direct evidence for the Mol comparison.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; SOT = sotrovimab
SOURCE: RWE SLR (see Appendix D.2)

B.2.9.2.2 Efficacy result: COVID-19 related hospitalisation or death

Four studies reporting the risk of COVID-19 related hospitalisation or death in outpatients with mild to moderate COVID-19 were included in the NMA (Figure 17; Table 43).

Figure 17. Network for COVID-19 related hospitalisation or death



SOURCE: RWE SLR (see Appendix D.2)

Table 43. Identified studies and interventions of interest: COVID-19 related hospitalisation or death

Publication (author/year)	Intervention	Country	Study design	Population
Studies that included molnupiravir as an intervention				
Xie 2023	Molnupiravir *versus* no treatment	US	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection with at least one risk factor for progression to severe disease
Zheng 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir *versus* sotrovimab	UK	Retrospective cohort	Non-hospitalised high-risk COVID-19 patients across England
Tiseo 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir *versus* remdesivir	Italy	Prospective cohort	Outpatients with documented COVID-19 who were at high risk of progression to severe disease
Manciulli 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir *versus* sotrovimab *versus* remdesivir	Italy	Retrospective cohort	Patients with mild or moderate COVID-19 treated with sotrovimab, remdesivir, nirmatrelvir plus ritonavir or molnupiravir as outpatients, who had ≥ 1 risk factor for severe disease

COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UK = United Kingdom; US = United States
SOURCE: RWE SLR (see Appendix D.2)

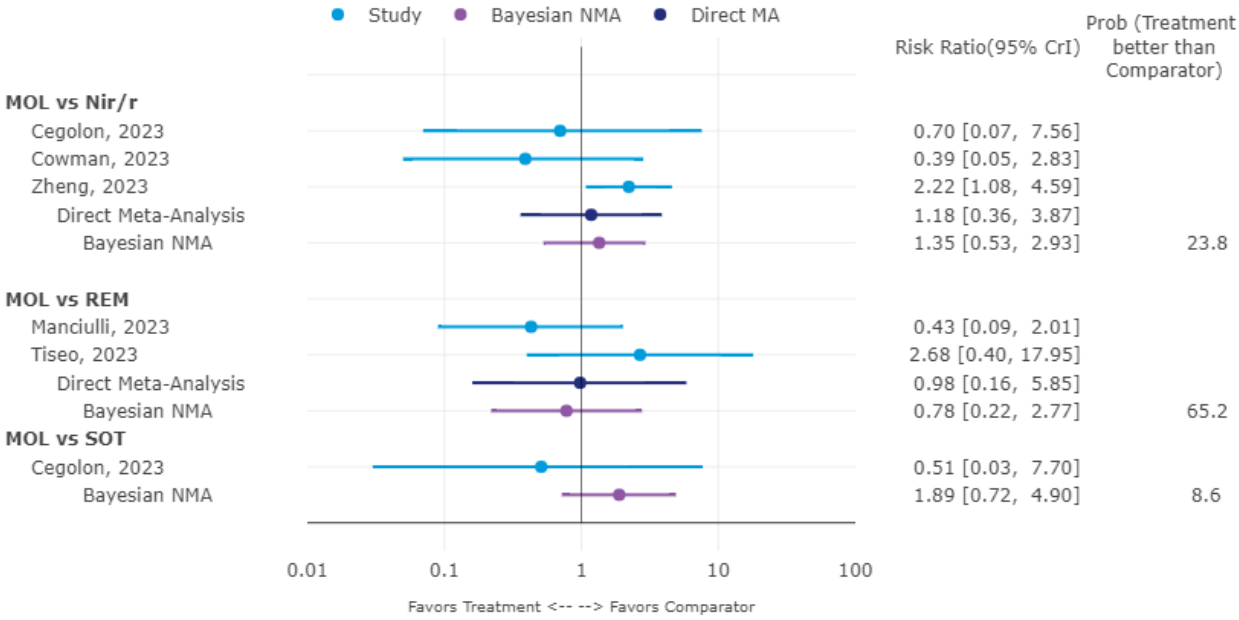
The base case NMA results derived from the active treatment network suggested that molnupiravir may have benefits over remdesivir but not nirmatrelvir plus ritonavir and

sotrovimab in reducing the risk of COVID-19–related hospitalisation or death in outpatients with mild to moderate COVID (Figure 18). Molnupiravir appeared to be favoured over remdesivir with an estimated RR of 0.78 (95% CrI: 0.22, 2.77). However, nirmatrelvir plus ritonavir appeared to be favoured over molnupiravir with an estimated RR of 1.35 (95% CrI: 0.53, 2.93). Results suggest molnupiravir is unlikely to be superior when compared to sotrovimab with an estimated RR of 1.89 (95% CrI: 0.72, 4.90). However, none of these results were statistically significant.

The results derived from the active treatment/control network suggests that molnupiravir reduces the risk of COVID-19 related hospitalisation or death relative to no treatment (RR 0.74, 95% CrI: 0.33, 1.20) (Figure 19). Additionally, when comparing molnupiravir to no nirmatrelvir plus ritonavir or no molnupiravir, an even greater treatment benefit is observed with an estimated RR of 0.46 (95% CrI: 0.22, 0.92). Molnupiravir also appeared more favourable compared to remdesivir (RR 0.82, 95% CrI: 0.26, 2.47). There was no statistically significant difference in COVID-19-related hospitalisation or death between molnupiravir and sotrovimab (RR 1.96, 95% CrI: 0.96, 4.28), nirmatrelvir plus ritonavir (RR 1.50, 95% CrI: 0.79, 2.42), or with remdesivir albeit that the RRs were numerically greater than 1.

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.2.

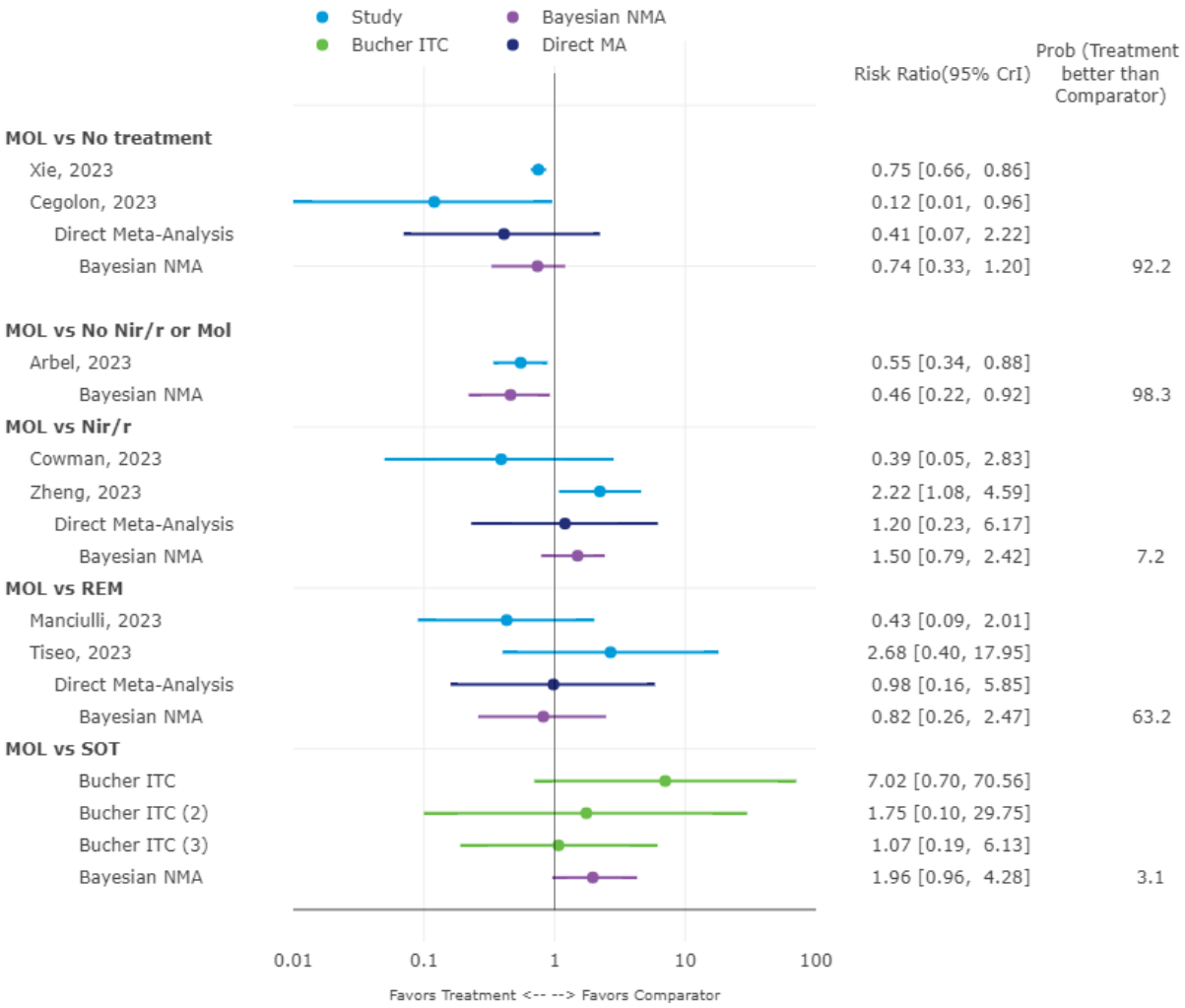
Figure 18. Active treatment evidence network NMA results for COVID-19 related hospitalisation or death plus COVID-19 related hospitalisation (random effects)



Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
Note: Zheng, 2022 specifically focussed on patients with renal failure and was therefore excluded from the base case and only included in the renal failure sensitivity analysis. Zheng, 2023 compared Nir/r vs. SOT and Nir/r vs. MOL - both data sets were included in the analysis, but the above figure only displays the direct evidence for the Mol comparison.

CrI = credible interval; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir; SOT = sotrovimab
SOURCE: RWE SLR (see Appendix D.2)

Figure 19. Active treatment/control evidence network NMA results COVID-19 related hospitalisation or death plus COVID-19 related hospitalisation (random effects)

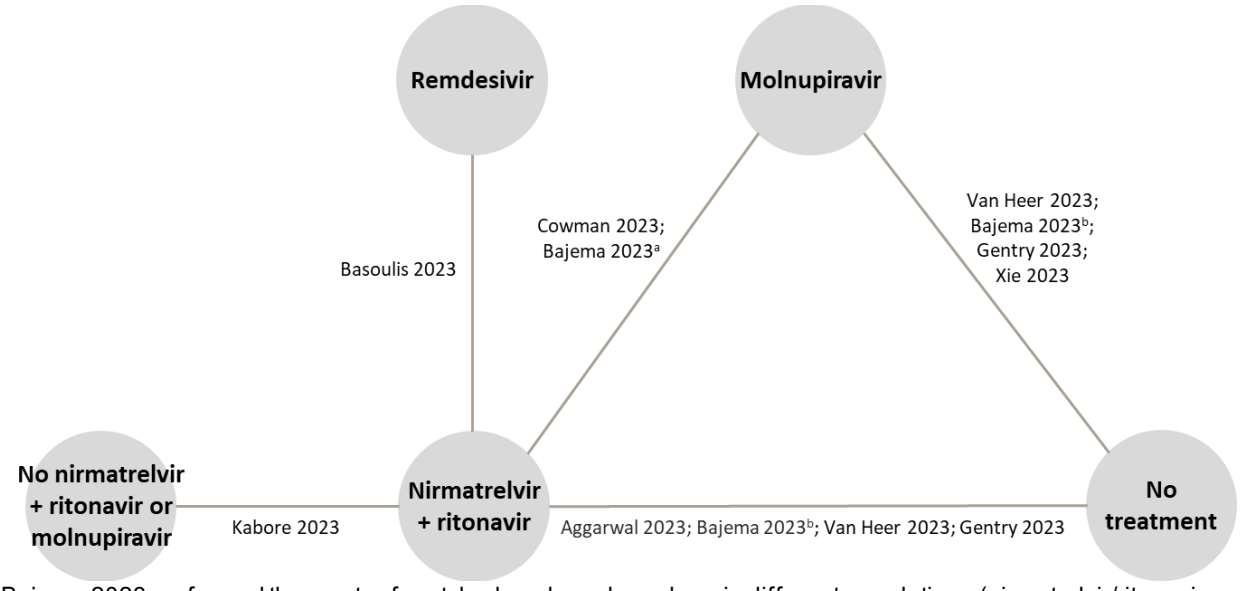


Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir; SOT = sotrovimab
SOURCE: RWE SLR (see Appendix D.2)

B.2.9.2.3 Efficacy results: All-cause hospitalisation

Eight studies reporting the risk of all-cause hospitalisation in outpatients with mild to moderate COVID-19 were included in the NMA (Figure 20 and Table 44).

Figure 20. Network for all-cause hospitalisation



Bajema 2023 performed three sets of matched analyses based on six different populations (nirmatrelvir/ritonavir population-1 versus untreated population-1; molnupiravir population-1 versus untreated population-2; nirmatrelvir/ritonavir population-2 versus molnupiravir population-2). The relative effectiveness estimates for nirmatrelvir/ritonavir versus molnupiravir derived from the direct and indirect comparisons were inconsistent therefore these data sets were handled as two separate studies. Bajema 2023a: direct evidence derived from the comparison of nirmatrelvir/ritonavir population-2 versus molnupiravir population-2. Bajema 2023b: indirect evidence derived from the comparison of nirmatrelvir/ritonavir population-1 versus untreated population-1 and molnupiravir versus untreated population-2.
The outcome of hospitalisation is not relevant for remdesivir as it can only be given while the patient is in hospital.
SOURCE: RWE SLR (see Appendix D.2)

Table 44. Identified studies and interventions of interest: All-cause hospitalisation

Publication (author/year)	Intervention	Country	Study design	Population
Studies that included molnupiravir as an intervention				
Xie 2023	Molnupiravir *versus* no treatment	US	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection with at least one risk factor for progression to severe disease
Gentry 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir	US	Matched case control	US Veterans ≥ 65 years of age with mild to moderate COVID-19 considered to be at high risk of disease progression
Cowman 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir		Retrospective cohort	High-risk, non-hospitalised adult patients with COVID-19
Bajema 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir *versus* no treatment	US	Retrospective cohort	Non-hospitalised veterans in VHA care who are at risk for severe COVID-19 and tested positive for SARS-CoV-2
Van Heer 2023	Molnupiravir *versus* nirmatrelvir plus ritonavir *versus* no treatment	Australia		Individuals ≥ 70 years of age diagnosed with COVID-19 and reported to the Victorian Department of Health

Publication (author/year)	Intervention	Country	Study design	Population
Studies that did not include molnupiravir as an intervention				
Basoulis 2023	Nirmatrelvir plus ritonavir *versus* remdesivir	Greece	Prospective cohort	High-risk adult patients with COVID-19, without requirements for supplemental oxygen on presentation
Kabore 2023	Nirmatrelvir plus ritonavir *versus* no nirmatrelvir plus ritonavir or no molnupiravir	Canada	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection with at least one risk factor for progression to severe disease
Aggarwal 2023	Nirmatrelvir plus ritonavir *versus* no treatment	US	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection

COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; US = United States; VHA = Veterans Health Administration
SOURCE: RWE SLR (see Appendix D.2)

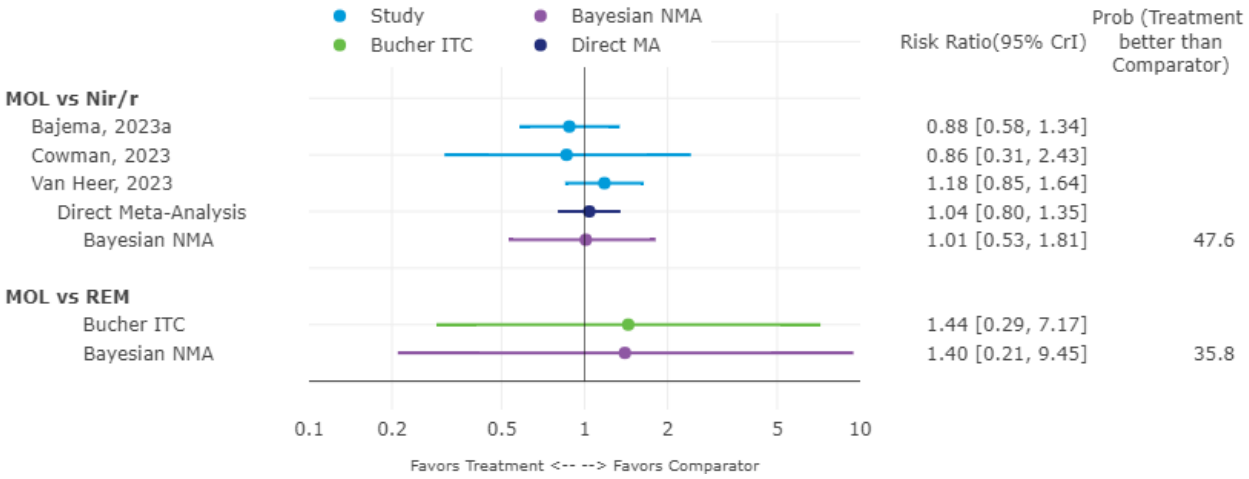
The base case NMA results derived from the active treatment network suggest similar effectiveness of molnupiravir relative to nirmatrelvir plus ritonavir and remdesivir in reducing the risk of all-cause hospitalisation in outpatients with mild to moderate COVID-19 (

Figure 21). Molnupiravir appeared similar to nirmatrelvir plus ritonavir with an estimated RR of 1.01 (95% credible interval [CrI]: 0.53, 1.81). Results indicated that molnupiravir is unlikely to be superior to remdesivir with an RR of 1.40 (95% CrI: 0.21, 9.45). A comparison between molnupiravir versus sotrovimab was not possible for this outcome.

Alternatively, the results derived from the active treatment/control network show that molnupiravir significantly reduces the risk of all-cause hospitalisation relative to no treatment with an estimated RR of 0.79 (95% CrI: 0.66, 0.92; Figure 22). When comparing molnupiravir to no nirmatrelvir plus ritonavir or no molnupiravir, there is an estimated RR of 0.37 (95% CrI: 0.25, 0.53). No statistically significant differences were observed between molnupiravir and nirmatrelvir/ritonavir (RR 1.19, 95% CrI: 0.98, 1.43) or remdesivir (RR 1.65, 95% CrI: 0.35, 8.63), although molnupiravir may be associated with numerically higher rate of events for this outcome .

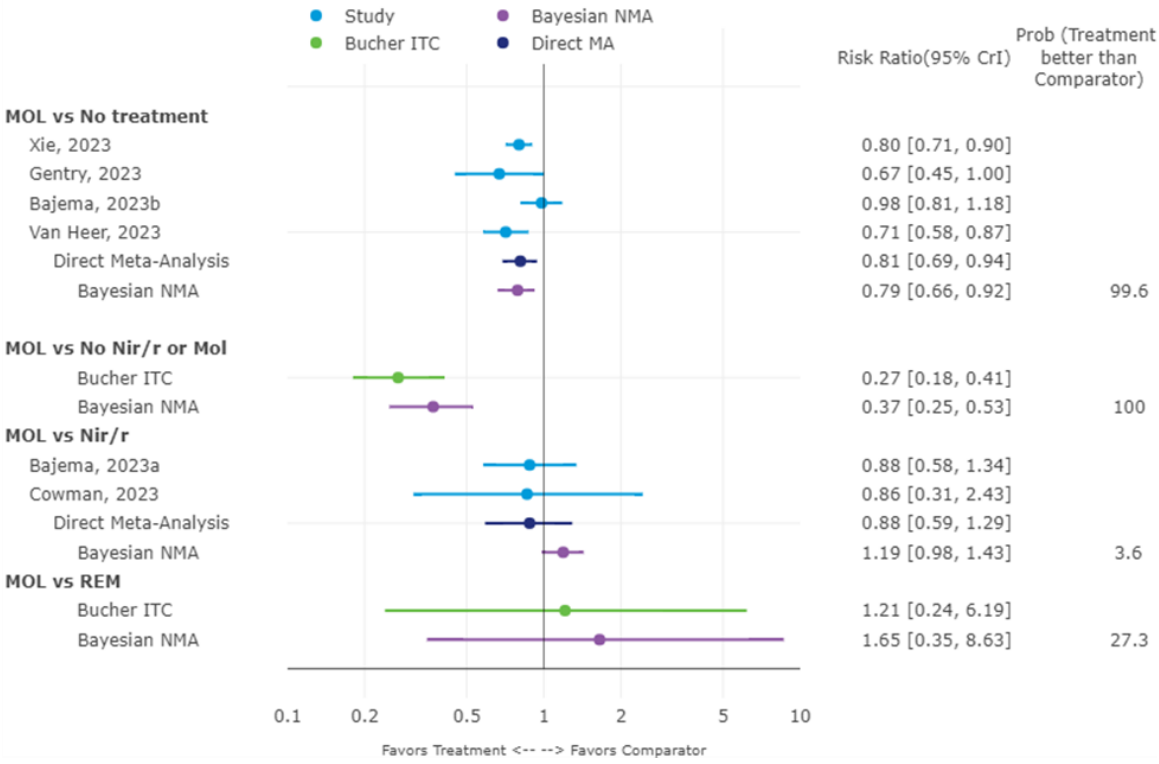
Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.2.

Figure 21. Active treatment evidence network NMA results for all-cause hospitalisation (random effects)



Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir
SOURCE: RWE SLR (see Appendix D.2)

Figure 22. Active treatment/control evidence network NMA results for all-cause hospitalisation (random effects)

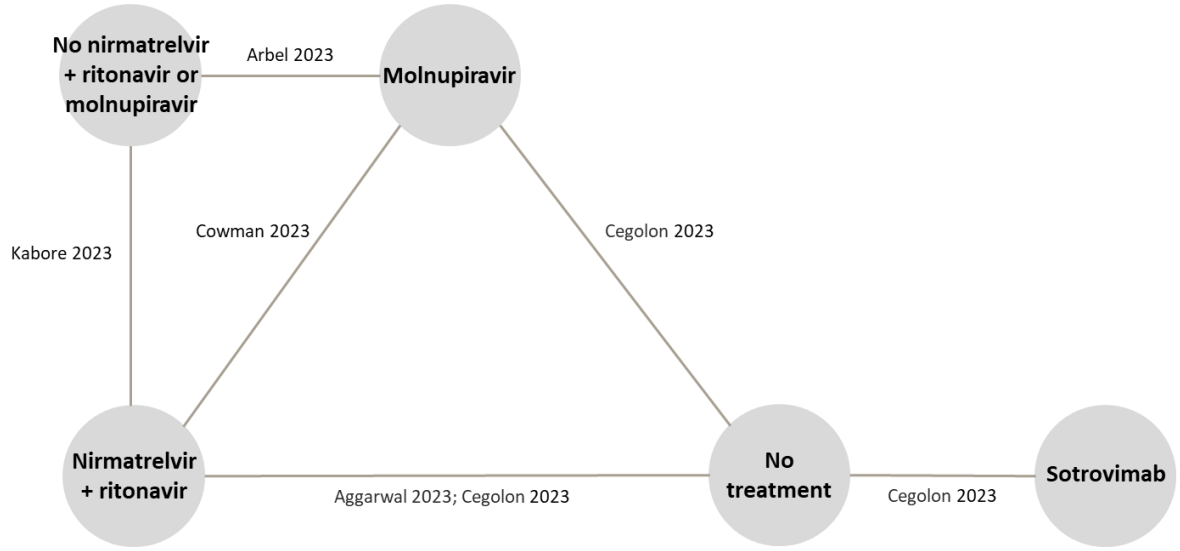


Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir
SOURCE: RWE SLR (see Appendix D.2)

B.2.9.2.4 Efficacy results: COVID-19 related hospitalisation

Five studies reporting the risk of COVID-19 related hospitalisation in outpatients with mild to moderate COVID-19 were included in the NMA (Figure 23; Table 45).

Figure 23. Network for COVID-19 related hospitalisation



The outcome of hospitalisation is not relevant for remdesivir as it can only be given while the patient is in hospital.
SOURCE: RWE SLR (see Appendix D.2)

Table 45. Identified studies and interventions of interest: COVID-19 related hospitalisation

Publication (author/year)	Intervention	Country	Study design	Population
Studies that included molnupiravir as an intervention				
Arbel 2023	Molnupiravir versus no treatment	Israel	Prospective cohort	Non-hospitalised patients (≥ 40 years of age), infected with Omicron and at high risk for progression to severe disease and who were ineligible for nirmatrelvir plus ritonavir
Cowman 2023	Molnupiravir versus nirmatrelvir plus ritonavir	US	Retrospective cohort	High-risk, non-hospitalised adult patients with COVID-19
Cegolon 2023	Molnupiravir versus nirmatrelvir plus ritonavir versus sotrovimab versus no treatment	Italy	Retrospective cohort	High-risk COVID-19 outpatients
Studies that did not include molnupiravir as an intervention				
Kabore 2023	Nirmatrelvir plus ritonavir versus no nirmatrelvir plus ritonavir or no molnupiravir	Canada	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection with at least one risk factor for progression to severe disease
Aggarwal 2023	Nirmatrelvir plus ritonavir versus no treatment	US	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection

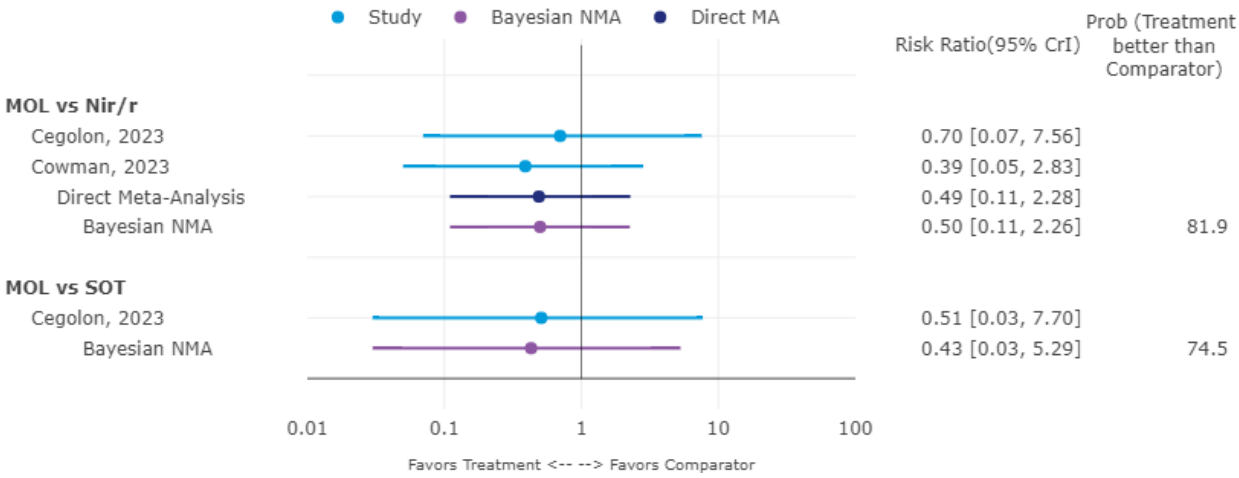
COVID-19 = coronavirus disease 2019; US = United States
SOURCE: RWE SLR (see Appendix D.2)

The base case NMA results derived from the active treatment network suggested there may be some benefit of molnupiravir relative to nirmatrelvir plus ritonavir and sotrovimab in reducing the risk of COVID-19 related hospitalisation in outpatients with mild to moderate COVID-19 (Figure 24). Molnupiravir appeared to be favourable in comparison with nirmatrelvir plus ritonavir with an estimated RR of 0.50 (95% CrI: 0.11, 2.56). The results indicated that molnupiravir appeared to be favorableversus sotrovimab with an RR of 0.43 (95% CrI: 0.03, 5.29).

Additionally, the results derived from the active treatment/control network suggested that molnupiravir reduced the risk of COVID-19 related hospitalisation relative to no treatment (RR 0.85, 95% CrI: 0.49, 1.53; Figure 25). Similarly, molnupiravir appeared to be favoured over no nirmatrelvir plus ritonavir or no molnupiravir with an estimated RR of 0.46 (95% CrI: 0.30, 0.73).

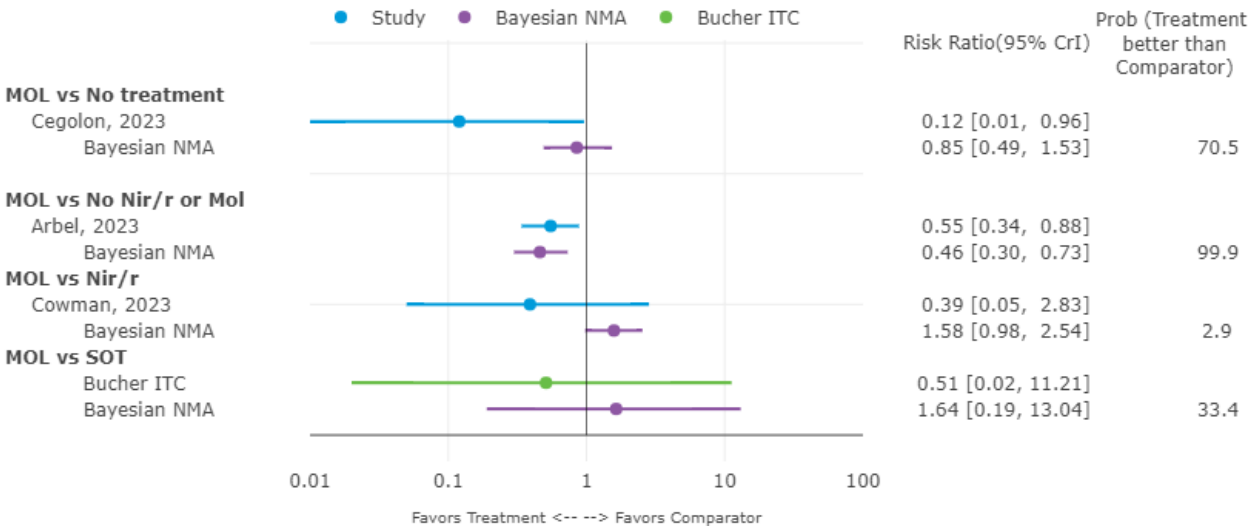
Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.2.

Figure 24. Active treatment evidence network NMA results for COVID-19 related hospitalisation (fixed effect)



Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
CrI = credible interval; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; SOT = sotrovimab
SOURCE: RWE SLR (see Appendix D.2)

Figure 25. Active treatment/control evidence network NMA results for COVID-19 related hospitalisation (fixed effect)

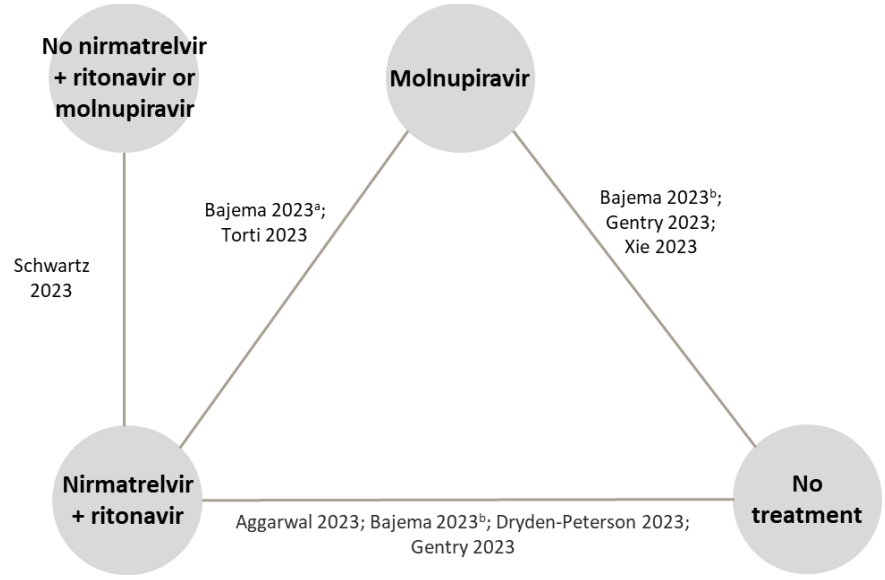


Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; SOT = sotrovimab
SOURCE: RWE SLR (see Appendix D.2)

B.2.9.2.5 Efficacy results: All-cause death

Seven studies reporting the risk of all-cause death in outpatients with mild to moderate COVID-19 were included in the NMA (Figure 26; Table 46).

Figure 26. Network for all-cause death



SOURCE: RWE SLR (see Appendix D.2)

Table 46. Identified studies and interventions of interest: All-cause death

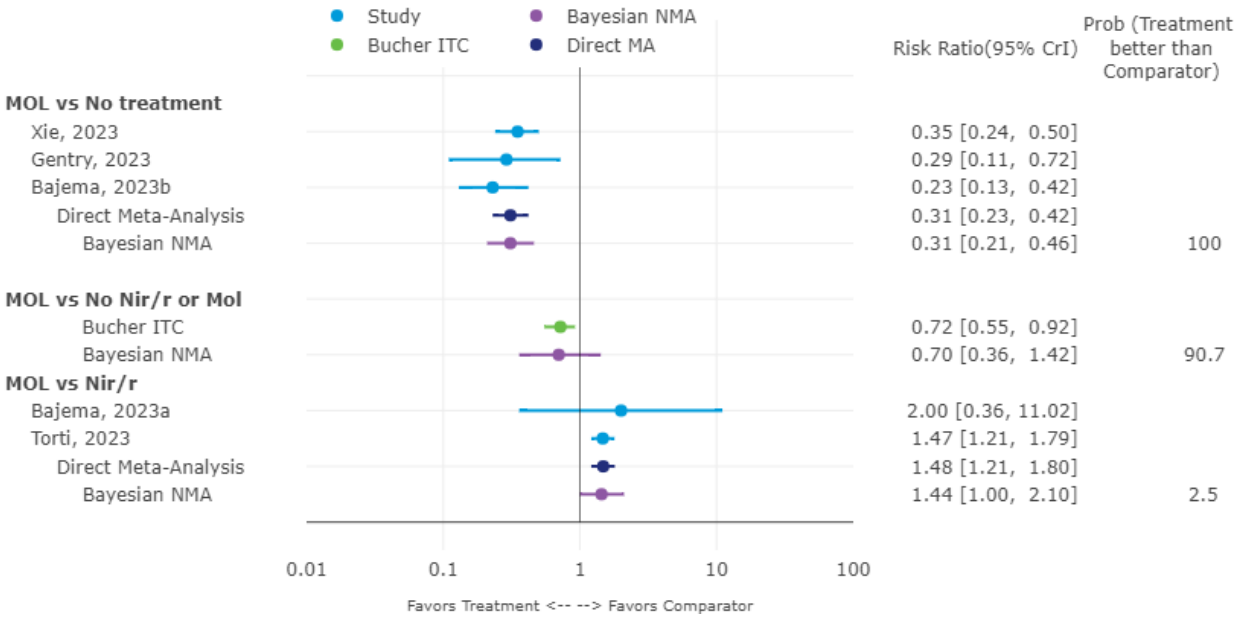
Publication (author/year)	Intervention	Country	Study design	Population
Studies that included molnupiravir as an intervention				
Xie 2023	Molnupiravir versus no treatment	US	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection with at least one risk factor for progression to severe disease
Gentry 2023	Molnupiravir versus nirmatrelvir plus ritonavir	US	Matched case control	US Veterans ≥ 65 years of age with mild to moderate COVID-19 considered to be at high risk of disease progression
Torti 2023	Molnupiravir versus nirmatrelvir plus ritonavir	Italy	Prospective cohort	Non-hospitalised patients aged ≥18 y with confirmed SARS-CoV-2 infection
Bajema 2023	Molnupiravir versus nirmatrelvir plus ritonavir versus no treatment	US	Retrospective cohort	Non-hospitalised veterans in VHA care who are at risk for severe COVID-19 and tested positive for SARS-CoV-2
Studies that did not include molnupiravir as an intervention				
Aggarwal 2023	Nirmatrelvir plus ritonavir versus no treatment	US	Retrospective cohort	Non-hospitalised adults with confirmed SARS-CoV-2 infection
Dryden-Peterson 2023	Nirmatrelvir plus ritonavir versus no treatment	US	Retrospective cohort	Non-hospitalised adults aged ≥50 y with early COVID-19
Schwartz 2023	Nirmatrelvir plus ritonavir versus no nirmatrelvir plus ritonavir or no molnupiravir	Canada	Retrospective cohort	Adults with confirmed SARS-CoV-2 infection

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UK = United Kingdom; US = United States
SOURCE: RWE SLR (see Appendix D.2)

The results derived from the active treatment/control network suggested that molnupiravir reduces the risk of all-cause death relative to no treatment (RR 0.31, 95% CrI: 0.21, 0.46; Figure 27). Similarly, molnupiravir was favoured over no nirmatrelvir plus ritonavir or no molnupiravir (RR 0.70, 95% CrI: 0.36, 1.42). However, molnupiravir appeared less effective when compared to nirmatrelvir plus ritonavir (RR 1.44 [95% CrI: 1.00, 2.10]). Comparisons against remdesivir or sotrovimab were not feasible for this outcome.

Further discussion on results for the NMA analyses for this outcome can be found in Appendix D.2.

Figure 27. Active treatment/control evidence network NMA results for all-cause death (random effects)



Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis
SOURCE: RWE SLR (see Appendix D.2)

B.2.9.2.6 Safety results

Studies identified in the RWE SLR reported limited information on the rates of AEs and in most cases these analyses were not adjusted for confounding factors. As a result, an NMA for safety outcomes was not performed.

B.2.9.3 Summary of findings from network meta-analysis

Based on the final scope by NICE, the comparative clinical effectiveness and safety of molnupiravir versus active treatments (nirmatrelvir plus ritonavir, remdesivir and sotrovimab) or no treatment, were evaluated in NMAs of evidence derived from RCTs and studies reporting RWE.

Of relevance to this submission, the NMAs generated estimates of effect for five efficacy outcomes of interest:

- All-cause hospitalisation or death (primary endpoint in the pivotal MOVe-OUT trial)
- COVID-19 related hospitalisation or death
- All-cause hospitalisation
- COVID-19 related hospitalisation
- All-cause death.

Safety outcomes were only evaluated in the NMA of RCT evidence and outcomes of relevance were the proportion of patients reporting AEs, SAEs and treatment discontinuation due to AEs.

Results from the RCT and RWE NMAs demonstrated molnupiravir to be a superior alternative to no treatment and a valuable alternative therapy option to existing NICE-recommended antivirals in the treatment of mild to moderate COVID-19 in patients at risk of developing severe illness.

Treatment effects across active treatments were compared using odds ratios, relative risk, and risk difference for all study outcomes and comparative estimates of treatment effects were summarised using associated 95% CrIs to evaluate uncertainty of the estimates (see Appendix D for detailed treatment effects). Overall, findings from the NMA of RWE were the preferred indirect evidence for clinical effectiveness of molnupiravir over findings from the NMA of RCT data due to narrower CrIs.

B.2.9.3.1 RCT NMA

Molnupiravir versus active treatments

Both nirmatrelvir plus ritonavir and remdesivir were superior in reducing COVID-19 related hospitalisation and COVID-19 related hospitalisation or death compared with sotrovimab and molnupiravir. Given that remdesivir can only be given in the inpatient setting, remdesivir's impact on hospitalisation is not relevant in the context of a community/outpatient setting, which is the focus of this appraisal. All evaluated active treatment options were demonstrated to be more efficacious in reducing all-cause hospitalisation, all-cause death and all-cause hospitalisation or death compared with molnupiravir in adult patients with confirmed COVID-19 treated in the community/outpatient setting.

Regarding safety outcomes, remdesivir was associated with a lower incidence of AEs and treatment discontinuation due to AEs compared with molnupiravir. Both remdesivir and sotrovimab had similar risk of developing SAEs, both of which were lower than those receiving molnupiravir.

Molnupiravir versus no treatment

The results of the NMAs of RCT evidence indicated molnupiravir to be favourable in comparison to no treatment for all efficacy outcomes.

In addition, in most of the trials included, molnupiravir performed better than placebo in terms of safety outcomes, which could be due to symptoms related to COVID-19 itself or the nocebo effect.

B.2.9.3.2 RWE NMA

Molnupiravir versus active treatments

Remdesivir was demonstrated to be superior in reducing all-cause hospitalisation, COVID-19 related hospitalisation, all-cause death, all-cause hospitalisation or death and COVID-19 related hospitalisation or death compared with molnupiravir.

Additionally, both nirmatrelvir plus ritonavir and sotrovimab showed favourable results relative to molnupiravir for most outcomes analysed, though results were mixed for COVID-19-related hospitalisation.

Molnupiravir versus no treatment

The results of the NMA of RWE data indicated that molnupiravir was favourable over no treatment for all efficacy outcomes.

B.2.9.4 Limitations in the indirect and mixed treatment comparisons

B.2.9.4.1 RCT indirect and mixed treatment comparisons

While each trial was thoroughly evaluated during the feasibility assessment based on data reported in the available literature, the key assumption of an NMA, namely that the included trials do not differ in factors that can modify treatment effects, could still be violated because of the cross-trial differences in study designs, settings and baseline population characteristics outlined below:

- First, due to the differences in study enrolment periods, geographic regions and permitted prior or concurrent treatments, trial populations may differ in the predominant variants of SARS-CoV-2 that were circulating at the time of the trial, in the vaccination coverage and vaccine type, and in the current treatment options available for COVID-19, all of which may affect the outcomes assessed in the NMAs.
- Second, the distributions of risk factors for developing severe COVID-19 (e.g., comorbidities) may differ across trials due to different inclusion/exclusion criteria.

In relation to the comparability-related issues noted above, another limitation of the NMAs is that, because a relatively small number of trials were considered appropriate for inclusion, most networks are sparse and contain only one trial per comparison link, which means that it

is not feasible to conduct analyses using random-effect models to account for between-trial heterogeneity of treatment effects. Similarly, the sparsity of the network makes it challenging for direct adjustments (e.g., via meta-regression) for observed cross-trial differences. Additionally, it allows for reliably adjusting for cross-trial differences in placebo arm response, which could reduce potential bias by accounting for the integrated effects of multiple observed and unobserved differences in trial-level factors that are also likely to impact treatment effects. The small number of trials also made it challenging to perform subgroup analyses to assess impacts of factors that can potentially modify treatment effects.

The number of death events were small across all studies, especially in the active treatment arms; thus, results from the analysis of all-cause mortality can be unstable and need to be interpreted with caution. Additionally, because the MONET trial (Mazzotta 2023) reported zero number of event of hospitalisation or death for the treatment arm of nirmatrelvir plus ritonavir, zero-event correction was applied to allow for NMA estimation in the networks of all-cause hospitalisation, COVID-19 related hospitalisation, all-cause hospitalisation or death, and COVID-19 related hospitalisation or death; because of this correction, the effect of nirmatrelvir plus ritonavir relative to sotrovimab could be underestimated.

Finally, not all clinically relevant efficacy outcomes (e.g., time to sustained recovery of COVID-19 related signs and symptoms) were included in this NMA due to important differences in outcome definitions across trials or lack of data availability.

B.2.9.4.2 RWE indirect and mixed treatment comparisons

To ensure the evidence base was representative of the UK setting, only studies conducted in countries with vaccination rates comparable to the UK were prioritised for full data extraction and assessed for inclusion in the RWE NMA. There was also concern as to whether some of the older studies would be representative of current UK clinical practice, given the heterogeneity in the SARS-CoV-2 variants studied across the different time periods; therefore, only studies conducted across mid-2022 and onward were included in the NMA. Despite efforts to minimise heterogeneity, the included studies inevitably cover time periods when different Omicron subvariants were dominant.

Several studies included in the analyses were retrospective database studies which inherently have limited control over potential sources of confounding and are often unable to provide detailed information on procedures such as treatment administration and outcome assessments. Studies with specific quality concerns, particularly those which did not adequately adjust for patients' baseline risk or other identified sources of potential

confounding, were excluded from the analyses. Nonetheless, the validity of the NMA results is contingent on several assumptions:

- Unless stated otherwise, it is assumed that treatments were administered according to their approved label and at the authorised doses and schedules.
- Unless otherwise specified, it is assumed that mortality/hospitalisation rates include deaths/hospitalisations due to any cause.
- It is assumed that studies used similar criteria to establish COVID-19 as the cause of death/hospitalisation.
- Outcomes assessed between 28 days and 35 days are assumed to be suitable for comparison.
- It is assumed that differences in the index date or study baseline (i.e., whether follow-up was measured from symptom onset, positive test, or drug administration) will not invalidate the analyses.

Control groups were often poorly described. Studies in which the control group were untreated and those in which there was ambiguity as to whether patients in the control may have received treatment other than the study intervention (no molnupiravir and no nirmatrelvir/ritonavir) were considered separate comparators in the NMA.

Some included studies used different cohorts for different treatment comparisons and in some cases did not clearly state whether these cohorts were mutually exclusive, therefore including multiple analyses from a single study may, in some cases, have resulted in double-counting patients. In addition, a few studies analysed data sets obtained from the same data source which could also have resulted in the double-counting of patient data.

Finally, there was the suggestion of significant and notable statistical heterogeneity for some outcomes in the overall active treatment/control network, in particular, the analysis of all-cause hospitalisation or death. Furthermore, the relatively low event rates observed in many of the studies included in the analyses likely reduces the power to detect heterogeneity, therefore any observed low statistical heterogeneity does not necessarily imply clinical homogeneity. Although there were no signals for inconsistency in any pair of consistency/inconsistency models, paired instances of high deviance scores for both consistency and inconsistency models are demonstrations of heterogeneity.

B.2.10 Adverse reactions

B.2.10.1 MOVe-OUT: Final analysis of safety

Safety analyses for the MOVe-OUT study were performed in the APaT population, which included 1,411 randomised patients who received at least one dose of molnupiravir or placebo.(76)

B.2.10.1.1 Day 14 follow-up (APaT population)

Overall, the safety profile of molnupiravir was comparable to placebo; no specific safety findings associated with molnupiravir were observed.(76) The percentage difference between molnupiravir and placebo was less than 3.0% for all AEs reported.(76)

AEs occurred in 31.7% of the total study population:(76)

- The most frequently reported (≥ 2%) AEs for molnupiravir and placebo were COVID-19 (7.9% versus 9.8%), COVID-19 pneumonia (6.3% versus 9.6%), diarrhoea (2.3% versus 3.0%) and bacterial pneumonia (2.0% versus 1.6%).
- No trends in AEs by intervention group were observed.

There were 14 AEs leading to death across the treatment groups, of which 12 patients (1.7%) were in the placebo group and two patients (0.3%) were in the molnupiravir group.(84) None of the deaths were considered by the investigator to be related to the study intervention.(84) Additionally, 20 patients (2.9%) in the placebo group experienced an AE leading to discontinuation of study intervention compared to ten patients (1.4%) in the molnupiravir group.(84)

The incidence of drug-related AEs was low for both molnupiravir and placebo groups (8.0% and 8.4%, respectively).(84) One serious drug-related AE was observed in the placebo group.(84) Four patients (0.6%) in the molnupiravir group and three patients (0.4%) in the placebo group had a drug-related AE that led to discontinuation to study intervention.(84)

The proportion of patients reporting SAEs in the molnupiravir and placebo groups was 6.9% and 9.6%, respectively.(84) None of the SAEs reported in the molnupiravir group were considered by the investigator to be related to the study intervention.(84)

Results from the primary safety analyses of the MOVe-OUT trial are summarised in Table 47.

Table 47. Summary of AEs during treatment and 14-day follow-up period in the MOVe-OUT trial (APaT population)

Adverse event	Molnupiravir (n = 710), %	Placebo (n = 701), %	Total (n = 1,411), %	Difference in % vs placebo estimate (95% CI)[a]
One or more AE	216 (30.4)	231 (33.0)	447 (31.7)	-2.5 (-7.4, 2.3)
Drug-related[b] AE	57 (8.0)	59 (8.4)	116 (8.2)	-0.4 (-3.3, 2.5)
SAE	49 (6.9)	67 (9.6)	116 (8.2)	-2.7 (-5.6, 0.2)
Serious drug-related AE	0	1 (0.1)	1 (0.1)	-0.1 (-0.8, 0.4)
AE leading to death	2 (0.3)	12 (1.7)	14 (1.0)	-1.4 (-2.7, -0.5)
AE leading to discontinuation of study intervention	10 (1.4)	20 (2.9)	30 (2.1)	-1.4 (-3.1, 0.1)
Drug-related AE leading to discontinuation of study intervention	4 (0.6)	3 (0.4)	7 (0.5)	0.1 (-0.8, 1.1)
SAE leading to discontinuation of study intervention	5 (0.7)	13 (1.9)	18 (1.3)	-1.2 (-2.5, 0)
Serious drug-related AE leading to discontinuation of study intervention	0	0	0	0 (-0.5, 0.5)

[a] Based on Miettinen & Nurminen method. [b] Determined by the investigator to be related to the drug.
AE = adverse event; APaT = all-participants-as-treated; CI = confidence interval; SAE = serious adverse event
SOURCE: Jayk Bernal et al., 2022.(84)

B.2.10.1.2 Month 7 follow-up (APaT population)

At Month 7, only serious drug-related AEs were collected.(144) Results from the Month 7 follow-up showed that of the APaT population (n=1,411), one patient (0.1%) from the placebo group experienced a serious drug-related AE of pancreatitis.(144) No serious drug-related AEs were reported for patients in the molnupiravir group.(144)

Overall, Month 7 safety results supported the Day 14 safety results, indicating molnupiravir is well tolerated in the treatment of adults with mild to moderate COVID-19 in non-hospitalised adults with a positive SARS-CoV-2 diagnostic test.(144)

B.2.11 Ongoing studies

PANORAMIC is an ongoing UK multicentre, open-label, prospective, platform adaptive trial which aims to evaluate the effect of molnupiravir in addition to current usual care and nirmatrelvir plus ritonavir in addition to usual care in reducing hospital admissions and death associated with COVID-19.(93)

The phase of PANORAMIC evaluating molnupiravir is complete, as such there is no expected additional data pertaining to the clinical effectiveness of molnupiravir. At the time of

this submission, PANORAMIC is currently evaluating the clinical effectiveness of nirmatrelvir plus ritonavir for the treatment of COVID-19.[60] [93]

Further details of PANORAMIC are described in Section B.2.2.2.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Direct evidence: MOVe-OUT

Direct evidence used to support the efficacy and safety of molnupiravir in patients with mild to moderate COVID-19 at risk of severe illness was taken from the phase III portion of the MOVe-OUT trial. MOVe-OUT was a randomised, double-blinded, parallel assignment, interventional, placebo-controlled trial designed to evaluate the efficacy and safety (up to 7-month follow-up) of molnupiravir for the treatment of mild to moderate COVID-19 in non-hospitalised adults with a positive SARS-CoV-2 diagnostic test and with symptom onset within five days prior to randomisation, who have at least one risk factor for developing severe illness.[84] The MOVe-OUT trial was conducted in 107 sites in 20 countries across the US, Europe and Asia, including six sites in the UK.[76], [84] After full enrolment, a total of 1,433 patients had been randomised 1:1 to the two treatment groups (molnupiravir: n=716; placebo: n=717).[84] The majority of patients completed the 5-day treatment regimen (95.3%), the Day 29 follow-up (95.8%) and the LFU at Month 7 (94.8%).

- **The primary efficacy objective** of MOVe-OUT was to evaluate the efficacy of molnupiravir compared to placebo in reducing the proportion of participants who were hospitalised for any cause or who died from study initiation to Day 29.[84]
- **The primary safety objective** of MOVe-OUT was to evaluate the safety and tolerability of molnupiravir compared to placebo as assessed by the number of AEs and AEs leading to discontinuation of study intervention from study initiation to Month 7.[84]

B.2.12.1.1 Efficacy analysis

Results from the interim analysis of MOVe-OUT demonstrated molnupiravir to be superior to placebo for the primary efficacy endpoint:

- The proportion of patients who were hospitalised for any cause or died from study initiation to Day 29 was statistically significantly lower in the molnupiravir group (28 patients; 7.3%) versus placebo (53 patients; 14.1%), corresponding to a 6.8 percentage-point reduction (95% CI: -11.3, -2.4; one-sided p=0.0012; approximately 50% relative risk reduction).

- All participants who died from study initiation to Day 29 were in the placebo group (8 patients; 2.1%).

Final analysis of the primary endpoint at Month 7 was consistent with results from the Day 29 follow-up, with molnupiravir demonstrated as favourable in reducing all-cause hospitalisation or death compared with placebo to treat mild to moderate COVID-19 in adults with a positive SARS-CoV-2 diagnostic test:[144]

- The proportion of patients who died from Day 30 to Month 7 was lower in the molnupiravir group (3 patients; 0.4%) versus the placebo group (6 patients; 0.6%).
    - One death in the molnupiravir group was considered to be COVID-19 related compared to two deaths in the placebo group.
- Fewer patients were hospitalised from Day 30 to Month 7 in the molnupiravir group (2 patients; 0.3%) versus the placebo group (3 patients; 0.4%).

B.2.12.1.2 Safety analysis

Safety analyses for the MOVe-OUT study were performed on the APaT population which included 1,411 randomised patients who received at least one dose of molnupiravir or placebo.[76] Overall, the safety profile of molnupiravir was comparable to placebo indicating molnupiravir is well tolerated in the treatment of adults with mild to moderate COVID-19 in non-hospitalised adults with a positive SARS-CoV-2 diagnostic test.[144] No specific safety findings associated with molnupiravir were observed.[76] The percentage difference between molnupiravir and placebo was less than 3.0% for all AEs reported.[76] Additionally, at Month 7, only serious drug-related AEs were collected.[144] Results from the Month 7 follow-up showed that of the APaT population (n=1,411), one patient (0.1%) from the placebo group experienced a serious drug-related AE of pancreatitis.[144] No serious drug-related AEs were reported for patients in the molnupiravir group.[144]

B.2.12.1.3 Strengths and limitations

The MOVe-OUT trial provides direct evidence demonstrating the beneficial clinical effectiveness and safety of molnupiravir as a treatment for mild to moderate COVID-19 in non-hospitalised adults who have at least one risk factor for developing severe illness. Molnupiravir met the primary efficacy endpoint of MOVe-OUT demonstrating statistically significant superiority over placebo.[84]

However, MOVe-OUT, as with the other RCTs identified in the SLR, was conducted prior to the emergence of the Omicron variants and consisted of a predominantly unvaccinated population. Nevertheless, there remains a small proportion of people who are unvaccinated

(or are under vaccinated). Therefore, the results from MOVe-OUT are still relevant, albeit for a small proportion.

Additionally, no direct RCT evidence was identified for molnupiravir versus active treatment, therefore, this has not been presented in this submission.

B.2.12.2 Indirect evidence: NMAs of RCT and RWE data

Both RCT and RWE SLRs were conducted to identify evidence on the efficacy and safety of molnupiravir versus no treatment and existing treatments in COVID-19. Feasibility assessments were then conducted to establish the viability of a NMA for indirect comparison of efficacy and safety outcomes of interest between molnupiravir and other treatments (nirmatrelvir plus ritonavir, sotrovimab and remdesivir) for mild to moderate COVID-19 in a community/outpatient setting.

B.2.12.2.1 RCT data

The RCT SLR yielded a total of 14 studies that evaluated four community/outpatient COVID-19 treatments (molnupiravir, nirmatrelvir plus ritonavir, sotrovimab and remdesivir), of which 11 were deemed suitable for analysis in the NMA.

Results of the NMA demonstrated that across treatments, patients receiving molnupiravir had no significant difference in all-cause hospitalisation, COVID-19 related hospitalisation or death versus those receiving nirmatrelvir plus ritonavir, remdesivir or sotrovimab. However, molnupiravir was associated with a lower risk of all-cause hospitalisation, COVID-19 related hospitalisation or death when compared with placebo.

B.2.12.2.2 RWE data

The RWE SLR yielded a total of 30 relevant studies prioritised for full extraction of which, 22 were deemed suitable by the feasibility assessment for analysis in the NMA.

Aligned with the findings of the RCT NMA, molnupiravir was demonstrated to be a suitable alternative to no treatment, associated with significantly improved outcomes versus placebo. Results from the RWE NMA suggested no significant difference in reducing the risk of all-cause hospitalisation or death for molnupiravir relative to nirmatrelvir plus ritonavir and sotrovimab in outpatients with mild to moderate COVID-19. Despite molnupiravir not demonstrating a numerically significant difference in efficacy versus nirmatrelvir plus ritonavir, remdesivir or sotrovimab for any of the outcomes assessed, the unmet need remains for a suitable alternative to current treatments.

B.2.12.2.3 Strengths and limitations of the indirect treatment comparisons

The NMAs of RCT and RWE data provide beneficial indirect evidence that demonstrates both the clinical effectiveness and safety of molnupiravir for the treatment of mild to moderate COVID-19 in a community/outpatient setting. The NMA approach allowed for indirect comparison of efficacy and safety outcomes across multiple treatments (molnupiravir, nirmatrelvir plus ritonavir, sotrovimab and remdesivir) in the absence of direct comparisons in head-to-head trials. Additionally, the analyses of both RCT and RWE data included the most up-to-date body of evidence comparing COVID-19 treatments of interest.[84] However, findings from the RCT NMAs came with high uncertainty (as measured by wide CrI of risk ratios) compared with findings from the RWE NMAs. Therefore, findings from the NMA of RWE data are the preferred indirect evidence of the clinical effectiveness of molnupiravir in this submission.

Additionally, studies in the SLR of RWE were conducted from 2022 onward so the NMA results specifically show effectiveness of active treatments versus Omicron variants in vaccinated populations, reflecting the current endemic nature of the disease. This is opposed to the SLR of RCTs, as many of these trials were conducted in unvaccinated populations before the emergence of the Omicron variants, so the relevance of their findings to the current situation is less clear. For example, data from the PINETREE trial (Gottlieb 2022) should be interpreted carefully in the current context of the COVID-19 pandemic, as an exclusively unvaccinated population was recruited. In addition, the study authors state that trial recruitment began before the emergence of the Delta variant of SARS-CoV-2.[104]

B.3 Cost-effectiveness

Key summary points

- An SLR of cost-effectiveness studies and evaluation of previous NICE assessments were used to consider cost-effectiveness analysis approaches for molnupiravir.
- A new and simplified approach was used to model the in-hospital pathway since molnupiravir is positioned predominantly as a community/outpatient treatment.
- The model assessed the cost-effectiveness of molnupiravir for the treatment of patients with mild to moderate COVID-19 at risk of developing severe illness, using a decision-tree like analysis for the acute phase of disease where patients are treated in the community as outpatients either recover or are hospitalised. Once hospitalised, patients switched from outpatient treatment to inpatient treatment and are either treated in general medical ward or intensive care unit (ICU) with or without mechanical ventilation. Patients who survive the acute phase enter a Markov model where patients recover or experience long-term sequelae.
- In contrast to previous cost-effectiveness analyses, the model includes a treatment effect for time to symptom resolution and quality of life impact for outpatients to reflect the additional endpoints of relevance in the endemic setting of COVID-19 which are important for patients.
- The model does not formally consider incidental COVID-19 acquired in hospital as the scope of the cost-effectiveness analysis is only for outpatients eligible for molnupiravir.
- The base case assessed molnupiravir in the overall population at risk of severe disease compared with nirmatrelvir plus ritonavir or sotrovimab. Additional subgroups assessed were patients aged > 70 years, patients contraindicated to nirmatrelvir plus ritonavir, immunocompromised patients and patients with chronic kidney disease.
- Inputs were mainly sourced from the RWE SLR and NMA for the base case and scenarios were performed using mainly trial-based data and recommended parameter values from TA878 and TA971.
- Base case results show that molnupiravir accumulated costs of £[redacted] and total quality-adjusted life years (QALYs) of [redacted]. The incremental cost-effectiveness ratio (ICER) of molnupiravir versus no treatment was £[redacted].

Compared to nirmatrelvir plus ritonavir and sotrovimab, molnupiravir had lower costs and lower QALYs, however absolute incremental differences in costs and QALYS between molnupiravir and nirmatrelvir plus ritonavir and sotrovimab are very small for patients with access to alternative options.

- Scenarios investigating the impact of using hospitalisation rate and mortality from the MOVe-OUT trial demonstrated a lower ICER compared to no treatment but a similar conclusion when comparing to nirmatrelvir plus ritonavir and sotrovimab.
- For the range of subgroups considered, the ICER for molnupiravir compared to no treatment was improved in comparison to the overall at-risk population.
- Molnupiravir offers significant benefits versus no treatment in patients which currently remain untreated for mild/moderate disease addressing residual unmet medical need and ongoing equity elements.

B.3.1 Published cost-effectiveness studies

B.3.1.1 Systematic review of cost-effectiveness studies

An SLR was conducted with a cut-off date of 22 January 2024 to identify economic evaluations and/or cost-effectiveness studies of therapies for patients with COVID-19 (specific details are provided in Appendix G). The SLR was conducted as per Cochrane guidelines,[148] and encompassed both electronic databases (i.e., Embase, Medline, CENTRAL, and EconLit) and relevant congresses (i.e., European Society of Clinical Microbiology and Infectious Diseases, International Society for Pharmacoeconomics and Outcomes Research, Conference on Retroviruses and Opportunistic Infections, and European Respiratory Society; years 2020–2024 for all).

The review found 9,271 unique records, and after screening, 36 economic evaluations were reviewed in depth as full text articles. Table 60 of Appendix G summarises the five economic evaluations that were subsequently identified as being related to molnupiravir and relevant comparators and that are also applicable to the UK population for this appraisal. Png et al., 2023 is a within trial analysis employing a 6-month time horizon (follow-up) and as such results cannot be used to generalise the cost-effectiveness of molnupiravir in the NHS.[149]

B.3.1.2 Relevant previous NICE assessments

Antivirals and monoclonal antibodies for the treatment of COVID-19 (in both outpatient and inpatient settings) have been assessed in a multiple technology appraisal, TA878,[43] and a partial review of nirmatrelvir plus ritonavir.[44] Subsequently, a separate multiple technology

appraisal for remdesivir and tixagevimab plus cilgavimab, TA971, was conducted.[74] All three assessments used the same cost-effectiveness analysis method, which is summarised in Table 48.

As set out in the final scope of this appraisal, a new approach has been taken to assess the cost-effectiveness of molnupiravir. The approach used is similar to other cost-effectiveness models such as Jo et al., 2021, Sheinson et al., 2021, Jovanoski et al., 2022 and models used in the ICER assessments.[150-154] The model used in this submission takes a simplified approach to the pathway within hospital as molnupiravir is positioned as an outpatient treatment. Tracking of ordinal scales and movement within hospital is unnecessarily complicated for an outpatient treatment and would be challenging to parameterise for the current setting. Any prior outpatient treatment would not be expected to impact the downstream inpatient treatment effectiveness for patients progressing to severe COVID-19. The model also aims to capture benefits not fully addressed in the cost-effectiveness model used for TA878 and TA971 as laid out in the Company Decision Problem Form,[155] such as inclusion of treatment effect for time to symptom resolution and inclusion of quality of life impact for outpatients. The model also considers the subgroup of patients contraindicated for nirmatrelvir plus ritonavir and accounts for the additional costs of testing for DDIs with nirmatrelvir plus ritonavir.

Table 48. Summary of previous cost effectiveness analyses used to evaluate treatments for COVID-19

Technology appraisal	**TA878** **Nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19**	**TA878** **Partial review of nirmatrelvir plus ritonavir for treating COVID-19**	**TA971** **Remdesivir and tixagevimab plus cilgavimab for treating COVID-19**
Form of assessment	Multiple technology appraisal		
Assessment group	ScHARR, University of Sheffield		
Publication date	29 March 2023	13 March 2024	08 May 2024
Summary of model	Approach: CEA informed by living systematic reviews Model type: Decision-tree and partitioned survival model Time horizon: Lifetime (depending on starting age, up to a maximum of 100 years) Treatment: Multiple interventions compared with each other and SoC compared to each intervention. Interventions included casirivimab/imdevimab, molnupiravir, tocilizumab, ritonavir, remdesivir, sotrovimab, baricitinib, baricitinib and remdesivir combination, and lenzilumab. Currency year:2019/2020 Perspective: UK NHS and Personal Social Services		
QALYs	Utility decrements for severe COVID-19 infection were based on Rafia et al., 2022[156] and were from a population with *C. Diff* and influenza infections. No impact of mild COVID-19 on HRQoL was assumed. Post-discharge long-COVID utility decrements were based on Evans et al., 2022.[157]		

Technology appraisal	TA878 Nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19	TA878 Partial review of nirmatrelvir plus ritonavir for treating COVID-19	TA971 Remdesivir and tixagevimab plus cilgavimab for treating COVID-19
Costs (currency, intervention, comparator)	Resource use cost data were taken from NHS National Schedule of NHS costs 2019-2020, and costs associated with long-COVID were assumed to be similar to the management of chronic fatigue syndrome		
ICER (per QALY gained) vs no treatment	Nirmatrelvir plus ritonavir: £7,892 per QALY gained Sotrovimab: NR	Around £20,000 per QALY gained	Remdesivir: > £20,000 per QALY gained Tixagevimab plus cilgavimab: NR

CEA = cost-effectiveness analysis; COVID-19 = coronavirus disease 2019; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; NR = not reported; QALY = quality-adjusted life years; RR = relative risk

B.3.2 Economic analysis

The economic analysis presented here is a cost-effectiveness analysis of molnupiravir for the treatment of mild to moderate COVID-19 in patients at risk of severe illness, compared to no treatment. This represents the marketing authorisation indication.

B.3.2.1 Patient population

The target population in the analysis was non-hospitalised adults (i.e. treated in community) with mild to moderate COVID-19 at risk of progression to severe illness leading to hospitalisation. Incidental COVID-19 while in hospital was not formally explored in the cost-effectiveness analysis (Section B.1.1 and Section B.3.2.3.1). The model used the MITT analysis from the MOVe-OUT trial, and thus the MOVe-OUT definition of high risk for severe illness, which most closely aligns with the Edmunds criteria of high risk.[42, 84] The following subgroups were also included:

- Aged over 70 years
- Contraindicated to nirmatrelvir plus ritonavir
- Immunocompromised
- Chronic kidney disease

Details of the subgroup inputs and results are presented in Appendix E and Section B.3.12 , respectively.

B.3.2.2 Model structure

The model structure was designed to reflect current UK clinical practice for patients in the outpatient setting with COVID-19 at high risk of severe illness. It uses a decision-tree like analysis for the acute phase of disease, followed by a Markov model for the patients who survived the acute phase. Figure 28 shows a schematic of the model structure.

- The acute phase, with a duration of 30 days, aligns with the COVID-19 infection period and considers the healthcare settings in which a patient with COVID-19 may be treated. These include outpatient, hospitalisation in general medical ward, or hospitalisation in high dependency unit or ICU with mechanical ventilation. Once in hospital, the treatment effect was driven by active in-patient treatment received (either remdesivir or tocilizumab).

- The treatment effect for molnupiravir and outpatient comparators includes prevention of progression to hospitalisation and reduction in the duration of symptoms. Reduction in duration of symptoms impacts the duration of reduced utility for symptomatic outpatients who are not hospitalised. As noted by clinical experts in the appraisal of remdesivir (TA971), efficacy measures such as these are becoming increasingly relevant in the endemic phase of the disease.[74]

- Patients who survive the acute phase enter the Markov model in the alive state and can either experience long-term sequelae before recovering or proceed directly to the recovered state. Those who experience long-term sequelae after hospitalisation have a standardised mortality ratio applied to background mortality for the duration of long-term sequelae. Readmission to hospital is also possible for patients with long-term sequelae, however readmission this is not formally modelled in the current assessment as costs of long-term sequelae included costs of readmission. In the post-acute phase Markov model, the cycle length was one week for the first year, followed by a yearly cycle until death or 100 years of age, whichever occurred first.

The analysis assessed the use of molnupiravir versus nirmatrelvir plus ritonavir, sotrovimab and no treatment as comparators, as appropriate (see Section B.3.2.3). The model also applied a treatment effect within hospitalisation for tocilizumab or remdesivir therapy as recommended by NICE for hospitalised molnupiravir-eligible patients.[43, 74]

- Remdesivir is recommended by NICE for the treatment of COVID-19 in hospital and therefore does not form part of the outpatient treatment pathway. If incidental COVID-19 is diagnosed in an inpatient setting, the usual outpatient pathway is followed, along with the option to use remdesivir, according to clinical judgement (Figure 1).[74] If a patient is admitted to hospital primarily to treat COVID-19, and remains on a general ward, with or without the use of low-flow oxygen, remdesivir can be administered as per TA971.[74] Remdesivir treatment is included in the model for patients in the general ward only. It is noted that TA971 stipulates that the use of remdesivir in adults extends to time spent under low-flow oxygen (with no such

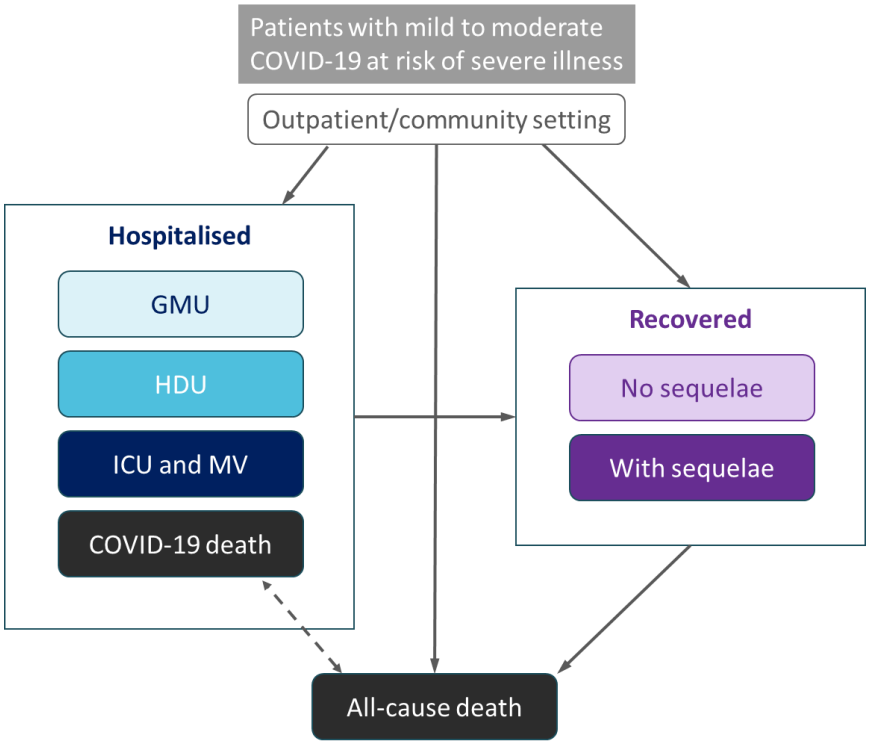
statements for any technologies approved in TA878).[44, 74] Therefore, we consider this to be a "treatment escalation" for patients in need and within the hospital setting.

- The model does not formally consider incidental COVID-19 acquired in hospital as the scope of the cost-effectiveness analysis is only for patients eligible for molnupiravir (i.e. with mild to moderate COVID-19, which is largely confined to the outpatient setting). Please see Section B.3.2.3.1 for more information on remdesivir and incidental COVID-19 in the model.

- No infectious disease component is included in the model owing to lack of data for onward transmission (in household or hospital), although any such benefits are positive externalities that need to feature in decision making.

The cost year for the analysis was 2024. Costs published for previous years were inflated using the Unit Costs of Health and Social Care 2023 Manual, PSSRU.[158] Costs and QALYs were discounted at 3.5% per year in accordance with NICE guidelines.[159]

Figure 28. Model schematic



*Note: the model does not track COVID-19 related deaths; it is assumed that in-hospital deaths in hospital are due to COVID-19.
Dashed line indicates deaths from those with long-term sequelae are considered as COVD-19 deaths
COVID-19 = coronavirus disease 2019; GMU = general medical ward; HDU = high dependency unit; ICU = intensive care unit; MV = mechanical ventilation

B.3.2.3 Intervention technology and comparators

The intervention used in the model was molnupiravir. Comparators were used as appropriate, according to NICE recommendations and available data (Figure 1 and Table 49):

- For the main analysis of patients at risk of severe COVID-19, nirmatrelvir plus ritonavir, sotrovimab and no treatment were used as comparators. In the absence of separate data for the McInnes and Edmunds criteria, this analysis covers settings (a) to (c) in Figure 1. In addition, this is used as a proxy for incidental COVID-19 as per setting (d), in the absence of specific data.
- For the subgroup analyses of patients > 70 years, a subset of patients in settings (a) and (c) in Figure 1, nirmatrelvir plus ritonavir and no treatment were used as comparators.
- For the subgroup analysis of immunocompromised patients, a subset of patients in settings (a) and (b) in Figure 1, nirmatrelvir plus ritonavir, sotrovimab and no treatment were used as comparators.
- For the subgroup analyses of patients with chronic kidney disease and those contraindicated to nirmatrelvir plus ritonavir, sotrovimab and no treatment were used as comparators. This analysis more specifically considers settings (b) and (c) in Figure 1.

As in Section B.1.3.2.2 MSD explores a positioning to enable clinicians to determine the most suitable treatment for each patient on an individual basis, accounting for personal and clinical aspects alongside the current NHS-E clinical commissioning criteria.

Table 49 below outlines the brief overview of comparators per proposed positioning and justification for clarity. Table 49. Comparators used in the subgroup analyses conducted

Subgroup analysis	Comparator(s)	Justification
Patients contraindicated to nirmatrelvir plus ritonvir	• Sotrovimab • No treatment	• As per TA878, patients at-risk according to the McInnes criteria and contraindicated for nirmatrelvir plus ritonavir are eligible to receive sotrovimab. • Patients at-risk according to the expanded Edmunds criteria (but falling outside the McInnes criteria) are not eligible to receive sotrovimab, so if they are contraindicated for nirmatrelvir plus ritonavir they would not be eligible to receive any other treatment in the absence of molnupiravir.
Patients aged 70 years and above	• Nirmatrelvir plus ritonavir • Sotrovimab • No treatment	• As per updated TA878, patients aged 70 years and above are eligible to receive nirmatrelvir plus ritonavir. • 65.32%[160] of those over 70 years also have at least one other risk condition as per the McInnes criteria, therefore these patients would be eligible to receive sotrovimab if contraindicated to nirmatrelvir plus ritonavir. • Those over 70 years without another risk condition are not eligible to receive sotrovimab, so *if* contraindicated for nirmatrelvir plus

Subgroup analysis	Comparator(s)	Justification
		ritonavir they would not be eligible to receive any other treatment in the absence of molnupiravir.
Immunocompromised patients	• Nirmatrelvir plus ritonavir • Sotrovimab • No treatment	• Immunocompromised patients fall within the McInnes criteria, so as per TA878 they are eligible to receive nirmatrelvir plus ritonavir, or sotrovimab if contraindicated. • Should patients be contraindicated for nirmatrelvir plus ritonavir and have difficulty accessing sotrovimab, which is delivered by i.v. infusion in a secondary care setting, they may not receive any other treatment in the absence of molnupiravir.
Patients with severe (stage 4-5) chronic kidney disease	• Sotrovimab • No treatment	• Patients with severe CKD are contraindicated for nirmatrelvir plus ritonavir, but as per TA878, they are at-risk according to the McInnes criteria and are therefore eligible to receive sotrovimab. • Should patients with severe CKD have difficulty accessing sotrovimab, which is delivered by i.v. infusion in a secondary care setting, they may not receive any other treatment in the absence of molnupiravir.

B.3.2.3.1 Incidental COVID-19 and remdesivir as a comparator in the model

Incidental COVID-19 occurs in patients admitted to hospital for other reasons unrelated to COVID-19. This patient group is not formally included in the cost-effectiveness model as there is no available trial evidence on the use of treatments for incidental COVID-19. The following text describes MSD's rationale for this decision.

Remdesivir is recommended by NICE for in-hospital treatment of COVID-19 in adults (TA971) and is no longer offered as a part of outpatient management of COVID-19.[74] In the case of incidental COVID-19, clinical experts suggest that the outpatient pathways for the management of COVID-19 are followed. This means that nirmatrelvir plus ritonavir would be offered first-line in those at risk of severe disease, followed by sotrovimab if nirmatrelvir plus ritonavir is contraindicated (Section B.1.3.2; Figure 1). Clinical opinion suggests that remdesivir is not normally used until low-flow oxygen is required as part of treatment management and therefore when there is an escalation in the severity of COVID-19. Molnupiravir, as part of the outpatient treatment pathway, is occasionally used in patients with incidental COVID-19 if nirmatrelvir plus ritonavir and sotrovimab are contraindicated.

As per TA971, MSD understands that while clinical evidence for remdesivir as an in-hospital treatment for COVID-19 in adults is uncertain, the drug was considered likely to increase the survival of patients using low-flow oxygen compared to the standard of care, slowing downstream patient deterioration with severe disease.[74] By contrast, TA878 for nirmatrelvir plus ritonavir and sotrovimab does not discuss any oxygen needs for the majority of patients.[43] As such, MSD interprets that remdesivir is a 'treatment escalation' for COVID-19 in hospitalised patients and in specific cases (i.e. for patients who have either progressed

from failure to treat mild or moderate COVID-19 in the outpatient setting or due to a diagnosis of incidental COVID-19 acquired in hospital).

Due to a lack of specific data, the incidental COVID-19 patient group in hospital is not formally modelled to avoid superimposing additional assumptions that would lead to uncertainty. Explicit modelling of this patient group would require a treatment sequence with the relevant outpatient treatment options from TA878, including nirmatrelvir plus ritonavir and sotrovimab, followed by molnupiravir and subsequently remdesivir (depending on the interpretation of the recommendations in TA971).

Instead, the model attempts to avoid unnecessary complexity by assuming that patients treated in the outpatient setting, if hospitalised, experience a COVID-19 treatment escalation. Similarly, patients with incidental COVID-19, who then go on to require supplemental oxygen as part of COVID-19 management, would be deemed to require a COVID-19 treatment escalation. This could include remdesivir for COVID-19 with low-flow oxygen and/or tocilizumab for severe COVID-19 alongside corticosteroids and supplemental oxygen (TA878).[43, 74] This is modelled as patients are distributed to the general medical ward and ICU with mechanical ventilation by the following breakdowns based on expert option:

- Tocilizumab: Patients in ICU with mechanical ventilation as they have severe disease (100% of patients)
- Remdesivir: Patients in general medical ward (50% of patients).

B.3.3 Clinical parameters and variables

Model parameters were obtained from two main sources:

- Published RWE identified from the SLR of RWE (see Section B.2.1.2.2 and Appendix D.2)
- The MOVe-OUT trial and dataset (see Section B.2.2)

Baseline characteristics used in the model are shown in Section B.3.9.1 and Table 70 for the base case population. These include the population size, which was based on numbers published by NICE for the expanded nirmatrelvir plus ritonavir indication,[45] mean age and proportion female. The mean age for the base case was taken from PANORAMIC as this was anticipated to be in line with the overall at-risk population of interest.[93] The proportion female was based on the total number of randomised patients from the MOVe-OUT trial.[84]

Parameters for disease characteristics, treatment effects and AEs are described in the following sections.

Disease characteristics and treatment effects can be greatly affected by timing of the studies used for input data, particularly with the shift of COVID-19 to a more endemic state, which is the case currently in the UK. Depending on when the studies were conducted, factors varied such as the predominant circulating SARS-CoV-2 variant and the choice of best supportive care. In trials conducted more recently, patients are likely to have higher vaccination rates, booster vaccinations and/or increased natural immunity (although some uncertainty around waning of vaccine effectiveness may remain).

Clinical trial-based treatment effects may therefore represent an upper range of plausible efficacy, although direct comparison between trials should be avoided due to generalisability issues of trial data compared to the current endemic state of COVID-19 and differences in high-risk patient groups recruited in each study. However, due to potential interaction issues (such as changing immunity levels alongside circulating variants and associated infectivity to name a few), it is not possible to adjust for these factors across clinical trials. To test the impact of clinical trial-based efficacy estimates, most of which reported results during the pandemic phase of COVID-19 , an 'upper-range' efficacy scenario was assessed using data from clinical trials.

An alternative to clinical trial-based estimates is RWE, which assesses treatment effectiveness in current clinical practice in the endemic setting. Section B.2.9 and Appendix D.2 describe the NMA of RWE, and thus treatment effects from RWE were also considered and used for a 'mid' efficacy scenario.

B.3.3.1 Disease characteristics

Disease characteristics included hospitalisation rate, distribution of highest setting of care for hospitalised patients, length of stay by highest hospitalisation setting and mortality. These parameters were also identified for the subgroups of interest and are presented in Appendix E. Disease parameters which were shared for the overall high-risk population and specific subgroups included:

- Number of symptomatic days for outpatients
- Proportion of hospitalised and non-hospitalised patients with long-term sequelae and the duration of long-term sequelae
- Standardised mortality ratio for hospitalised patients surviving the acute phase

It should be noted that some of the above parameters are likely to vary between subgroups; however, due to a lack of detailed data, despite the extensive literature searches, it was assumed these parameters do not vary.

B.3.3.1.1 Hospitalisation rate

Hospitalisation rate is a key driver for the model. Ideally, values used for this parameter should be for patients not receiving any outpatient COVID-19 treatment and reflect the current endemic state. However, given the continuing changing nature of COVID-19, there is uncertainty around this input, and it is particularly difficult to find accurate data for subgroups.

Hospitalisation rates for both all-cause hospitalisation and COVID-19-related hospitalisations are available from the placebo arm of the MOVe-OUT trial and are presented in Table 50. However, the trial was conducted in early 2021 when the incidence of COVID-19 was higher, vaccination rates were lower and hospital practices were different, compared to current conditions.

Table 50. Summary of hospitalisation rates for patients with COVID-19 from MOVe-OUT

Parameter	Value	95% CI	Source
All-cause hospitalisation rate, %	[redacted]	[redacted]	MOVe-OUT[161]
COVID-19 related hospitalisation rate, %	[redacted]	[redacted]	MOVe-OUT[162]

CI = confidence interval; COVID-19 = coronavirus disease 2019
SOURCE: MOVe-OUT Statistical reports[161, 162]

Alternative sources for hospitalisation rates in untreated patients include studies based on the OpenSAFELY and DISCOVER-NOW databases, which both report COVID-19-related hospitalisation rates (Table 51). Both studies are retrospective cohort studies from the UK and were used in TA878 and TA971 for nirmatrelvir plus ritonavir and remdesivir, respectively. However, to maximise the potential available data, the pooled hospitalisation rate from the untreated arm in the RWE studies included in the RWE NMA (Section B.2.1.2.2, Appendix D.2) was used for this cost-effectiveness analysis. The baseline hospitalisation rate was obtained by conducting a random-effect pairwise meta-analysis (MA) of all 'no treatment' event rates for a given outcome for studies included in the NMA. If a study provided more than one 'no treatment' event rate (for example, if a study had more than one cohort), we calculated a weighted average of the event rate for that study and used that estimate in the pairwise MA.

The RR (with its 95% interval) was then estimated from the NMA for all active treatments versus no treatment, to the point estimate derived from the pairwise MA, which provided a point estimate and 95% CI of baseline hospitalisation rate for all active treatments.

Values for all-cause and COVID-19 related hospitalisation are presented in Table 52. All-cause hospitalisation rate was used for the base case to reflect the primary treatment effect assessed across studies being on all-cause hospitalisation. It was noted that the COVID-19-related hospitalisation rate from the NMA was similar to vales reported in OpenSAFELY and DISCOVER-NOW, confirming the validity of the input.

Table 51. Summary of base case hospitalisation rates for patients with COVID-19 from alternative sources

Parameter	Value	Uncertainty	Source
COVID-19 related hospitalisation rate, %	2.41	NR	OpenSAFELY[44]
COVID-19 related hospitalisation rate, %	2.82	95% CI: 2.30, 3.30	DISCOVER-NOW[163]

CI = confidence interval; COVID-19 = coronavirus disease 2019; NR = not reported
SOURCE: OpenSAFELY[44]; DISCOVER-NOW[163]

Table 52. Summary of hospitalisation rates for patients with COVID-19 from pooled untreated arm of studies in RWE NMA

Parameter	Value	95% CI	Source
All-cause hospitalisation rate, %	3.79	1.87, 7.67	RWE NMA, Section B.2.9.2, Appendix D.2
COVID-19 related hospitalisation rate, %	2.93	0.46, 18.55	RWE NMA, Section B.2.9.2, Appendix D.2

CI = confidence interval; COVID-19 = coronavirus disease 2019; NMA = network meta-analysis; RWE = real-world evidence
SOURCE: RWE NMA Section B.2.9.2 and Appendix D.2

B.3.3.1.2 Distribution of highest setting of care received for hospitalised patients

The proportional distribution of patients by highest hospital setting is available from the MOVe-OUT trial (Table 53). The treatment arms were pooled and WHO 11-Point Scale category 4 and 5 were combined to calculate the proportion in general ward, category 6 was used for the proportion in high dependency unit and category 7–9 was used for the proportion in ICU with mechanical ventilation. These data show a high proportion of patients in high dependency unit and ICU with mechanical ventilation, reflecting that these data were collected in 2021 when incidence of COVID-19 was higher, and treatment was different compared to current conditions.

Table 53. Summary of distribution of patients with COVID-19 in different hospital settings from MOVe-OUT

Parameter	Value	95% CI	Source
Proportion by highest hospital setting, %			
GW	[redacted]	[redacted]	MOVe-OUT[162]
High dependency unit	[redacted]	[redacted]	MOVe-OUT[162]

Parameter	Value	95% CI	Source
ICU with MV	[redacted]	[redacted]	MOVe-OUT[162]

CI = confidence interval; COVID-19 = coronavirus disease 2019; GW = general ward; ICU = intensive care unit; MV = mechanical ventilation
SOURCE: MOVe-OUT statistical report[162]

The limitations around the generalisability of MOVe-OUT to the current endemic state of COVID-19 were highlighted in recent discussions with clinical experts in May 2024. The model allows for three hospital settings: general medical ward, high dependency unit, and ICU with mechanical ventilation. However, according to recent discussions with clinical experts, patients are typically treated in the general ward setting and only moved to the ICU if mechanical ventilation is required, thus, in the base case, the assumption is that all COVID-19 patients are either in the general ward or in ICU receiving mechanical ventilation.[2] Use of the trial distribution in hospital, including high dependency unit, is explored in scenario analysis.

COVID-19 hospital activity data from the NHS[164] represent the most up-to-date source for patients in hospital with COVID-19, and data from 31st March 2024 are shown in Table 54. The proportion of patients in ICU with MV was calculated by dividing the number of COVID-19 ICU patients by the total number of inpatients being treated primarily for COVID-19, as percentages themselves were not published.

Table 54. Summary of distribution of patients with COVID-19 in different hospital settings from NHS data, 31st March 2024

Parameter	Value	95% CI	Source
Proportion by highest hospital setting, %			
GW	85.6	–	NHS data[165]
ICU with MV	14.4	10.88, 18.24	

CI = confidence interval; COVID-19 = coronavirus disease 2019; GW = general ward; ICU = intensive care unit; MV = mechanical ventilation; NHS = National Health Service
SOURCE: NHS data[165]

In further discussions with clinicians, the proportion of patients with COVID-19 in the different hospital settings was noted to be approximately 85% in general ward and 15% in ICU (receiving mechanical ventilation), in line with the NHS data.[2] Similarly, a retrospective cohort study from the UK reported that 14.8% of patients hospitalised with COVID-19 were in critical care.[53] For this reason, NHS data were used in the base case of the model.

B.3.3.1.3 Length of stay

Length of stay is also an important input for the cost-effectiveness analysis; however, data are limited, particularly for subgroups of interest and by risk definitions of interest. Most data are from early in the pandemic, or not relevant to the UK healthcare system.

One source of length of stay data identified is a retrospective cohort study by Yang et al., 2023 reporting healthcare resource utilisation (HCRU) and costs associated with COVID-19 in patients at high risk of severe COVID-19 illness in England.[53] Although data in this study were collected from August 2020 to March 2021, data are reported for critical care duration in addition to assessing different high-risk definitions (including McInnes), age and subgroups, unlike other sources.[53] The study reports overall mean length of stay (general ward and critical care), the proportion of patients in critical care and length of stay in critical care. [53] Mean length of stay in general ward was calculated as overall mean length of stay less the product of the proportion of patients in critical care and length of stay in critical care (Table 55).[53] It is assumed the length of stay in critical care is a reasonable proxy for ICU with MV.

A retrospective cohort study from Scotland reported similar overall length of stay (general ward and ICU) for all-cause and COVID-19 related hospitalisations at 8.4 days and 10.8 days, respectively; however, length of stay in ICU alone was not reported.[166] The Yang et al., study from England was therefore considered the most appropriate to use for the base case.

Table 55. Summary of base case length of stay for patients hospitalised with COVID-19 by hospital setting

Parameter	Value in use	SD	Source
Length of stay by highest hospital setting, days			
GW	8.29	–	Yang et al., 2023[53]
ICU with MV	11.40	10.9	

COVID-19 = coronavirus disease 2019; GW = general ward; ICU = intensive care unit; MV = mechanical ventilation; SD = standard deviation
SOURCE: Yang et al., 2023[53]

B.3.3.1.4 Mortality

Mortality data by highest hospital setting and overall are available from the MOVe-OUT trial (Table 56). Data were calculated by pooling the treatment arms and the proportion in general ward calculated by combining WHO 11-Point Scale category 4 and 5, category 6 was used for the proportion in high dependency unit and category 7–9 was used for the proportion in ICU with mechanical ventilation. Limitations of these data include the generalisability issues of the trial with the current COVID-19 disease situation, with lower incidence, higher vaccination rates and different hospital practices, but also low numbers of patients in the trial at different hospital locations experiencing events.[162]

Table 56. Summary of COVID-related mortality variables from MOVe-OUT

Parameter	Value in use	95% CI	Source
Overall mortality in hospital, %	[redacted]	[redacted]	MOVe-OUT[162]
Mortality rate by highest hospital setting, %			
GW	[redacted]	[redacted]	MOVe-OUT[162]
High dependency unit	[redacted]	[redacted]	
ICU and MV	[redacted]	[redacted]	

CI = confidence interval; COVID-19 = coronavirus disease 2019; GW = general ward; ICU = intensive care unit; MV = mechanical ventilation
SOURCE: MOVe-OUT statistical reports[162]

Alternative sources of mortality data were used in TA971, which originate from a study of the UK OpenSAFELY database (Table 57). These data were collected in 2023 and are thus likely to reflect the current endemic state of COVID-19,[167] therefore these values were considered the best source for mortality in the base case.

Table 57. Summary of base case mortality variables from alternative sources

Parameter	Value in use	95% CI	Source
Mortality rate by highest hospital setting, %			
GW	1.71	1.60, 1.82	OpenSAFELY[167]
ICU and MV	4.15	3.37, 4.93	OpenSAFELY[167]
GW	2%	-	Clinical expert opinion TA971[74]
ICU and MV	12%	-	Clinical expert opinion TA971[74]

CI = confidence interval; GW = general ward; ICU = intensive care unit; MV = mechanical ventilation
SOURCE: OpenSAFELY[167] and TA971[74]

B.3.3.1.5 Outpatient parameters

Parameters for outpatients included in the model were duration of symptoms, number of outpatient visits and proportion of outpatients with accident and emergency (A&E) visits, as well as the number of A&E visits for these patients.

While previous assessments of COVID-19 treatments have focussed on hospitalisation and mortality, duration of symptoms is becoming a more relevant outcome to assess COVID-19 treatments in the current endemic environment where fewer patients are hospitalised and/or die from the disease. Duration of symptoms warrants exploration as it may translate to lower rates of onward transmission within the community as a means of capturing any additional indirect benefits to the wider population. However, few studies provide data on duration of symptoms.

Values for duration of symptoms from the usual care arm in the prospective PANORAMIC trial are presented in Table 58. The study has a number of limitations including a broader

definition of high risk of severe COVID-19 illness compared to MOVe-OUT and McInnes,[41, 84] the patient population likely not including patients at highest risk of severe illness, and use of COVID-19 treatments in the usual care arm (Section B.2.2.2).[93] However, PANORAMIC is one of few studies providing data on duration of symptoms, and therefore is the best source available to use in the model.

Inputs for outpatient visits, proportion of outpatients with A&E visits and the number of A&E visits for these patients were set to zero for the base case analysis, based on assumptions made in TA971 for remdesivir; however, the model has the functionality to include values for these parameters in scenario analysis.

Table 58. Summary of variables for outpatients with COVID-19

Parameter	Value	IQR	Source
Outpatient duration of symptoms, days	15	7 to not reached	PANORAMIC[93]
Outpatient visits, n	0	–	NICE TA971[74]
Outpatient A&E visits, n	0	–	
Outpatient A&E visits[a], %	0	–	

[a] Assumption for patients who are never hospitalised
A&E = accident and emergency; COVID-19 = coronavirus disease 2019; IQR = interquartile range
SOURCE: PANORAMIC[93]; NICE TA971[74]

B.3.3.1.6 Long-term sequelae

The parameters included in the model for long-term sequelae were the rates of long-term sequelae in hospitalised and non-hospitalised patients, and the duration of these long-term sequelae.

Values for the rates and duration of long-term sequelae (Table 59) were obtained based on the assumptions made in the cost-effectiveness analysis in TA878 and TA971, and although the values were considered conservative, alternative evidence has not been identified.[44, 74, 168]

Table 59. Summary of long-term sequelae variables

Parameter	Value	Uncertainty	Source
Long-term sequelae, %			Metry et al., 2023[168]
Non-hospitalised patients	10	–	
Hospitalised patients	100	–	
Long-term sequelae duration, weeks	113.60	–	

SOURCE: Metry et al., 2023[168]

Similarly, in line with the approach taken in previous assessments, a standardised mortality ratio (SMR) was applied for patients who had been hospitalised and subsequently had long-term sequelae. The increased mortality was only applied for the duration of long-term

sequelae. The SMR used in the model was 7.7 based on the value used in the cost-effectiveness analysis in TA878 and TA971.[44, 74, 168]

B.3.3.2 Treatment effects

Treatment effects were applied using the relative risk of hospitalisation and relative risk of symptom duration resolution for molnupiravir and its appropriate comparator(s) depending on subgroups of interest. Treatment effects were also applied after hospitalisation for severe COVID-19 with the treatment pathway assumed to be composed of remdesivir and tocilizumab (TA971 and TA878 respectively). Relative risk of mortality and relative risk of discharge were applied for inpatient treatment.

B.3.3.2.1 Hospitalisation

Treatment effects for all-cause and COVID-related hospitalisation were assessed in the RCT and RWE NMAs (Section B.2.9 and Appendix D) and are presented in Table 60 and Table 61. Using NMA data allows for adjustments for differences in populations and provides more robust direct comparisons as the evidence base captures any temporal effects. Both NMA analyses had a number of limitations including differences in high-risk definitions and, as such, baseline risks, and lack of data for certain outcomes or subgroups to enable further interrogation. The generalisability of clinical trial data to the current COVID-19 endemic state may be limited due to factors discussed above. This may also be partially true for RWE data; however, RWE is more likely to reflect the current setting given the data were obtained more recently in clinical practice and encompass a larger number of studies. For this reason, the relative risk of all-cause hospitalisation from the RWE NMA was used in the analysis for molnupiravir versus no treatment in the base case. As data were not available for molnupiravir compared to sotrovimab, the relative risk of COVID-related hospitalisations was used for this comparison and for molnupiravir compared to nirmatrelvir plus ritonavir.

Table 60. Summary of outpatient treatment effects on hospitalisation based on RCT NMA (Random effects)

Treatment	Value	95% CI	Source
All-cause hospitalisation, RR			
Molnupiravir vs. placebo	0.65	0.45, 0.93	RCT NMA Section B.2.9.1, Appendix D.1
Molnupiravir vs. nirmatrelvir plus ritonavir	8.15	0.57, 312.35	
Molnupiravir vs. Sotrovimab	3.22	1.31, 9.26	
COVID-19 related hospitalisation, RR			
Molnupiravir vs. placebo	0.69	0.47, 1.00	RCT NMA Section B.2.9.1, Appendix D.1
Molnupiravir vs. nirmatrelvir plus ritonavir	6.52	2.57, 20.51	

Treatment	Value	95% CI	Source
Molnupiravir vs. Sotrovimab	2.63	0.12, 41.91	

CI = confidence interval; COVID-19 = coronavirus disease 2019; NMA = network meta-analysis; RCT = randomised controlled trial; RR = relative risk
SOURCE: RCT NMA Section B.2.9.1 and Appendix D.1

Table 61. Summary of outpatient treatment effects on hospitalisation based on RWE NMA (Random effects)

Treatment	Value	95% CI	Source
All-cause hospitalisation, RR			
Molnupiravir vs. untreated	0.79	0.66, 0.92	RWE NMA, Section B.2.9.2, Appendix D.2
Molnupiravir vs. nirmatrelvir plus ritonavir	1.19	0.98, 1.43	
Molnupiravir vs. Sotrovimab	NA	NA	
COVID-19 related hospitalisation, RR			
Molnupiravir vs. untreated	0.85	0.49, 1.53	RWE NMA, Section B.2.9.2, Appendix D.2
Molnupiravir vs. nirmatrelvir plus ritonavir	1.58	0.98, 2.54	
Molnupiravir vs. Sotrovimab	1.64	0.19, 13.04	

COVID-19 = coronavirus disease 2019; NA = not available; NMA = network meta-analysis; RWE = real-world evidence; RR = relative risk
SOURCE: RWE NMA Section B.2.9.2 and Appendix D.2

B.3.3.2.2 Symptom duration

Limited data are available for symptom duration, as noted in Section B.3.3.1.5. Treatment effects have only been reported in the PANORAMIC trial and are only available for molnupiravir. In the trial, the hazard ratio for median days to symptom resolution was reported as 1.36 (95% credible interval: 1.32, 1.40) for molnupiravir compared to usual treatment,[93] and thus the inverse was calculated for usual treatment versus molnupiravir for use in the analysis (Table 62).

As data are not available for nirmatrelvir plus ritonavir or sotrovimab for symptom duration, the treatment effect was assumed to be the same as molnupiravir.

Table 62. Summary of outpatient treatment effects on symptom duration

Treatment	Value	Uncertainty	Source
Molnupiravir, HR	0.74	Uncertainty is incorporated through uncertainty in duration of symptoms	PANORAMIC[93]
Nirmatrelvir plus ritonavir vs. molnupiravir, HR	1	–	Assumption
Sotrovimab vs. molnupiravir, HR	1	–	Assumption

HR = hazard ratio
SOURCE: PANORAMIC[93]

B.3.3.2.3 Inpatient treatments

The choice of inpatient treatment was split, with remdesivir assumed to only be available for patients in the general ward setting, and tocilizumab only administered in the ICU setting with mechanical ventilation. Inputs used in the model are summarised in Table 63 and aligned with values used in TA878 and TA971.[44, 74] The impact of no inpatient treatment effect on discharge was tested as a scenario.

Table 63. Summary of inpatient treatment effects

Treatment	Parameter	Value	95% CI	Source
Remdesivir	RR mortality	0.88	0.81, 0.94	COVID-NMA (18 studies) [44, 74, 169]
	RR discharge	1.05	0.88, 1.25	metaEvidence (2 studies) [44, 74, 170]
Tocilizumab	RR mortality	0.91	0.74, 1.11	COVID-NMA (7 studies) [44, 74, 169]
	RR discharge	1.27	1.10, 1.46	Beigel et al., 2020[171]

CI = confidence interval; RR = relative risk
SOURCE: COVID-NMA[44, 74, 169]; MetaEvidence[44, 74, 170]; Beigel et al., 2020[171]

B.3.3.3 Adverse events

AEs related to treatment were also incorporated in the model for molnupiravir and its comparators using frequencies of the most common AEs. Data for molnupiravir and no treatment were taken from the MOVe-OUT trial,[76] and data for nirmatrelvir plus ritonavir and sotrovimab were obtained from their respective European Medicines Agency Summary of Product Characteristics.[68, 72] Only AEs with a frequency of ≥ 1% for any treatment were included in the model.

Costs associated with these AEs are described in Section B.3.5.3.

Table 64. Summary of adverse event frequencies for molnupiravir and comparators

Adverse event	Molnupiravir	Nirmatrelvir plus ritonavir	Sotrovimab	No treatment
Nausea	1.40%	0%	0.96%	0.70%
Headache	0.60%	1.2%	0.76%	0.00%
Diarrhoea	0.00%	3.0%	1.53%	0.10%
Dysgeusia	0.00%	4.6%	0.00%	0.00%
Vomiting	0.00%	1.2%	0.00%	0.00%

SOURCE: MOVe-OUT[76]; Paxlovid SmPC[68]; Xevudy SmPC[72]

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

Utility data were not collected in the MOVe-OUT trial and data for the model were collected from an SLR and vignette study.

B.3.4.2 Health-related quality of life studies

An SLR was conducted to identify all relevant studies reporting health state utility values in patients with COVID-19 or in patients with analogous conditions (pneumonia or influenza). A vignette study was also performed to support data on HRQoL. It should be noted that a poster publication of the vignette study was captured within the SLR.

B.3.4.2.1 SLR of HRQoL studies

An SLR was conducted with a cut-off date of 23rd January 2024 to identify health state utility values in patients with COVID-19 or analogous conditions of pneumonia or influenza which can provide an indication of the immediate impact of COVID-19 on patient HRQoL. The SLR encompassed electronic databases (Embase, Medline, Evidence-Based Medicine (EBM) Reviews) and relevant congresses (IDWeek, The European Congress of Clinical Microbiology and Infectious Diseases, American Thoracic Society and The International Society for Health Economics and Outcomes Research; years 2020 to January 2024 for all).

The search identified 5,219 records for COVID-19 and 615 records for influenza or pneumonia. After screening, 42 primary reports were included and prioritised for extraction. None of these studies were for pneumonia or influenza.

Of the prioritised studies:

- 33 studies presented true 'index' utility values anchored on a scale between 0.0 (death) and 1.0 (perfect health)
- 6 studies only reported EQ-5D-VAS results
- 1 study reported granular data on EQ-5D domains and levels following SARS-CoV-2 infection and how these were associated with long-COVID-19 risk in children
- 1 study reported SF instrument results
- 1 study reported time trade-off (TTO) results
- No studies reported data using mental scales to measure utility values.

Full details of the HRQoL SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix H.

B.3.4.2.2 Vignette study

A *de novo* utility study was conducted to derive utility values for the health states included in the economic model. A series of patient descriptions, or vignettes, were developed for the study to describe a range of different health states relevant to the cost-effectiveness model; the general public completed the EQ-5D-5L for these health states acting as proxies on behalf of patients.[172]

Vignettes were informed by a large UK COVID-19 ONS infection survey, relevant clinical trials and observational studies, and designed to reflect health states relevant to patients who would be eligible for molnupiravir in clinical practice:[172]

- Baseline (pre-infection) (S1)
- Outpatient (mild) (S2)
- Outpatient (moderate) (S3)
- General hospital ward (severe) (S4)
- High dependency unit (severe) (S5)
- ICU (critical) (S6)
- Recovered, no long-term sequelae (S7)
- Recovered with long-term sequelae (S8).

Overall 500 members of the UK general public were recruited via crowdsourcing in September 2021 with the participant demographic distribution reflective of the UK population.[172] Participants first completed the EQ-5D-5L descriptive system based on their own health before completing the EQ-5D-5L for the vignettes.[172] EQ-5D-3L utility index scores were estimated using the EQ-5D-5L cross-walk algorithm as per NICE recommendations.[172]

Full details of the vignette study methodology and results are presented in Appendix H.

B.3.4.3 Mapping

Mapping was not performed.

B.3.4.4 Adverse reactions

Due to the mild nature of AEs associated with molnupiravir and comparator treatments, no utility impacts of AEs in the form of decrements are included in the model.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

Utility values were applied for each possible health state included in the model, including a baseline utility for the overall high-risk population as summarised in Table 65. Baseline quality of life by age and gender was applied based on Hernández Alava et al., 2022.[173]

The vignette study was used as the source for the utility values, by pooling the mean utility of S2 and S3 for symptomatic outpatient, S4 for hospitalised on general ward, S6 for ICU with mechanical ventilation and S8 for long-term sequelae. No utility value was included for readmission after long-term sequelae; however, the model has the functionality to include this in scenario analyses.

For symptomatic outpatients the utility value is applied for the duration of symptoms after which utility returns to baseline. For patients treated with molnupiravir or other active treatments this duration is reduced depending on the hazard ratio from PANORAMIC.

Table 65. Summary of utility values for cost-effectiveness analysis

Healthcare state	Value	Uncertainty	Source
Baseline overall population	0.8508	95% CI: 0.38 0.99	Based on average age of cohort Hernández Alava et al., 2022[173]
Symptomatic outpatient	0.30	SE: 0.0102	Vignette study, Appendix H
	Hospitalised by highest hospital setting		
GW	-0.18	SE: 0.0107	Vignette study, Appendix H
ICU and MV	-0.38	SE: 0.0063	
Long-term sequelae	0.21	SE: 0.0127	Vignette study, Appendix H

[a] Based on a default standard error of 20%
GW = general ward; ICU = intensive care unit; MV = mechanical ventilation; SE – standard error
SOURCE: Hernández Alava et al., 2022[173]; Vignette study(Appendix H)

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Costs and healthcare resource use data were identified in an economic SLR, in addition to individual studies and published NHS data. Details of how data were identified are presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

Treatment costs associated with molnupiravir and its comparators were applied in non-hospitalised patients in the model. These costs are summarised in Table 66. Each outpatient treatment was assumed to have an acquisition cost and administration cost. Acquisition costs were sourced from the British National Formulary (BNF) or previous NICE assessments.[44, 174] Administration costs varied by treatment due to different methods and location of administration and healthcare resource required, and any requirement for DDI assessment. Molnupiravir is an oral treatment that can be administered at home requiring minimal resource. By contrast, nirmatrelvir plus ritonavir is associated with additional resource to assess DDIs at the healthcare professional level (such as a pharmacist). The administration cost for nirmatrelvir plus ritonavir is based on the agreed value used in TA878 of £117.[43] This reflects the additional time required for a comprehensive assessment and aligns closely with £113.58 that was reported for complex patients in a published survey of pharmacists, which provides a detailed breakdown and costing of the prescribing time for oral antivirals in the UK.[175] The administration cost for molnupiravir is also based on this published survey of healthcare professionals, removing the cost for DDI review and taking the average cost for simple and complex patients and taking the average for both values. The true administration cost for molnupiravir is likely to be substantially less than the value used in the base case for this submission (£31.85 – see Table 66) considering the primary care setting and the fact that most patients who are at risk of progression to severe COVID-19 disease may already be treated for other chronic conditions meaning that they could be exempt from community pharmacy prescription costs. Further, if assumed that the assessment has already taken place for nirmatrelvir plus ritonavir eligibility, the true administration cost for molnupiravir, for those who are otherwise contraindicated to alternative treatments is £0.

Sotrovimab is administered intravenously in an outpatient healthcare setting, which requires capacity considerations notwithstanding any additional risk for onward transmission dynamics within the healthcare setting.

Treatment costs were also applied to treatments administered in hospital. These costs were sourced from the Drugs and Pharmaceutical Electronic Market Information Tool (eMIT) and summarised in Table 67.

Table 66. Costs associated with outpatient treatments in the economic model

Items	Value	Source
Molnupiravir		

Items	Value	Source
Treatment acquisition cost	[redacted]	CIC - Please refer to Table 2 in this document
Treatment administration cost	£31.85[a]	Butfield et al., 2023[175]
Total	[redacted]	CIC - Please refer to Table 2 in this document
Nirmatrelvir plus ritonavir		
Treatment acquisition cost	£829.00	Metry et al., 2022[168] – Table 12 MTA report October 2022.
Treatment administration cost	£117.00	TA878[44]
Total	£1,298.49	
Sotrovimab		
Treatment acquisition cost	£2,209.00	BNF[174]
Treatment administration cost	£287.00	NHS reference cost SB12Z[176]
Total	£2,496.00	

BNF = British National Formulary; DDI = drug-drug interaction; NHS = National Health Service
SOURCE: TA878[44]; Metry et al., 2022[168]; BNF[174]; NHS reference costs 2021/2022[176]
a Calculated as the average of "overall clincial review, prescribing and dispensing for standard and complex patients" minus "costs associated for DDI assessment for standard and complex patients" (£113.58-£85.88)+(£78.94-£42.94).

Table 67. Costs associated with inpatient treatment

Items	Cost	Route	Posology	Source
Tocilizumab	£798.72	IV	8 mg/kg	BNF[177]
Remdesivir	£1,445.00	IV	200 mg loading dose on day 1, 100 mg thereafter	BNF[178]
Systemic steroids	£7.80	IV		eMIT National Database HRG code: DJA304 [174]

BNF = British National Formular; eMIT = Drugs and Pharmaceutical Electronic Market Information Tool; IV = intravenous.
SOURCE: eMIT National Database[174]

B.3.5.2 Health state unit costs and resource use

Costs associated with the health states in the model are summarised in Table 68. General management costs were applied for patients in the outpatient setting. In addition, these non-hospitalised patients could also incur costs associated with A&E visits. In the hospital setting, patients incurred a daily hospitalisation cost depending on the highest hospital setting. Costs for one A&E visit was also applied to hospitalised patients. All these costs were sourced from NHS reference costs.[176]

Patients who were discharged from hospital incurred a one-time monitoring cost. This was based on an assumption that patients receive on average two chest x-rays and six GP e-consultations after discharge resulting in a one-off cost of £384 (cost year 2021/2022), as used in TA878 and TA971.[43, 74, 156] An annual cost for management of long-term sequelae

was applied based on data for chronic fatigue syndrome (as used in TA878 and TA971), which included costs for hospital readmissions.[43, 74, 179]

Table 68. Costs of health state management in the economic model

Healthcare parameter	Cost	Source
Outpatient management	£223.70	340 and 341 Respiratory Medicine Service and Respiratory Physiology Service unit cost; NHS reference cost 2022[74, 176]
A&E visit, per visit	£242.03	XC07Z; NHS reference cost 2022[74, 176]
Cost of hospitalisation by highest hospital setting, per day		
GW	£438.20	DZ11R to DZ11V; NHS reference cost 2022[74, 176]
High dependency unit	£2,404.29	XC01Z to XC07Z; NHS reference cost 2022[74, 176]
ICU and MV	£3,623.29	XC01Z to XC07Z and WC08; NHS reference cost 2022[74, 176]
Monitoring following discharge	£411.00	Rafia et al., 2022[74, 156]
Long-term sequelae, annual	£2,426.37	Vos-Vromans et al., 2017[74, 179]

A&E = accident and emergency; GW = general ward; ICU = intensive care unit; MV = mechanical ventilation; NHS = National Health Service
SOURCE: NHS reference cost 2022[176]; Rafia et al., 2022[156]; Vos-Vromans et al., 2017[179]

B.3.5.3 Adverse reaction unit costs and resource use

Costs were applied for AEs associated with treatment in the model, which are summarised in Table 69. Data were sourced from eMIT ensuring the lowest pack cost was applied for formulations which are available over-the-counter to access without prescription. The total cost per pack is applied to account for unused medicine costs. It should be noted that these are most commonly out-of-pocket costs for the patient and not reimbursed by the NHS (ie fall outside the strict NHS+PSS perspective definition), however due to a lack of other data it is assumed these costs are representative. Whilst AEs and related costs have a negligible impact in the analyses presented, downstream consequences remain important for the endemic setting.

Table 69. Adverse reactions and associated costs

Adverse event	Value	Source
Nausea	£2.45	eMIT National Database: Cyclizine cost[174]
Headache	£0.27	eMIT National Database: Paracetamol cost[174]
Diarrhoea	£0.46	eMIT National Database: Loperamide cost[174]
Dysgeusia	£0.00	–

Adverse event	Value	Source
Vomiting	£0.86	eMIT National Database: Prochlorperazine cost[174]

eMIT = Drugs and Pharmaceutical Electronic Market Information Tool; NSAIDs = non-steroidal anti-inflammatory drugs
SOURCE: eMIT National Database[174]

B.3.6 Severity

Severity weighting was not considered appropriate for the COVID-19 disease area and thus no weighting was applied. It is acknowledged that some of the subgroups considered, namely immunocompromised patients and patients with chronic kidney disease, are likely to have a lower life expectancy and utility compared to the background population, which may warrant consideration of a severity modifier. However, due to lack of specific data for these subgroups, such aspects were not considered in the analysis. MSD understands that the approach is consistent with that taken when considering the immunocompromised subgroup in TA971, that is, no severity multiplier was considered, and no adjustment was made to background mortality and utilities for any subgroup.

B.3.7 Uncertainty

As highlighted in TA878 and TA971[43, 74, 168] there is a high level of uncertainty in many key model parameters relating to the current COVID-19 situation and impact of care. Levels of surveillance, testing and reporting of COVID-19 have shifted over the course of the pandemic in the UK, meaning timely and accurate data are currently difficult to source. Much clinical trial data were collected during early stages of the pandemic, making their use for assessment of cost-effectiveness in the current situation problematic. Therefore, more recent RWE data have been used widely in this analysis, however the RWE used is from a range of locations and timeframes and so is impacted by uncertainty.

Hospitalisation and mortality rates are key model drivers as they define how many people are included in hospital with the associated higher cost and lower utility. These key parameters are also those with some of the highest level of uncertainty. In TA878, the committee acknowledged significant uncertainty in these parameters which is difficult to irradicate due to the nature of the data available. For this reason, a pooled hospitalisation rate from the no treatment arms of RWE studies was used to provide a robust estimate of hospitalisation based on the widest range of recent evidence available.

Data by subgroup are especially difficult to identify making the assessment of cost-effectiveness of molnupiravir in these important subgroups challenging to estimate. Due to

lack of data for many parameters, the conservative assumption that the inputs are the same as for the overall at-risk population was made.

Uncertainty was explored through deterministic and probabilistic uncertainty analysis and through investigating appropriate scenarios.

B.3.8 Managed access proposal

Molnupiravir is not currently a candidate for managed access.

B.3.9 Summary of base case analysis inputs and assumptions

B.3.9.1 Summary of base case analysis inputs

A summary of the inputs and variables used in the cost-effectiveness analysis of the base case is presented in Table 70.

Table 70. Summary of base case baseline variables

Parameter	Value	Uncertainty	Source
Model characteristics			
Perspective	UK NHS and Personal Social Services		
Patient population	Non-hospitalised adults with mild to moderate COVID at risk of progression to severe illness leading to hospitalisation		
Time horizon	Lifetime		
Cycle length	One week for the first year followed by yearly cycle		
Discount rate (costs and outcomes)	3.5% per year		
Patient characteristics			
Mean age, years	57	–	PANORAMIC[93]
Female, %	51.3	95% CI: 41.04, 61.56[a] (beta)	MOVe-OUT[84]
Mean weight, kg	78.0	95% CI: 51.88, 112.76[a] (log-normal)	Assumption TA878 RIA
Baseline utility	0.8508	95% CI: 0.39, 0.99[a] (beta)	Hernández Alava et al., 2022[173]
Disease characteristics			
All-cause hospitalisation rate, %	3.79	95% CI: 1.87, 7.67 (beta)	RWE NMA (Section B.2.9.2, Appendix D.2)
Proportion by highest hospital setting, % GW ICU with MV	 85.63 14.37	 – 95% CI: 10.88, 18.24 (beta)	NHS data[165]
Length of stay by highest hospital setting, days GW	 8.29	 95% CI: 6.63, 9.95[a]	Yang et al., 2023[53]

Parameter	Value	Uncertainty	Source
ICU with MV	11.40	95% CI: 11.08, 11.72 (Gamma)	
Mortality rate by highest hospital setting, %			
GW	1.71	95% CI: 1.60, 1.82 (beta)	OpenSAFELY[167]
ICU with MV	4.15	95% CI: 3.37, 4.93 (beta)	
Outpatient duration of symptoms, days – treated with molnupiravir	9	95% CI: 5.99, 13.01[a] (log-normal)	PANORAMIC[93]
Long-term sequelae, %			
Non-hospitalised patients	10	95% CI: 6.43, 14.24[a] (beta)	Metry et al., 2023[168]
Hospitalised patients	100		
Long-term sequelae duration, years	113.60	95% CI: 1, 3 (log-normal)	Metry et al., 2023[168]
Standardised mortality rate	7.70	95% CI: 7.20, 8.30 (log-normal)	Metry et al., 2023[168]
Treatment effect			
RR all-cause hospitalisation			
Molnupiravir vs. no treatment	0.79	95% CI: 0.66, 0.92 (log-normal)	RWE NMA, Section B.2.9.2, Appendix D.2
Nirmatrelvir plus ritonavir vs. molnupiravir	1.19	95% CI: 0.99, 1.43 (log-normal)	
Sotrovimab vs. molnupiravir[b]	1.64	95% CI: 0.19, 13.04 (log-normal)	
RR inpatient mortality			
Tocilizumab	0.88	95% CI: 0.81, 0.94 (log-normal)	COVID-NMA[44, 74, 169]
Remdesivir	0.91	95% CI: 0.74, 1.11 (log-normal)	
HR discharge			
Tocilizumab	1.05	95% CI: 0.88, 1.25 (log-normal)	Beigel et al., 2020[171]
Remdesivir	1.27	95% CI: 1.10, 1.46 (log-normal)	metaEvidence[44, 74, 170]
Utilities			
Symptomatic	0.302	95% CI: 0.28, 0.32 (beta)	Vignette study, Appendix H
GW	-0.181	95% CI: -0.20, -0.16 (normal)	
ICU with MV	-0.376	95% CI: -0.39, -0.36 (normal)	
Long-term sequelae	0.209	95% CI: 0.19, 0.24 (beta)	
Costs			
Molnupiravir			
Treatment acquisition cost	£[redacted]		[redacted]; CIC price

Parameter	Value	Uncertainty	Source
Treatment administration cost	£31.85	95% CI: 20.61, 45.49[a] (gamma)	Butfield et al., 2023[175]
Total	£[redacted]		Contains CIC price
Nirmatrelvir plus ritonavir			
Treatment acquisition cost	£829.00		Metry et al., 2023[168]
Treatment administration cost	£117.00	95% CI: 75.71, 167.12[a] (gamma)	TA878[44]
Total	£1,298.49		
Sotrovimab			
Treatment acquisition cost	£2,209.00		BNF[174]
Treatment administration cost	£287.00	95% CI: 185.73, 409.95[a] (gamma)	NHS reference cost[176]
Total	£2,496.00		
Tocilizumab	£798.72		eMIT[174]
Remdesivir	£1,445.00		eMIT[174]
Systemic steroids	£7.80	95% CI: 2.55, 5.63 (gamma)	eMIT[174]
Outpatient management	£165.00	95% CI: 144.77, 319.53[a] (gamma)	NHS reference cost 2022[176]
A&E visit, per visit	£1,640.00	95% CI: 156.63, 345.71[a] (gamma)	NHS reference cost 2022[176]
Cost of hospitalisation by highest hospital setting, per day			
GW	£438.20	95% CI: 283.58, 625.93[a] (gamma)	NHS reference cost 2022[176]
ICU and MV	£3,623.29	95% CI: 2344.80, 5175.52[a] (gamma)	
Monitoring following discharge	£457.94	95% CI: 296.35, 654.12 (gamma)	Rafia et al., 2022[156]
Long-term sequelae, annual	£2,703.52	95% CI: 1749.58, 3861.72 (gamma)	Vos-Vromans et al., 2017[179]

[a] Based on a default standard error of 20%
[b] Sotrovimab hospitalisation RR is for COVID-19 related hospitalisation
A&E = accident and emergency; CI = confidence interval; COVID-19 = coronavirus disease 2019; GW = general ward; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; MV = mechanical ventilation; RR = relative risk; RWE = real-world evidence; SD = standard deviation
SOURCE: PANORAMIC[93]; MOVe-OUT[84]; NICE press release[45]; Hernández Alava et al., 2022[173]; RWE NMA (see Section B.2.9.2 and Appendix D.2); NHS data[165]; Yang et al., 2023[53]; OpenSAFELY[167]; Metry et al., 2023[168]; Vignette study (Appendix H); COVID-NMA[44, 74, 169]; Beigel et al., 2020[171]; metaEvidence[44, 74, 170]; Butfield et al., 2023[175]; BNF[174]; eMIT[174]; NHS reference cost 2022[176]; Rafia et al., 2022[156]; Vos-Vromans et al., 2017[179]

B.3.9.2 Assumptions

Assumptions made in the model base case are summarised in Table 71.

Table 71. Summary of assumptions and corresponding rationale

Description of assumption used in the base case	Justification
Hospital length of stay from 2020/2021 is relevant in current endemic setting	More recent length of stay data for general ward and ICU settings relevant to the UK are not available. Overall length of stay (in general ward and ICU) data from 2020/2021 is comparable with data from 2021/2022.[52, 180]
All hospitalised patients will have long-term sequelae	In the absence of alternative evidence, this assumption was maintained from previous NICE assessments TA878 and TA971.[43, 74, 168]
Nirmatrelvir plus ritonavir and sotrovimab have the same treatment effect on symptom duration as molnupiravir	There are limited data on symptom duration, and none for nirmatrelvir plus ritonavir or sotrovimab. To avoid bias, the same treatment effect as molnupiravir was assumed.
Cost for AEs are for over-the-counter medication costs	Due to lack of specific data on the costs of the mild adverse events experienced by patients, values are based on an assumption of the types of over-the-counter medications that could be used. Whilst outside the NHS+PSS perspective, and of limited impact, costs are relevant to patients in an endemic setting.
No disutility associated with AEs is included	Due to lack of specific data on the utility impact of the AEs experienced a simplifying and conservative assumption is that there are no disutilities associated with AEs.
Risk of mistreatment and/or QALY loss as a result of pausing treatments for comorbidities due to contraindications	This was not formally captured due to data limitations but will likely underestimate the true effect of molnupiravir to society and overestimate the cost-effectiveness of current oral treatment options.
Readmission for long-term sequelae following discharge from hospital	Readmissions were not formally captured as this was included within the long-term sequelae cost estimate. The effect of this is unclear as variants evolve.
Wider externalities associated with multiple treatments for mild/moderate COVID-19 in the outpatient setting for the health system and the society overall.	These elements were not formally captured due to data limitations. This will likely underestimate the true effect of molnupiravir to society as some vulnerable patients may be infected as a result of COVID-19 admissions for severe disease that could have been prevented with oral alternative options that require no complex patient assessment. Any benefits resulting from the prevention of onward in-hospital or household transmission due to easily accessible oral alternative treatment in the community setting have not been formally captured due to data limitation. Onward transmission in hospital and between health care professionals were not captured due to issues in quantifying these elements. This will likely underestimate the true effect of molnupiravir to society.

AEs = adverse events; ICU = intensive care unit; NICE = National Institute for Health and Care Excellence

B.3.10 Base case results

B.3.10.1 Base case incremental cost-effectiveness analysis results

The expected positioning of molnupiravir in UK clinical practice is for the treatment of patients with mild to moderate COVID-19 at risk of developing severe illness as follows (Section B.1.3.2.2):

- As an alternative to *nirmatrelvir plus ritonavir* in patients at risk of severe illness according to the McInnes and Edmunds definitions;
- As an alternative to *sotrovimab* for patients at risk of severe illness according to the McInnes criteria, who are unsuitable for treatment with *nirmatrelvir plus ritonavir*; and
- For patients at risk of severe illness according to the Edmunds definition, who are unsuitable for treatment with *nirmatrelvir plus ritonavir*.

In line with this positioning, the cost-effectiveness analysis is presented below.

The base case results are calculated based on the key parameters listed above in Table 70, with results are presented in Table 72. Due to the recognised high level of uncertainty in these analyses a deterministic base case is presented. Disaggregated results are provided in Appendix J.

Molnupiravir was associated with total costs of [redacted] and total quality-adjusted life years (QALYs) of [redacted]. Compared to no treatment, molnupiravir was associated with higher cost and higher QALYs, and the ICER of molnupiravir versus no treatment was [redacted]. Compared to comparator treatments (i.e., nirmatrelvir plus ritonavir and sotrovimab), molnupiravir had lower costs and lower QALYs. With respect to the ICERs for nirmatrelvir plus ritonavir versus molnupiravir, and sotrovimab versus molnupiravir, molnupiravir had lower cost lower effects (LCLE) with ICERs in the SW quadrant of [redacted] and [redacted] respectively. The price of nirmatrelvir plus ritonavir is not currently in the public domain and therefore this analysis is based on a price based on that used in Metry et al 2022 for TA878. Results for the comparison versus nirmatrelvir plus ritonavir should be viewed with this in mind.

It should be noted that the base case incremental net health benefit (NHB) versus nirmatrelvir plus ritonavir, was very small [redacted]) in the overall population, indicating that the cost and QALYs between the treatments are extremely similar and therefore with a low overall decision risk, with the potential for conclusions to switch between quadrants of the cost-effectiveness analysis curve demonstrated in the probabilistic sensitivity analysis (PSA). However this only applies for comparisons in the overall population and for patients/comparisons versus other active treatment options. Molnupiravir versus no treatment (ie for contraindicated patients to name a few) generates a positive incremental net health benefit as would be expected.

Table 72. Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	957	16.257	12.873	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	[redacted]
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Covid-19 related hospitalisation used to inform estimates
ICER = incremental cost-effectiveness ratio; LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

A PSA was conducted to assess the impact of parametric uncertainty in the model results. Parameters were assigned an appropriate distribution based on parameter type and random samples were drawn from the distribution. One thousand iterations were run. Parameters with known correlations were preserved. Distributions used are shown in Table 70.

The cost-effectiveness plane and multi-way cost-effectiveness acceptability curves for molnupiravir compared to no treatment, nirmatrelvir plus ritonavir and sotrovimab are presented in Figure 29 to Figure 32. Probabilistic results are presented in Table 73.

Table 73. Probabilistic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	867	16.262	12.903	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; QALYs = quality-adjusted life years

Figure 29. Cost-effectiveness acceptability curve

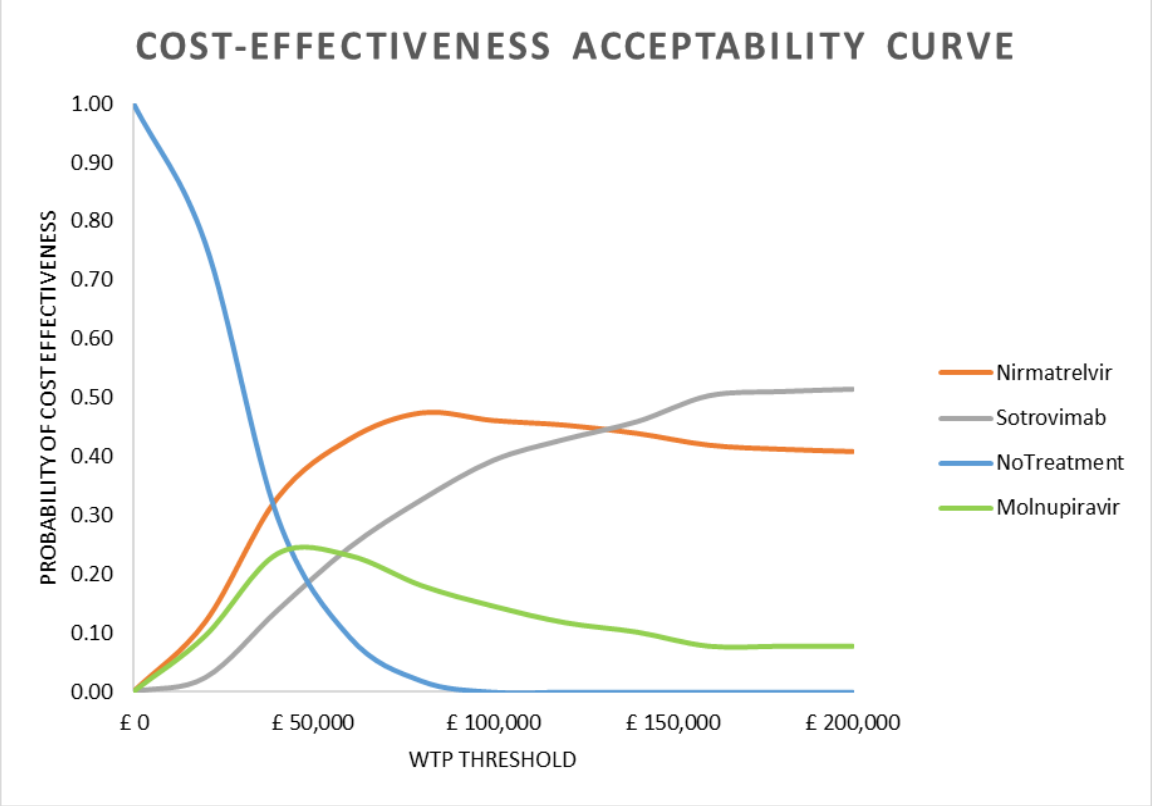


Figure 30. Probabilistic sensitivity analysis results – molnupiravir versus no treatment

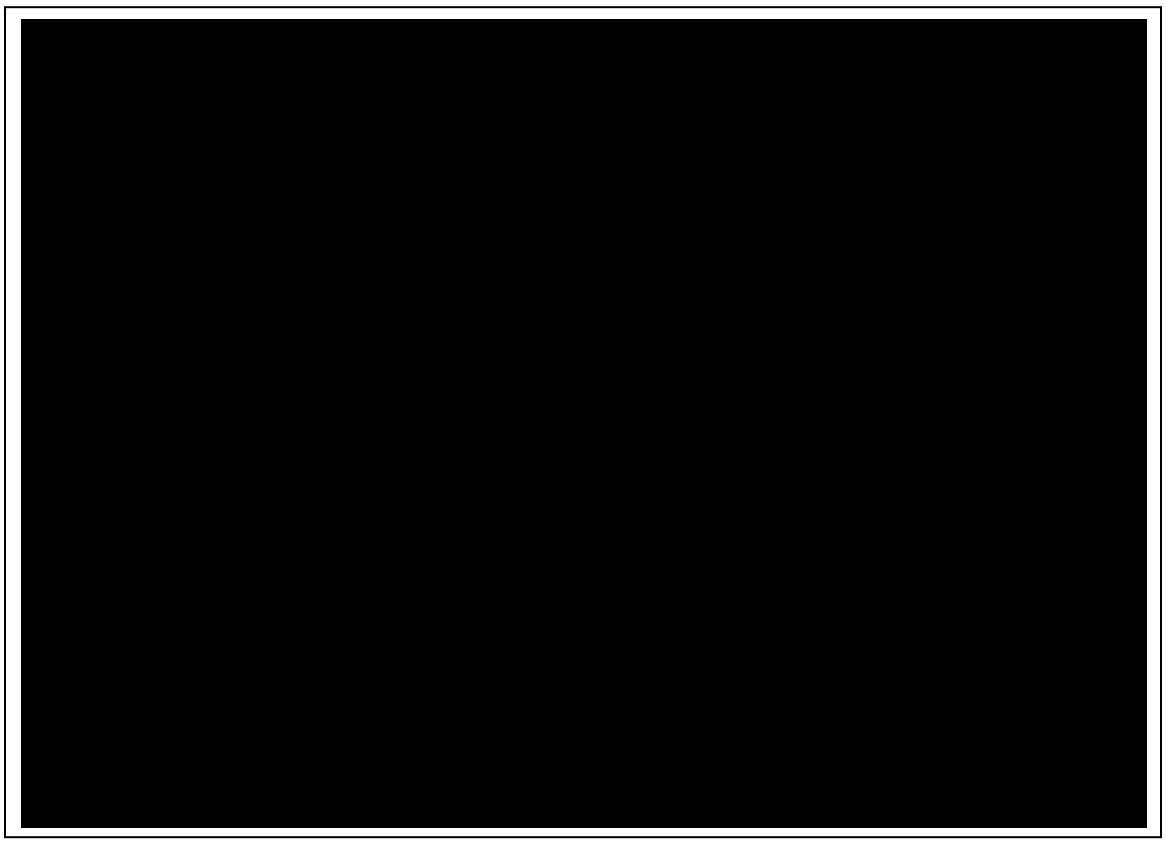


Figure 31. Probabilistic sensitivity analysis results – molnupiravir versus nirmatrelvir plus ritonavir

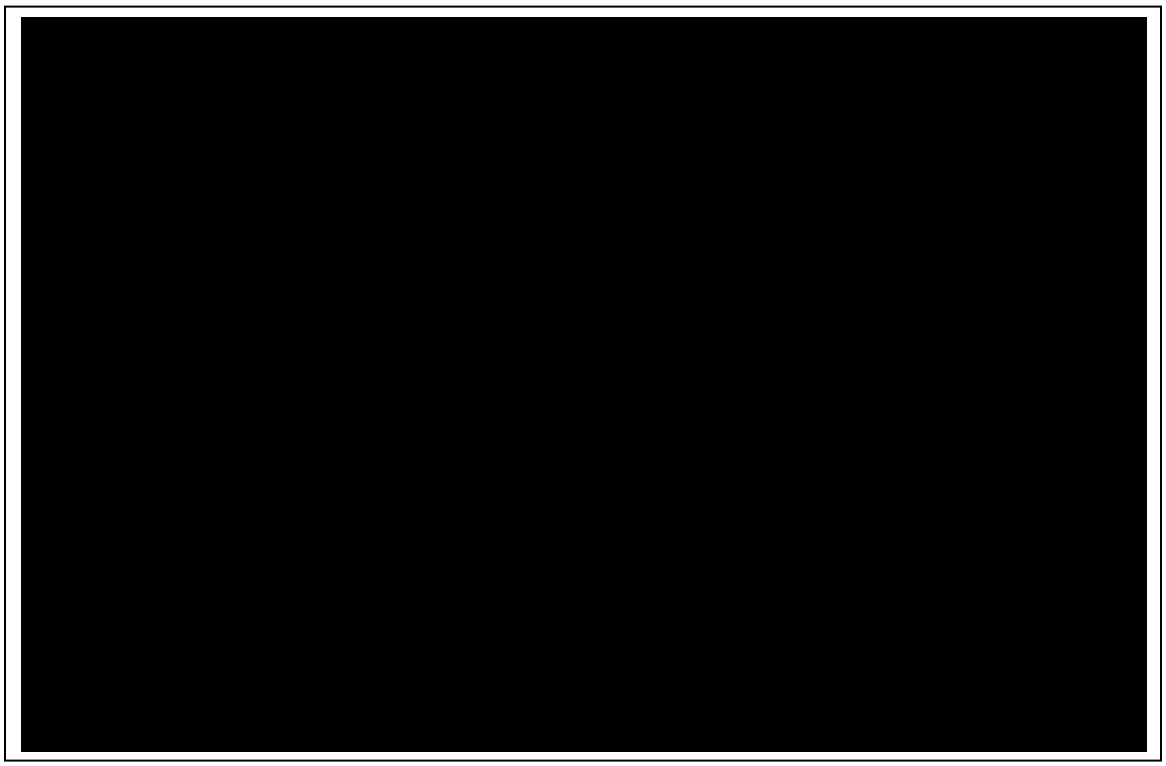
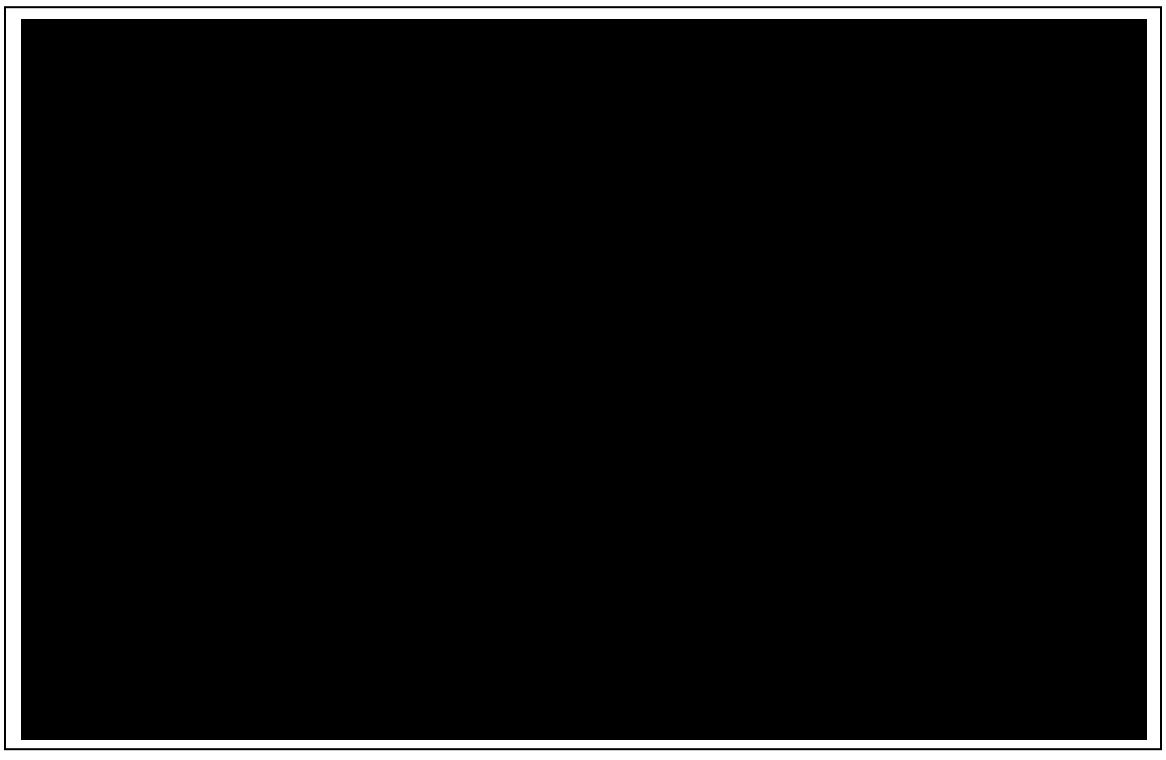


Figure 32. Probabilistic sensitivity analysis results – molnupiravir versus sotrovimab



B.3.11.2 Deterministic sensitivity analysis

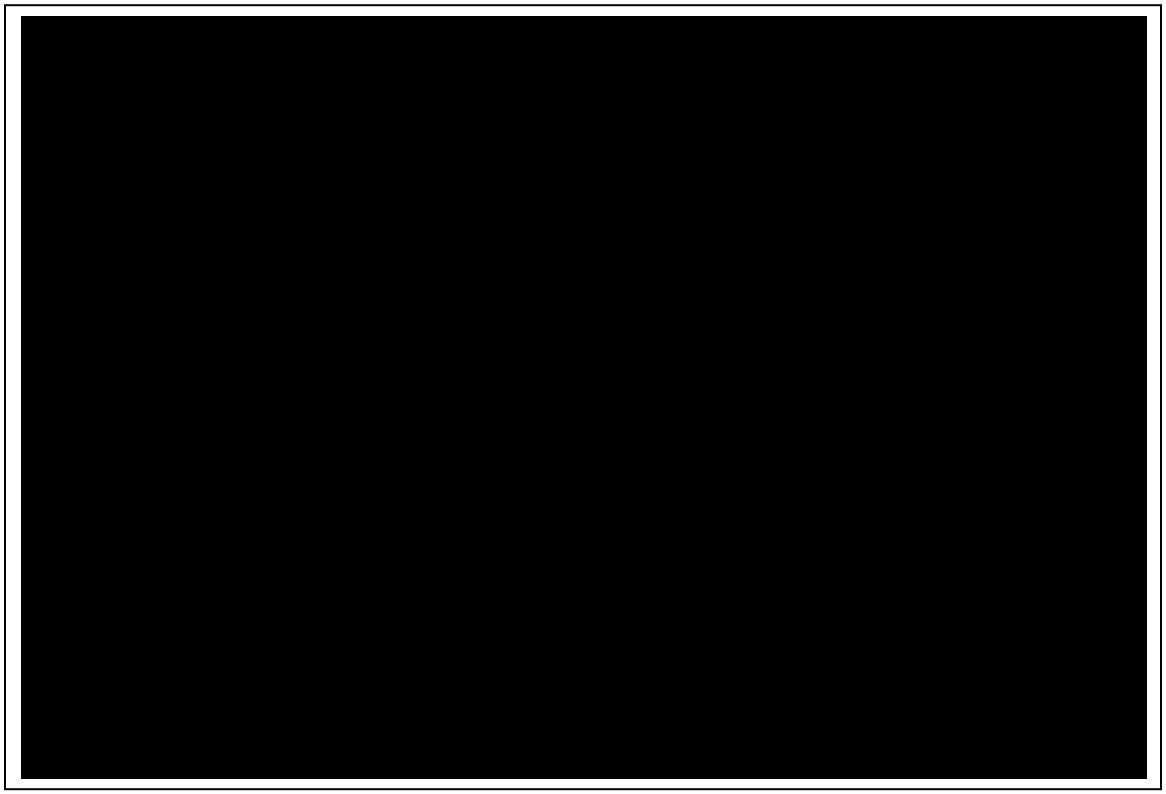
One-way deterministic sensitivity analysis (DSA) was performed for the parameters listed in Table 70; the upper and lower bound values used to vary the parameters are shown, which

were based on 95% confidence intervals or standard errors, or if those were not available, based on ± 20% variation around the mean.

The results of the DSA for the ten most influential parameters on incremental net monetary benefit (NMB) against no treatment, nirmatrelvir plus ritonavir and sotrovimab are shown in Figure 33, Figure 34 and Figure 35, respectively. For all comparators the underlying hospitalisation rate of those at risk is the one of the two most influential parameters. Higher hospitalisation rates lead to improved ICER and NMB for molnupiravir compared to no treatment, as this increase means greater gains in terms averting QALY loss and costs associated with hospitalisation and death; this is a key driver of cost-effectiveness and has wide uncertainty bounds due to the method of derivation from the RWE NMA (as described in Section B.3.3.1.1). Relative risk for treatment effect on hospitalisation is also one of the two most influential parameters.

The DSA for the comparison between molnupiravir and nirmatrelvir plus ritonavir demonstrated that plausible variations in several parameters have the potential to result in a positive NMB for molnupiravir compared with nirmatrelvir plus ritonavir (Figure 34). These include the parameters relating to the rate and relative risk of hospitalisation, which are subject to some uncertainty given the range of reported values and the evolving nature of COVID-19 epidemiology. The only situation in which the NMB for molnupiravir compared with sotrovimab was negative was when a higher relative risk of hospitalisation for molnupiravir compared with sotrovimab was used (Figure 35). It should however be noted that sotrovimab comparisons are caveated by limitations in data (ie use of COVID-19 related hospitalisation vs all-cause hospitalisation being used as input).

Figure 33. Deterministic sensitivity analysis results, net monetary benefit – molnupiravir versus no treatment

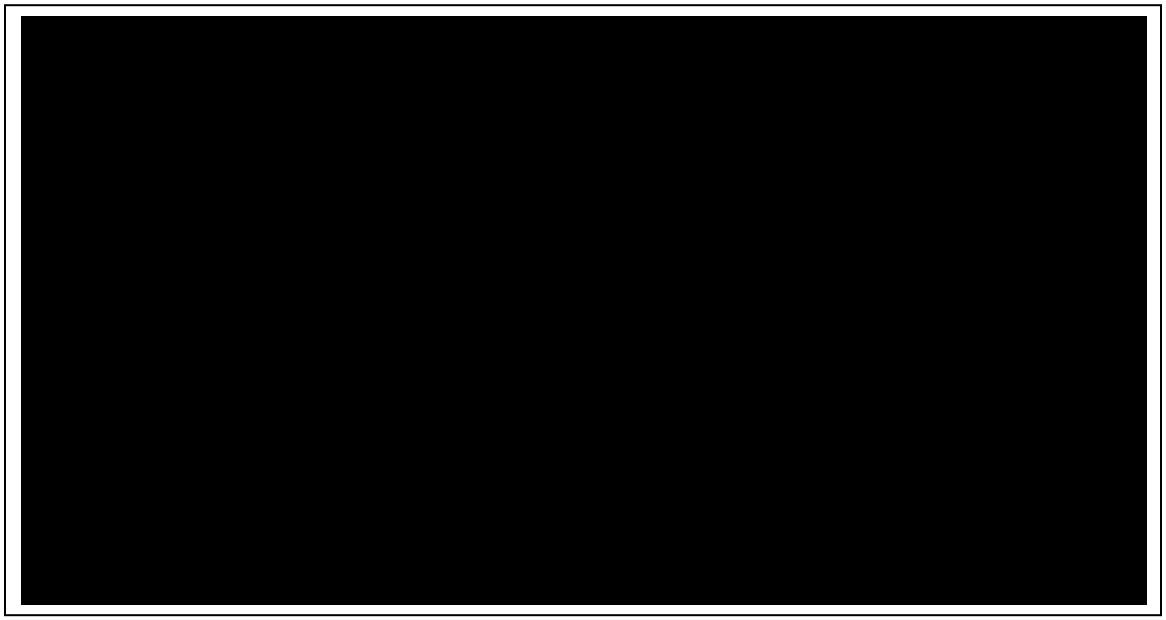


NMB = net monetary benefit

Figure 34. Deterministic sensitivity analysis results, net monetary benefit – molnupiravir versus nirmatrelvir plus ritonavir

NMB = net monetary benefit; qol = quality of life; SMR = standardised mortality ratio

Figure 35. Deterministic sensitivity analysis results, net monetary benefit – molnupiravir versus sotrovimab.



NMB = net monetary benefit; qol = quality of life; SMR = standardised mortality ratio

B.3.11.3 Scenario analysis

To investigate the impact of key parameters, two additional scenarios are investigated. In these scenarios, groups of different inputs are investigated concurrently rather than by investigating the impact of each input individually as this is demonstrated in the DSA. The base case analysis utilises RWE data due to potential issues with generalisability of data from MOVe-OUT and other randomised control trials. However, the trial data are still useful to investigate the higher end of the potential impact of outpatient treatments. Therefore, a trial-based scenario is presented utilising the trial all-cause hospitalisation rate (Table 50), distribution within hospital (Table 53), and mortality (Table 56). All other inputs were assumed to be the same as the base case.

An alternative scenario was investigated using values from the preferred base case of the remdesivir assessment for hospitalisation rate for the at-risk population (Table 51) and expert opinion based mortality by location in hospital (Table 57), combined with the treatment effect for COVID-19 specific hospitalisation from the RWE NMA.

Results for the trial-based scenario using mortality by highest level of care in hospital or overall within hospital mortality from MOVe-OUT are shown in Table 74 and Table 75. For both scenarios, the ICER is improved compared to the base case analysis when compared to no treatment. As in the base case, for the comparisons of nirmatrelvir plus ritonavir versus molnupiravir, and sotrovimab versus molnupiravir, molnupiravir had LCLE but with lower ICERs. The key difference in the scenarios is the higher hospitalisation and mortality which drives the more favourable ICERs.

Table 74. Trial-based scenario results- mortality by highest level of care

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	1,894	16.106	12.703	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	[redacted]
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years

Table 75. Trial-based scenario results- overall mortality

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inv. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	951	16.236	12.858	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	[redacted]
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years

The results for the alternative scenario are shown in Table 76. Due to the lower hospitalisation rate in this scenario (2.82% from DiscoverNow), the ICER for molnupiravir compared to no treatment is higher than in the base case.

Table 76. Alternative scenario results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	824	16.263	12.888	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	[redacted]
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years

B.3.12 Subgroup analysis

B.3.12.1 Patients aged > 70 years

Subgroup analysis was performed on patients with mild to moderate COVID-19 aged > 70 years in line with the age criterion within the Edmunds expanded definition of those at high risk of severe COVID. In line with NICE guidelines, nirmatrelvir plus ritonavir was used as the comparator to molnupiravir in this subgroup. Inputs for the subgroup are shown in Appendix E.1.

For the subgroup aged > 70 years, molnupiravir accumulated costs of £[redacted] and total QALYs of [redacted]. Compared with no treatment, molnupiravir was associated with higher cost and higher QALYs, and the ICER of molnupiravir versus no treatment was [redacted]. Compared to nirmatrelvir plus ritonavir, molnupiravir had lower costs and lower QALYs. With respect to the ICER for nirmatrelvir plus ritonavir versus molnupiravir, molnupiravir had LCLE and an ICER of [redacted]. Patients aged > 70 years have a higher hospitalisation rate, and molnupiravir has a greater treatment effect compared to the base case, resulting in a higher incremental QALYs which drives the key difference in ICER against no treatment. For the trial-based scenario, the ICER for molnupiravir versus no treatment was £[redacted], due to the lower treatment impact on hospitalisation predicted from the trial than the RWE NMA in this subgroup.

Table 77. Base case results for patients aged > 70 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	2,074	8.011	5.721	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	1,338
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference

Table 78. Trial-based scenario results for patients aged > 70 years*

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	2,564	7.828	5.593	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference
*Owning to data limitations and need of additional assumptions for other comparators, only comparisons of molnupiravir versus no treatment are presented for subgroup-related scenario analyses

B.3.12.2 Contraindicated to nirmatrelvir plus ritonavir

Subgroup analysis was performed on patients with mild to moderate COVID-19 at risk of progression to severe illness and contraindicated to nirmatrelvir plus ritonavir. This was defined as patients with eGFR < 45 ml/min/1.73m^3 or patients with current or expected used of any medications with CYP3A4 clearance or inductions[ix]. Sotrovimab and no treatment were used as comparators to molnupiravir, as some of these patients (those falling within the McInnes criteria) fall within the sotrovimab recommendation, while those covered by the Edmunds expanded criteria do not and are not currently eligible to receive a COVID-19 antiviral according to NICE recommendations. Further, some patients eligible for sotrovimab may not receive sotrovimab treatment due to a geographic barrier in receiving IV treatment. Inputs for the subgroup are shown in Appendix E.2.

For the subgroup of patients contraindicated to nirmatrelvir plus ritonavir, molnupiravir accumulated costs of £[redacted] and total QALYs of [redacted]. Compared to no treatment, molnupiravir was associated with higher cost and higher QALYs, and the ICER of molnupiravir versus no treatment was £[redacted]. With respect to the ICER for sotrovimab versus molnupiravir, molnupiravir had LCLE, with an ICER of £[redacted]. Due to a lack of data on subgroup specific indirect comparisons from the RWE NMA, it was assumed that treatment effects in patients contraindicated to nirmatrelvir plus ritonavir were the same as the age > 70 years population. Similarly, there was a lack of specific data on hospitalisation rates for this subgroup, and the value used is based on advanced renal disease.(43) From the MOVe-OUT trial, hospitalisation rates for patients contraindicated to nirmatrelvir plus ritonavir are higher than for the overall at-risk population demonstrating that the hospitalisation rate used is likely an underestimate. In the trial-based scenario, molnupiravir is dominant compared to no treatment due to the substantially higher hospitalisation rate and greater treatment effect predicted by the trial in this subgroup.

Table 79. Base case results for patients contraindicated to nirmatrelvir plus ritonavir

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	984	16.254	12.869	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[ix]An overview of drug-drug interactions for nirmatrelvir plus ritonavir can be found at https://www.covid19-druginteractions.org/prescribing_resources [accessed 21 February 2024]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference

Table 80. Trial-based scenario results for patients contraindicated to nirmatrelvir plus ritonavir*

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	3,926	15.819	12.379	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference
*Owning to data limitations and need of additional assumptions for other comparators, only comparisons of molnupiravir versus no treatment are presented for subgroup-related scenario analyses

B.3.12.3 Immunocompromised

Subgroup analysis was performed on patients who were immunocompromised with mild to moderate COVID-19. 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.[87] In line with NICE guidelines, nirmatrelvir plus ritonavir was used as the comparator to molnupiravir in this subgroup. Inputs for the subgroup are shown in Appendix E.3.

For the immunocompromised subgroup, molnupiravir accumulated costs of £[redacted] and total QALYs of [redacted]. Compared to no treatment, molnupiravir was associated with lower cost and higher QALYs, and the therefore is dominant over no treatment. With respect to the ICERs for nirmatrelvir plus ritonavir versus molnupiravir and sotrovimab in this subgroup, molnupiravir had LCLE with an ICER of £[redacted] and £[redacted] respectively. Immunocompromised patients have substantially higher hospitalisation and mortality rates compared to the base case value, resulting in a higher incremental QALYs which drives the key difference in ICER against no treatment. In the trial-based scenario, molnupiravir is dominant compared to no treatment due to the greater treatment effect predicted by the trial in this subgroup.

Table 81. Base case results the immunocompromised subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	3,357	15.625	12.204	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	MOV is Dominant	Dominated
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	Reference
Nirmatrelvir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference

Table 82. Trial-based scenario results for the immunocompromised subgroup*

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	3,490	15.472	12.092	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	MOV is Dominant
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference
*Owning to data limitations and need of additional assumptions for other comparators, only comparisons of molnupiravir versus no treatment are presented for subgroup-related scenario analyses

B.3.12.4 Chronic kidney disease

Subgroup analysis was performed on patients with chronic kidney disease and mild to moderate COVID-19. In line with NICE guidelines, sotrovimab was used as the comparator to molnupiravir in this subgroup. Inputs for the subgroup are shown in Appendix E.4.

For the chronic kidney disease subgroup molnupiravir accumulated costs of £[redacted] and total QALYs of [redacted]. Compared to no treatment, molnupiravir was associated with higher cost and higher QALYs, and the ICER of molnupiravir versus no treatment was £[redacted]. With respect to the ICER for sotrovimab versus molnupiravir, molnupiravir had with an ICER of £[redacted]. The subgroup of patients with chronic kidney disease have a similar hospitalisation rate compared to the overall at-risk population, and due to a lack of data on subgroup specific indirect comparisons from the RWE NMA it was assumed that treatment effects in these patients were the same as in the aged > 70 years population. In the trial-based scenario, molnupiravir is dominant compared to no treatment due to the substantially higher hospitalisation rate and greater treatment effect predicted by the trial in this subgroup.

Table 83. Base case results for patients with chronic kidney disease

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc NHB	Inc NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	1,042	18.737	15.278	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference

Table 84. Trial-based scenario results for patients with chronic kidney disease*

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	3,303	18.491	15.008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	MOV is Dominant
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference
*Owning to data limitations and need of additional assumptions for other comparators, only comparisons of molnupiravir versus no treatment are presented for subgroup-related scenario analyses

B.3.13 Benefits not captured in the QALY calculation

While other NICE assessment cost-effectiveness analyses have not taken into account duration of symptoms,[44, 74] this variable has been taken into account in the current analysis. A reduction in duration of symptoms may allow individuals to return to work and other normal activities sooner as well as result in lower rates of onward transmission within the community. This may result in indirect benefits to the wider population, not captured within the QALY.

Molnupiravir offers significant benefits to patients and society that are not captured in the QALY. The QALY framework does not capture potential long-term consequences of COVID-19 illness and suboptimal treatment, for example the potential harm caused by emergent DDIs which can range in resolution and health impact from a few days with minimal disutility to long-term with large overall disutility.

The indirect workforce impacts of COVID-19 on the social and healthcare services are important for specific individuals and fall outside the strict patient QALY framework. Control of infection rates and onward transmission would have a positive impact on vulnerable individuals in addition to a positive impact for the NHS and society overall. Finally, by having an additional treatment option for patients with mild to moderate COVID-19 at risk of developing severe illness, the health system is provided with a level of insurance that patients will be able to receive a treatment and ultimately reducing the burden of the disease. This is invaluable given that COVID-19 appears to be settling into a seasonal endemic pattern, with peaks in incidence in the winter months, when the health system is already stretched due to other seasonal infections such as influenza and pneumonia.

B.3.13.1 Addressing residual health inequalities

Molnupiravir offers an option for community/outpatients, addressing residual inequalities for populations that currently cannot receive any of the recommended treatments for mild to moderate COVID-19, leaving them vulnerable to progression to severe disease.

For example, patients with high risk of severe illness and their carers may be at increased risk of mental health issues as a result of social isolation, health anxiety and fear of contagion. Molnupiravir could alleviate these issues by offering high-risk patients an alternative treatment option to allow them to re-engage in social interactions more quickly and reduce health concerns. For those patients contraindicated to nirmatrelvir plus ritonavir, and meeting the McInnes criteria for high risk, sotrovimab is currently the only NICE-recommended antiviral. This requires attendance at a hospital for IV infusion, adding the burden of travel time and costs, plus potential anxiety around contagion, for a patient already unwell and at risk of severe COVID-19. The option to receive an oral antiviral such as molnupiravir instead, which can be taken at home, would be of significant benefit to many vulnerable patients. Recommending molnupiravir for routine use in the NHS would resolve any residual access inequalities towards vulnerable individuals that currently remain untreated.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The selection and development of the modelling approach and structure considered various factors. These factors included the ability to effectively capture the significant elements of the clinical benefits and treatment pathway, as well as incorporating accepted model structures and taking into consideration feedback from appraisal committees in previous NICE submissions TA878 and TA971 [43, 74, 168] and aspects covered in the multiple technology appraisal (MTA) appeal documents.

Internal validation was ensured via a comprehensive and rigorous quality check, performed by an internal peer reviewer not involved in the original implementation of the model. This included validating the logical structure of the model, mathematical formulas, sequences of calculations and the values of numbers supplied as model inputs. A range of extreme value tests were conducted to examine the behaviour of the model and ensure that the results were logical. Any unexpected model behaviour, implementation and typing errors were all identified by this review.

Unit costs were sourced from the most recent NHS reference costs, eMiT, Unit Costs of Health and Social Care (PSSRU), and the BNF to ensure that the results of the economic analysis are appropriate for decision making in the UK setting.

In comparison to cost-effectiveness estimates presented in the MTA submitted to NICE in 2022 [ID4038], results from this cost-effectiveness analysis generated somewhat higher total QALYs (e.g., the MTA estimated 10.05 total discounted QALYs for no treatment compared to 12.26) for all technologies. The higher total QALYs generated in the model presented here compared with the MTA report may be attributed to a higher utility value used for long-term sequelae (0.21 versus 0.13). However, incremental differences generated in both the MTA model and our model were similar.

B.3.15 Interpretation and conclusions of economic evidence

Molnupiravir is an effective, safe and well tolerated treatment option in outpatients with mild to moderate COVID-19 at risk of progression to severe disease, showing significant benefit in all-cause hospitalisation at 28 days compared to no treatment as demonstrated by both direct clinical trial evidence and indirect NMA data from RWE and RCTs. Patients with mild to moderate COVID-19 also demonstrate reduced duration of symptoms after treatment with molnupiravir compared to no treatment. As well as being clinically effective, molnupiravir is also cost-effective compared to no treatment with an ICER in the overall at-risk population of £[redacted] with all PSA iterations falling in the north-east quadrant of the cost-effectiveness plane. When compared with nirmatrelvir plus ritonavir and sotrovimab, molnupiravir is a less costly treatment option. Although molnupiravir has lower effects when compared with nirmatrelvir plus ritonavir and sotrovimab, there is a very small incremental difference with some overlap in the direction of the incremental QALYs observed in the PSA driven by relatively wide uncertainty in relative treatment effects which is inherent in the evidence base of all comparators. major limitation with the comparison against nirmatrelvir plus ritonavir is the lack of a publicly available price for this treatment, meaning conclusions against this comparator, at present, should be viewed with caution. However, it is important to note that in real life patients and clinicians may value other treatment relevant attributes alongside the very small incremental net health benefits differences, when multiple alternatives can be prescribed (i.e., SW quadrant decisions).

Healthcare professionals who operate COVID-19 antiviral services have confirmed the existence of a situation in which patients with mild to moderate COVID-19 at risk of developing severe disease do not receive appropriate antiviral therapy due to contraindications to nirmatrelvir plus ritonavir and either falling outside the NICE

recommendation for sotrovimab or being unable to attend a clinical service for sotrovimab infusion, meaning a comparison with no treatment is relevant for this population which raises residual health inequality issues for patients.

The potential for molnupiravir to be cost-effective compared with no treatment was also demonstrated in the subgroups of interest, in particular patients aged > 70 years and immunocompromised patients. In the subgroup of patients contraindicated to nirmatrelvir plus ritonavir, molnupiravir represents a suitable alternative treatment option for patients unable to attend a clinical service for sotrovimab infusion, filling the unmet medical need in this group of patients.

In scenarios using trial-based hospitalisation and mortality rates, distributions in hospital demonstrate for the higher end of the potential settings and molnupiravir has lower ICERs than the base case compared to no treatment as expected since hospitalisation rates drive the cost-effectiveness results.

The key strength of the cost-effectiveness analysis presented here is that it addresses concerns with the model used in TA878 and TA971, capturing more benefits of outpatient treatments through the inclusion of outpatient utilities, COVID-19 specific utilities and the impact of treatment on outpatient symptom duration. The model takes a simplified approach to in hospital progression appropriate for the decision problem. The use of RWE NMA data makes use of the most recent and robust data available to inform the modelling.

Limitations of the analysis include the consideration of only the direct impact of treatment and not the potential indirect benefit such as potential reduction in onward transmission, impact on carers, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity and scientific spillovers (see also Section B.3.13). As discussed above, there are also limitations in the data available, specifically for the subgroups of interest where the potential benefits of molnupiravir may be the most valuable.

The very small incremental differences in health benefits are primarily driven by the relatively wide uncertainty in relative treatment effects which is inherent in the evidence base of all comparators. It also means that the associated decision risk is overall very low when it comes to recommending a treatments in relation to clinical effectiveness. For most patients such small differences over a life time are unlikely to have a major impact on the overall health, especially for those which can receive alternative interventions. However, there remains a group of patients which cannot receive any of the recommended treatment options based on clinical expert discussions and this raises issues for residual health inequalities.

Molnupiravir offers an effective treatment option in patients with mild to moderate COVID-19 at risk of progression to severe disease and fulfils an unmet need for those with no viable treatment option.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Molnupiravir for treating COVID-19 [ID6340]

Summary of Information for Patients (SIP)

Final – 18th June 2024

File name	Version	Contains confidential information	Date
ID6340_Molnupiravir_COVID-19_SIP	1.0	No	18 June 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

Section 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Molnupiravir **Brand name:** Lagevrio™

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

Molnupiravir is used to treat mild to moderate COVID-19 (caused by SARS-CoV-2) in adults with a positive COVID-19 virus diagnostic test and who have at least one risk factor for developing severe illness.

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Molnupiravir has a conditional marketing authorisation in Great Britain, granted on 4th November 2021. https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir [accessed 6 June 2024]

1d) Disclosures.

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

None

Section 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is COVID-19?

Coronavirus disease 2019 (COVID-19) is a disease caused by the SARS-CoV-2 virus, which causes upper respiratory tract infection. The virus is spread by coming into contact with an infected person; coughs and sneezes release small droplets that can transfer the virus to another person through breathing in the droplets.(1, 2)

People with COVID-19 may have mild illness linked with upper respiratory tract infection, such as fever, sore throat, cough and tiredness, but may also not have any symptoms (1-5). However, some people with COVID-19 get moderate, severe or critical illness, with pneumonia, low blood oxygen and/or acute respiratory distress.(1-5)

It is not clear why some people get more serious illness, but some factors are thought to increase a person's risk of progressing to severe disease. People at risk of getting severe illness include older adults, those with certain health conditions, and those getting specific drugs to treat another condition.(6-12) COVID-19 was identified in 2020 and, since its first reporting, there has been considerable research into COVID-19, which has led to an increased understanding around risk factors for severe disease. This means that, over time, the factors used to classify someone as high risk have changed. Published NICE guidance has used two key definitions of high risk (Table 1) based on the McInnes report(13) and the Edmunds report.(14)

Table 1. Definitions of high risk for severe COVID

McInnes report	Edmunds report
Adults with the following health conditions: • Down's syndrome and other genetic disorders • Cancer • Blood diseases and stem cell transplant recipients • Kidney diseases • Liver diseases • Organ transplant recipients • Inflammatory disorders linked to the immune system • Respiratory diseases • Immune deficiencies • HIV/AIDS • Neurological disorders	In addition to the health conditions in the McInnes report, also adults with: • Age ≥70 years • Diabetes • Obesity (defined as BMI ≥35 kg/m2) • Heart failure

How many people get COVID-19?

SARS-CoV-2 was first identified in January 2020 and, in March 2020, the World Health Organisation (WHO) announced that the disease had become a global pandemic.(15, 16) To date, over 24.9 million confirmed cases of COVID-19 have been recorded in England, with 570,000 cases reported in 2023 alone.(17, 18) While COVID-19 cases are seen all year round, there are increases in cases in the winter months, suggesting it may become mainly a winter seasonal illness. In Autumn 2023/2024, recorded infections peaked at a 7-

day rolling average of 2,392 cases in the seven days to 2nd October 2023,(19) while latest data reported 1,820 cases in the seven days to 21st May 2024.(19)

It is estimated that there are 3.9 million people at high risk of severe COVID-19 in the UK by the McInnes definition.(20) When including the additional risk factors in the Edmunds report, the estimate of people at high risk of severe COVID-19 in the UK is increased to 5.3 million people.(20)

What is the impact of COVID-19 on a person's quality of life?

COVID-19 has a substantial impact on the quality of life of patients, caregivers and family members, particularly if patients have been treated in hospital. A study of 100 patients with COVID-19 at the Leeds Teaching Hospitals NHS Trust in 2021 reported that 69% of patients who had treatment in the intensive care unit (ICU), and 46% of patients treated on the general ward had a decrease in health-related quality of life.(21)

In the same study, 47% of patients who were treated in the ICU experienced symptoms of post-traumatic stress disorder (PTSD) after discharge from hospital.(21) Overall, 35% of patients experienced anxiety and depression after COVID-19 illness, most of whom had no previous mental health conditions.(21)

How many people die from COVID-19?

As of 13th April 2024, 232,112 people in the United Kingdom have died due to COVID-19. It has been reported that 171,383 excess deaths occurred between the start of the pandemic (27th March 2020) and 29th December 2023.(22)

The risk of death from COVID-19 increases with age and is higher in men and people with certain health conditions, including but not limited to, diabetes, cardiovascular disease, cancer, kidney disease, liver disease and neurological conditions.(6-11) It is not clear if the risk of death differs by ethnicity, with some studies reporting increased risk of death from COVID-19 for people with black, Asian/Asian British and mixed ethnicities compared to white ethnicity and other studies reporting no difference in risk of death from COVID-19 for different ethnicities (though an increase in hospital admissions for Asian men, Asian women and black women).(6)

Vaccines have been developed that provide protection against death from COVID-19, as well as against infection and hospitalisation.(23, 24) At first, the vaccination programme in the UK prioritised older adults and those with certain health conditions. Later, the programme was widened and eventually most people could be vaccinated. By October 2021, 85% of adults in the UK had received 2 doses of COVID-19 vaccine.(25) Since Autumn 2022, COVID-19 vaccinations have been offered in a regular autumn booster programme for people aged over 65 years, residents in care homes, people in a risk group and health and social care staff.(23, 26) However, UK COVID-19 vaccine surveillance reports suggest that there have been some waning effects since the autumn 2023 seasonal vaccine booster campaign.(27) There are also people who continue to be vulnerable to COVID-19, despite receiving seasonal booster vaccinations.(28)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
The virus causing COVID-19 can be detected using testing such as reverse-transcription polymerase chain reaction (RT-PCR), which has to be done in a laboratory, or a lateral flow kit, which can be done at home.(1) Currently, for patients not in a healthcare setting, UK guidelines recommend testing in only symptomatic patients who are eligible for COVID-19 treatment, that is, those at highest risk of severe COVID-19.(29) Testing should

be conducted with a lateral flow device, but RT-PCR may also be used in healthcare settings to support diagnosis.(29)

The extent of testing carried out has an impact on the true number of cases identified and then treated at early stages of disease.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Mild to moderate COVID-19 can generally be treated at home with treatments for managing symptoms.(5) However, people with severe illness are likely to need treatment in hospital to help support breathing. Medications for patients with severe COVID-19 include antivirals, corticosteroids and/or anti-inflammatory drugs.(5) Patients who get COVID-19 in hospital (incidental COVID-19) that is mild to moderate in severity are treated the same way as patients who are not in hospital.

For patients at risk of developing severe COVID-19, treatments are available when the disease is mild or moderate to help prevent the progression to severe illness. The only treatments currently recommended by NICE (TA878) for these patients are nirmatrelvir plus ritonavir (Paxlovid™), sotrovimab (Xevudy®), and remdesivir (Veklury®).(30) Molnupiravir is an alternative option for use in the NHS for these patients.

Nirmatrelvir plus ritonavir

Nirmatrelvir plus ritonavir is the first treatment option recommended for people with mild or moderate COVID-19 at risk of severe illness according to the Edmunds definition of high risk (including McInnes).(31) It has been shown to decrease hospitalisations and death in these people and is considered to be cost effective. However, it is associated with a number of limitations:

- Treatment with nirmatrelvir plus ritonavir is contraindicated (should not be given) for up to 36% of patients.(32) These patients include people with severe liver or kidney impairment, which are health conditions linked with increased risk of severe COVID-19 illness.(13, 30)
- Additionally, people taking certain medications alongside nirmatrelvir plus ritonavir are at risk of drug-drug interactions. These medications include, but are not limited to, drugs given to treat irregular heart rhythms, blood clotting, seizure, anxiety and cancer, and medications that suppress the immune system.(33, 34) Treatment with nirmatrelvir plus ritonavir in patients taking these medicines may lead to serious or life-threatening side effects, and therefore additional specialist resources are needed to check for interactions.(35) It is estimated that up to 27% of high-risk patients may be taking medications that would prevent them from receiving nirmatrelvir plus ritonavir.(32)

Sotrovimab

Sotrovimab is recommended for the treatment of people with mild or moderate COVID-19 at risk of severe illness according to the McInnes definition of high risk and who are contraindicated to, or unsuitable for treatment with, nirmatrelvir plus ritonavir.(30, 36) Sotrovimab can also be used in young people aged 12 years and over who weigh at least 40 kg.(30, 36) In clinical trials, sotrovimab has been shown to lower the risk of hospitalisation and death in these people.(30, 36-38) However, NICE have commented that clinical effectiveness is uncertain due to conflicting data for different variants (a new form of the original virus) of the COVID-19 virus.(30)

- Sotrovimab may be less effective in the future as new COVID-19 virus variants emerge. This is because sotrovimab works by binding to the spike protein on the virus, which can change over time as the virus evolves and mutates.(30)
- Other limitations of sotrovimab are that it is given by intravenous injection (given into a vein or veins). Patients need to attend a hospital or clinic to receive the treatment, which raises concerns about accessibility to treatment and NHS capacity to deliver it.(36)

Remdesivir

Remdesivir is recommended for the treatment of patients with COVID-19 at risk of severe illness and who are in hospital.(39) Clinical experts have advised MSD that patients with incidental COVID-19 (patients who get COVID-19 while in hospital) who are on a general ward and do not require supplementary oxygen are treated with nirmatrelvir plus ritonavir or sotrovimab, like patients not in hospital. Remdesivir may be used in these patients if the clinician considers it to be the best treatment option.(40) Remdesivir may also be used for patients at risk of severe COVID-19 disease who are admitted to hospital after receiving a COVID-19 treatment (such as nirmatrelvir plus ritonavir or sotrovimab) outside of hospital.(31, 39)

Because remdesivir can only be used in patients who are in hospital, it is not considered a direct comparator of interest for molnupiravir in the submission, which focusses on treatment of patients outside of hospital.

2d) Patient-based evidence (PBE) about living with the condition

Context: Patient-based evidence (PBE) is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about patient needs and disease experiences. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Not available.

Section 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
Molnupiravir is an antiviral medication that is taken orally. Once molnupiravir is given it is modified within the body's cells to an active metabolite (also known as active substance) referred to as NHC-TP.(41) NHC-TP is used by the body's cells to build the genetic material (RNA; ribonucleic acid) of the virus, which introduces errors into the virus' RNA. The number of errors increases over time and, in the end, prevents the virus from replicating.(41) Once the virus cannot replicate, the immune system can clear the infection, which results in the patient improving, and leads to lower hospitalisations and/or deaths (as shown in the primary clinical study assessing molnupiravir, MOVe-OUT).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? Yes/No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
No, molnupiravir is not intended for use in combination with other medicines.(41)

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Molnupiravir is for oral use. Capsules of 200 mg should be taken with or without food. The dose of molnupiravir is 800 mg twice daily for 5 days.(41)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
The key trial providing direct evidence for molnupiravir is the pivotal phase II/III MOVe-OUT trial sponsored by MSD, which assessed the efficacy and safety of molnupiravir compared with placebo. Other smaller trials assessing the clinical effectiveness of molnupiravir versus placebo/no treatment were identified in a systematic literature review (SLR) but were not considered suitable for inclusion in the submission. For further information about the trial, see Jayk Bernal et al. 2022.(42) **Title:** MOVe-OUT, a randomised, double-blinded, parallel assignment, interventional, placebo-controlled trial **Location:** The trial was conducted in 107 sites in 20 countries across the US, Europe and Asia, including 6 sites in the UK.(43) **Population:** Non-hospitalised adults with mild to moderate COVID-19 with at least one risk factor for developing severe illness. **Patient group size:** 1,433 patients randomised 1:1

Comparators: Placebo

Inclusion/exclusion criteria:

Inclusion criteria	Exclusion criteria

• Aged ≥ 18 years
• Positive SARS-CoV-2 test result
• Initial onset of signs/symptoms of COVID-19 at least 5 days prior to randomisation and at least one sign/symptom attributable to COVID-19 on the day of randomisation
• Mild or moderate COVID-19 and at least one of the following risk factors associated with an increased risk of severe illness:
  ○ Age > 60 years
  ○ Active cancer
  ○ Chronic kidney disease
  ○ Chronic obstructive pulmonary disease
  ○ Obesity
  ○ Serious heart conditions such as heart failure, coronary artery disease or cardiomyopathies
  ○ Diabetes mellitus
	• Currently hospitalised or expected to need hospitalisation for COVID-19 within 48 hours of randomisation
	• On dialysis or reduced eGFR <30 mL/min/1.73m^2
	• Any of the following conditions:
	  ○ HIV or an AIDS-defining illness in the past 6 months
	  ○ A neutrophilic granulocyte absolute count < 500/mm^3
	• History of HBV or HCV infection
	• Platelet count < 100,000/μL or received a platelet transfusion in the 5 days prior to randomisation

AIDS = acquired immunodeficiency syndrome; COVID-19 = coronavirus disease 2019; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

SOURCE: Jayk Bernal et al. 2022(42)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition. In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The efficacy of molnupiravir has been shown in the pivotal randomised, double-blinded, parallel assignment, interventional, placebo-controlled MOVe-OUT trial,(42) in addition to comparative analyses using data from randomised controlled trials (RCT) and real-world evidence (RWE) identified in SLRs.

MOVe-OUT

From study initiation to Day 29, fewer patients were hospitalised for any cause or died from any cause with molnupiravir compared to placebo (28 patients [7.3%] vs 53 patients [14.1%]).(42) This corresponds to a 6.8 percentage point reduction (95% CI: -11.3, -2.4; one-sided p=0.0012; approximately 50% relative risk reduction).(42) All participants who died from study initiation to Day 29 were in the placebo group (8 patients; 2.1%).(42)

Results of the trial by Month 7 were consistent with results up to Day 29, with fewer patients dying from any cause with molnupiravir compared with placebo (3 patients [0.4%] vs 6 patients [0.6%]) and fewer patients being hospitalised for any cause with molnupiravir compared with placebo (2 patients [0.3%] vs 3 patients [0.4%]).(44) One death in the molnupiravir group was considered to be COVID-19 related compared to two deaths in the placebo group.(44)

For further information see Section B.2.6 of submission Document B.

Additional evidence

Analyses comparing molnupiravir with other active treatments for COVID-19 have shown that the effectiveness of molnupiravir is similar to that of nirmatrelvir plus ritonavir, sotrovimab and remdesivir in reducing the risk of all-cause hospitalisation or death in non-hospitalised patients with mild to moderate COVID-19. Additionally, the analyses show that molnupiravir has a lower risk of all-cause hospitalisation, COVID-19 related hospitalisation or death when compared with placebo or no treatment. Given the current treatment pathway for mild to moderate COVID-19 in patients at risk of severe disease in England, the unmet need remains for a suitable alternative to current treatments, which could be filled by molnupiravir.

For further information see Section B.2.9.1 and Section B.2.9.2 of submission Document B.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life data were not collected in the MOVe-OUT trial. Data are not available from other sources investigating the impact of molnupiravir on quality of life.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Molnupiravir is considered a safe treatment, with few side effects and no contraindications or dose adjustments required for special populations.(42)

Based on the MOVe-OUT trial of patients with mild to moderate COVID-19 at risk of developing severe illness, the most common adverse reactions with molnupiravir, experienced in ≥1% of patients, were diarrhoea (2%), nausea (1%), and dizziness (1%), all of which were mild or moderate in severity.(41)

In the trial, 14 patients experienced adverse events leading to death, of whom 12 patients (1.7%) received placebo and two patients (0.3%) received molnupiravir. None of the deaths was considered to be related to the drug the patient was taking.(42) Four patients (0.6%) in the molnupiravir group and three patients (0.4%) in the placebo group had a drug-related adverse event that led to them stopping treatment.(42)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Molnupiravir can provide an alternative to current treatments and already has a marketing authorisation for patients with mild to moderate COVID-19 at risk of severe illness. The MOVe-OUT clinical trial and comparative analyses show that molnupiravir is clinically effective compared to placebo or usual care.

Molnupiravir has some key benefits:

- Unlike nirmatrelvir plus ritonavir, molnupiravir can be used in patients with severe kidney or liver impairment
- Molnupiravir can be used in patients taking certain drugs (such as treatments for irregular heart rhythm, blood clotting, seizures, anxiety, and cancer, and drugs that affect the immune system), who would be at risk of drug-drug interactions with nirmatrelvir plus ritonavir
- Unlike sotrovimab, which is administered by intravenous infusion and is currently the only alternative to nirmatrelvir plus ritonavir, molnupiravir is an oral medication and can be administered at home instead of in a healthcare setting reducing healthcare resource
- Unlike remdesivir, which is only approved for use in hospital, molnupiravir can be given to patients who are not in hospital. But, for patients with incidental COVID-19, molnupiravir is an additional treatment option

Healthcare professionals have told MSD that, based on current treatment guidance, there are situations where there is no treatment option available to patients in the community with mild to moderate COVID-19 at risk of severe illness.(40) This is likely due to contraindications to nirmatrelvir plus ritonavir and either not being eligible for sotrovimab (Edmunds definition of high risk) or being unable to attend a clinical service for sotrovimab infusion.(40) Molnupiravir is also a treatment option for these patients who may not otherwise be able to receive treatment.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Molnupiravir is a more costly option for healthcare providers than no treatment. However, molnupiravir is also associated with greater health benefits in patients with mild to moderate COVID-19 at risk of severe disease compared with no treatment, including reducing the risk of hospitalisation, death and the duration of symptoms.

Questions can also be asked about the efficacy of molnupiravir compared with other treatments currently recommended for use in the NHS. In comparative analyses, molnupiravir was not better than nirmatrelvir plus ritonavir or sotrovimab for some of the outcomes explored. Nevertheless, molnupiravir was not statistically significantly worse

either, suggesting that efficacy is comparable. Thus, molnupiravir is a valuable alternative option to existing treatments recommended by NICE.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

How the condition, taking the new treatment compared with current treatments affects your quality of life.

Molnupiravir has been shown to be a safe and effective treatment for patients with mild or moderate COVID-19 at risk of developing severe disease in a randomised controlled trial and is a valuable alternative option to currently available treatments.

For the group of patients highlighted by healthcare professionals operating COVID-19 antiviral services who have mild or moderate COVID-19 at risk of severe illness and do not currently receive any therapy, molnupiravir is a more expensive but more effective treatment option than no treatment (see Section B.3.10 of submission Document B).

Molnupiravir also provides cost savings compared with other treatments:

- Molnupiravir has lower administration costs and requires less healthcare resource than nirmatrelvir plus ritonavir. This is due to the additional time and cost associated with the need for a healthcare professional (such as a pharmacist) to assess for potential drug-drug interactions or dose adjustments.
- Molnupiravir also has lower administration costs and requires less healthcare resource than sotrovimab. As sotrovimab is given by intravenous infusion, it must be administered in a healthcare setting, requiring specialist time, capacity and resource, unlike molnupiravir which is an oral medication and can be taken at home.
- As molnupiravir is an oral medication that can be taken at home, it has additional benefits for patients and carers compared to sotrovimab, as it does not require travel to a clinic and the associated time off work needed for treatment.
- Treatment with remdesivir is expensive, with a treatment course that costs more than molnupiravir because remdesivir is given by intravenous infusion. It is noted again that, as described in Section 2c), remdesivir is only a comparator for molnupiravir in the context of incidental COVID-19 (i.e., COVID-19 that is acquired in hospital) as remdesivir can only be given to patients who are in hospital.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any

QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
There are wider health-related benefits that could be gained from having an alternative treatment option for patients with mild or moderate COVID-19 at risk of severe disease. For example, high-risk patients and their carers may be at increased risk of mental health issues due to social isolation and health anxiety, and fear of contagion. Molnupiravir offers these patients a treatment option to be able to re-engage in social interactions more quickly and reduce health concerns. Potential harm from drug-drug interactions should also be taken into account. Suboptimal management of these can range from having minimal health consequences for a few days to long-term impacts on quality of life. As molnupiravir is not associated with any drug-drug interactions, no such harm would be experienced. An alternative treatment option would also have an indirect effect on the social and health care services workforce and vulnerable individuals, by controlling infection rates. This could have a positive impact for the NHS and society overall.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Molnupiravir is a treatment option for patients with protected characteristics, such as older adults or those with long-term conditions and/or disabilities. These patients are more likely to be in the group of patients at risk of developing severe illness with COVID-19. • As an oral medication taken at home, molnupiravir can reduce exposure of these patients with protected characteristics to other patients with communicable diseases in healthcare settings • Molnupiravir is a simple treatment option with no drug-drug interactions for patients with protected characteristics who may have multiple medical conditions and taking a number of medications • Molnupiravir is not contraindicated in patients with kidney problems, which are more common in Black, Asian and other minority ethnic backgrounds.(45) These groups also have a higher risk of death from COVID-19.(46) • Molnupiravir can be used for patients who are contraindicated to nirmatrelvir plus ritonavir and find it difficult to get to a health care facility to access sotrovimab. This could be due to inability or unwillingness to travel long distances if they do not live near a health care facility, lack of capacity in local health care facilities to see and treat patients, and/or general preference for an alternative oral treatment option instead of an intravenous infusion drug.

Section 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
•

4b) Glossary of terms

AEs/adverse reactions: Also known as side effects, these are unexpected medical problems that arise during treatment with a drug or other therapy. Adverse events may be mild, moderate or severe.
Antiviral: Treatment used for viral infections and directly target the virus.
Comparative analysis: A technique that compares multiple treatments in a single analysis.
Contraindicated: When a treatment should not be used in the case in question.
Drug-drug interaction: A reaction between two (or more) drugs that can cause adverse reactions, or one (or more) of the drugs to be less effective.
Edmunds report: A list of criteria that increase the risk of severe COVID-19 illness (see Table 1 in Section 2a)). The criteria include those listed in the McInnes report and the Edmunds criteria therefore form a broader definition of high risk.
General ward: Hospital ward where patients require treatment but are not critically ill.
Healthcare resource: Facilities, supplies, equipment and healthcare staff time required to treat patients.
ICU/intensive care unit: Hospital ward where patients are critically ill and require specialist monitoring and treatment.
Incidental COVID-19: COVID-19 caught when a patient is already in hospital for another reason.
McInnes report: A list of criteria that are thought to increase the risk of severe COVID-19 illness (see Table 1 in Section 2a)).
QoL/quality of life: Well-being or the overall enjoyment of life.
RCT/randomised controlled trial: Clinical trials where factors are controlled to compare the effects of medical treatments versus each other or versus no treatment.
RWE/real-world evidence: Clinical evidence about the use and potential benefits of a medical treatment using data collected outside a highly controlled clinical trial, usually during delivery of the treatment in the healthcare setting.
SARS-CoV-2: The virus which causes COVID-19.
SLR/systematic literature review: A systematic search for publications or literature using predefined search criteria.
Supplementary oxygen: Oxygen therapy that is additional to the oxygen breathed in from the air. This may be given using a nasal cannula or face mask, but can also be given through a breathing tube using a ventilator in critically ill patients.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:
1. BMJ Best Practice. Coronavirus disease 2019 (COVID-19) 2023 [Available from: https://bestpractice.bmj.com/topics/en-us/3000168. 2. Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J. 2021;97(1147):312-20.

3. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215:108427.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Molnupiravir for treating COVID-19 [ID6340]

Clarification questions

July 2024

File name	Version	Contains confidential information	Date
ID6340 Molnupiravir EAG clarification letter to PM_MSD_FINAL_19-07-2024_CON	1.2	No	19 July 2024

Notes for external assessment groups (EAGs) and NICE

[TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision Problem

A1. Company submission (CS) Table 1 states that "data did not allow" virological outcomes (viral shedding and viral load) to be included. However, this contradicts the information reported in CS Appendix Tables 19 and 20 which list the studies

reporting these outcomes that could be included in network meta-analyses (NMAs). As virological outcomes are specified in the NICE scope:

a) Please summarise the viral outcomes from the MOVe-OUT trial.

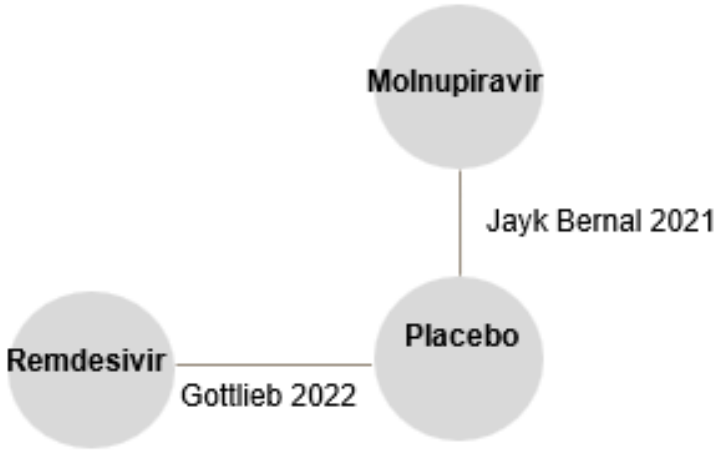
- It should be noted that data did not allow for viral outcome measures to be included in the cost-effectiveness analysis portion of this submission. Viral outcomes from MOVe-OUT are as follows:
    - Jayk Bernal 2022: The mean change from baseline in SARS-CoV-2 nasopharyngeal RNA titre (log_{10} copies/mL) by Day 3 and Days 14/15 for both treatment groups were:[1]
        - Molnupiravir: -1.08 (SD: 1.287) and -3.61 (SD: 1.740)
        - Placebo: -0.84 (SD: 1.258) and -3.48 (SD: 1.836)

b) Please provide the results of the NMAs of the RCTs for viral load change and viral clearance.

Viral load change – Day 3

- Two trials comparing an intervention with placebo or usual care (one evaluating molnupiravir and one evaluating remdesivir) were included in the analysis of reported proportions of patients with viral load change by Day 3 following randomisation (Figure 1).
    - The total number of patients and the mean/standard error of viral load change by Day 3 in each trial arm are summarised in Table 1.
    - Comparing across treatments, patients receiving molnupiravir had greater viral load reduction by Day 3 than those receiving remdesivir (Table 2). Additionally, compared with placebo, viral load reduction by Day 3 was greater for patients receiving molnupiravir or remdesivir (Table 3).

Figure 1. Network for viral load change on Day 3 and Day 14 or Day 15



Source: RCT SLR (see Appendix D.1)

Table 1. Event rates for the analysis of viral load change by Day 3

Trial name / Author and year	Treatment	Sample Size	Mean	Standard Error
Gottlieb 2022	Placebo	187	-0.91	0.08
	Remdesivir	195	-1.03	0.08
Jayk Bernal 2021	Placebo	507	-0.84	0.06
	Molnupiravir	499	-1.08	0.06

Table 2. Median difference of viral load change (log_{10} copies) by Day 3 comparing each pair of treatments

	Placebo	Molnupiravir	Remdesivir
Placebo	0	-0.24 (-0.40, -0.08)	-0.13 (-0.35, 0.09)
Molnupiravir	0.24 (0.08, 0.40)	0	0.11 (-0.16, 0.38)
Remdesivir	0.13 (-0.09, 0.35)	-0.11 (-0.38, 0.16)	0

Table 3. Difference in viral load change (log_{10} copies) by Day 3 of each treatment versus placebo

	Mean difference vs. placebo		
Treatment	Mean	Median	95% CrI
Molnupiravir	-0.24	-0.24	(-0.40, -0.08)
Remdesivir	-0.13	-0.13	(-0.35, 0.09)

CrI = credible interval

Viral load change – Day 14 or Day 15

- Two trials comparing an intervention with placebo or usual care (one evaluating molnupiravir and one evaluating remdesivir) were included in the analysis of reported proportions of patients with viral load change by Day 14 or Day 15 following randomisation (Figure 1).
    - The total number of patients and the mean/standard error of viral load change by Day 14 or Day 15 in each trial arm are summarised in Table 4.
    - Comparing across treatments, patients receiving molnupiravir had greater viral load reduction by Day 14 or Day 15 than those receiving remdesivir (Table 5). Additionally, compared with placebo, viral load reduction by Day 14 or Day 15 were greater for patients receiving molnupiravir or remdesivir (Table 6).

Table 4. Event rates for the analysis of viral load change by Day 14 or Day 15

Trial name / Author and year	Treatment	Sample Size	Mean	Standard Error
Gottlieb 2022	Placebo	169	-3.16	0.14
	Remdesivir	184	-3.13	0.13
Jayk Bernal 2021	Placebo	413	-3.48	0.09
	Molnupiravir	424	-3.61	0.08

Table 5. Median difference of viral load change by Day 14 or Day 15 comparing each pair of treatments

	Placebo	Molnupiravir	Remdesivir
Placebo	0	-0.13 (-0.37, 0.11)	0.03 (-0.35, 0.40)
Molnupiravir	0.13 (-0.11, 0.37)	0	0.16 (-0.29, 0.60)
Remdesivir	-0.03 (-0.40, 0.35)	-0.16 (-0.60, 0.29)	0

Table 6. Difference in viral load change by Day 14 or Day 15 of each treatment versus placebo

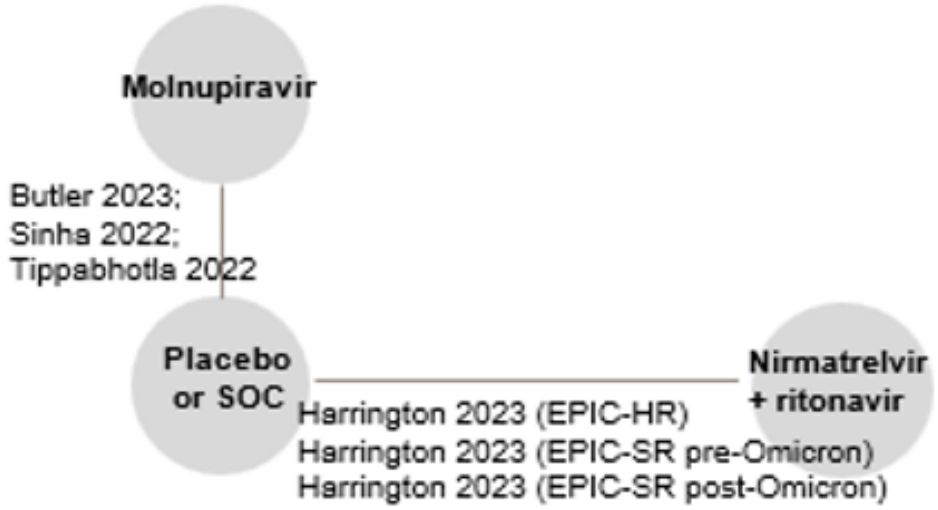
	Mean difference vs. placebo		
Treatment	Mean	Median	95% CrI
Molnupiravir	-0.13	-0.13	(-0.37, 0.11)
Remdesivir	0.03	0.03	(-0.35, 0.40)

CrI = credible interval

Viral clearance – Day 5

- Five trials comparing an intervention with placebo or usual care (three evaluating molnupiravir and two evaluating nirmatrelvir plus ritonavir) were included in the analysis of reported proportions of patients with viral clearance by Day 5 following randomisation (Figure 2).
    - The total number of patients and the number/proportion of patients with viral clearance by Day 5 in each trial arm are summarised in Table 7.
    - Comparing across treatments, patients receiving molnupiravir had a higher chance of viral clearance by Day 5 than those receiving nirmatrelvir plus ritonavir (Table 8 and Table 9). Additionally, compared with placebo, proportions of patients with viral clearance by Day 5 were higher for those receiving molnupiravir and nirmatrelvir plus ritonavir (Table 10).

Figure 2. Network for viral clearance by Day 5



SOC = standard of care
Source: RCT SLR (see Appendix D.1)

Table 7. Event rates for the analysis of viral clearance by Day 5

Trial name / Author and year	Treatment	Outcome	Sample Size	Event Rate (%)
Butler 2022	Placebo	8	280	2.86
	Molnupiravir	20	238	8.4
Harrington 2023 (EPIC-HR)	Placebo	415	942	44.06
	Nirmatrelvir plus ritonavir	447	936	47.76
Harrington 2023 (EPIC-SR post-Omicron)	Placebo	38	104	36.54
	Nirmatrelvir plus ritonavir	60	106	56.6
Harrington 2023 (EPIC-SR pre-Omicron)	Placebo	199	492	40.45
	Nirmatrelvir plus ritonavir	251	509	49.31
Sinha 2022	Placebo	179	610	29.34
	Molnupiravir	469	608	77.14
Tippabhotla 2022	Placebo	106	610	17.38
	Molnupiravir	497	610	81.48

Table 8. Median odds ratio of viral clearance by Day 5 comparing each pair of treatments

	Placebo	Molnupiravir	Nirmatrelvir plus ritonavir
Placebo	1	12.09 (10.02, 14.64)	1.30 (1.13, 1.50)
Molnupiravir	0.08 (0.07, 0.10)	1	0.11 (0.08, 0.14)
Nirmatrelvir plus ritonavir	0.77 (0.67, 0.89)	9.30 (7.35, 11.81)	1

Table 9. Median risk ratio of viral clearance by Day 5 comparing each pair of treatments

	Placebo	Molnupiravir	Nirmatrelvir plus ritonavir
Placebo	1	2.72 (2.58, 2.86)	1.19 (1.08, 1.30)
Molnupiravir	0.37 (0.35, 0.39)	1	0.44 (0.39, 0.48)
Nirmatrelvir plus ritonavir	0.84 (0.77, 0.92)	2.28 (2.07, 2.53)	1

Table 10. Odds ratio and risk ratio of viral clearance by Day 5 of each treatment versus placebo

	Odds ratio vs. placebo			Risk ratio vs. placebo		
Treatment	**Mean**	**Median**	**95% CrI**	**Mean**	**Median**	**95% CrI**
Molnupiravir	12.15	12.09	(10.02, 14.64)	2.72	2.72	(2.58, 2.86)
Nirmatrelvir plus ritonavir	1.30	1.30	(1.13, 1.50)	1.19	1.19	(1.08, 1.30)

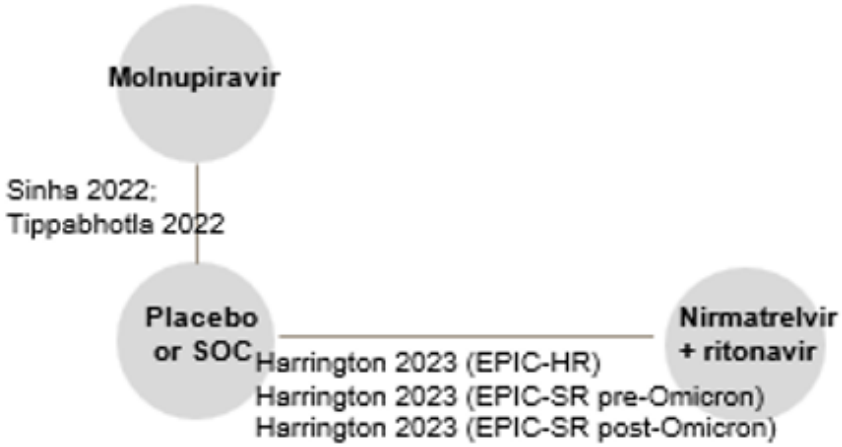
CrI = credible interval

Viral clearance – Day 10

- Four trials comparing an intervention with placebo or usual care (two evaluating molnupiravir and two evaluating nirmatrelvir plus ritonavir) were included in the analysis of reported proportions of patients with viral clearance by Day 10 following randomisation (Figure 3).
    - The total number of patients and the number/proportion of patients with viral clearance by Day 10 in each trial arm are summarised in Table 11.
    - Comparing across treatments, patients receiving molnupiravir had a higher chance of viral clearance by Day 10 than those receiving

nirmatrelvir plus ritonavir (Table 12 and Table 13). Additionally, compared with placebo, proportions of patients with viral clearance by Day 10 were higher for those receiving molnupiravir and nirmatrelvir plus ritonavir (Table 14).

Figure 3. Network for viral clearance by Day 10



SOC = standard of care
Source: RCT SLR (see Appendix D.1)

Table 11. Event rates for the analysis of viral clearance by Day 10

Trial name / Author and year	Treatment	Outcome	Sample Size	Event Rate (%)
Harrington 2023 (EPIC-HR)	Placebo	622	903	68.88
	Nirmatrelvir plus ritonavir	702	922	76.14
Harrington 2023 (EPIC-SR post-Omicron)	Placebo	79	102	77.45
	Nirmatrelvir plus ritonavir	89	103	86.41
Harrington 2023 (EPIC-SR pre-Omicron)	Placebo	352	488	72.13
	Nirmatrelvir plus ritonavir	382	494	77.33
Sinha 2022	Placebo	428	610	70.16
	Molnupiravir	555	608	91.28
Tippabhotla 2022	Placebo	283	610	46.39
	Molnupiravir	548	610	89.84

Table 12. Median odds ratio of viral clearance by Day 10 comparing each pair of treatments

	Placebo	Molnupiravir	Nirmatrelvir plus ritonavir
Placebo	1	7.23 (5.79, 9.11)	1.42 (1.20, 1.68)
Molnupiravir	0.14 (0.11, 0.17)	1	0.20 (0.15, 0.26)
Nirmatrelvir plus ritonavir	0.70 (0.60, 0.83)	5.10 (3.87, 6.77)	1

Table 13. Median risk ratio of viral clearance by Day 10 comparing each pair of treatments

	Placebo	Molnupiravir	Nirmatrelvir plus ritonavir
Placebo	1	1.43 (1.39, 1.47)	1.12 (1.06, 1.16)
Molnupiravir	0.70 (0.68, 0.72)	1	0.78 (0.74, 0.82)
Nirmatrelvir plus ritonavir	0.90 (0.86, 0.94)	1.28 (1.22, 1.35)	1

Table 14. Odds ratio and risk ratio of viral clearance by Day 10 of each treatment versus placebo

	Odds ratio vs. placebo			Risk ratio vs. placebo		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI
Molnupiravir	7.29	7.23	(5.79, 9.11)	1.43	1.43	(1.39, 1.47)
Nirmatrelvir plus ritonavir	1.42	1.42	(1.20, 1.68)	1.11	1.12	(1.06, 1.16)

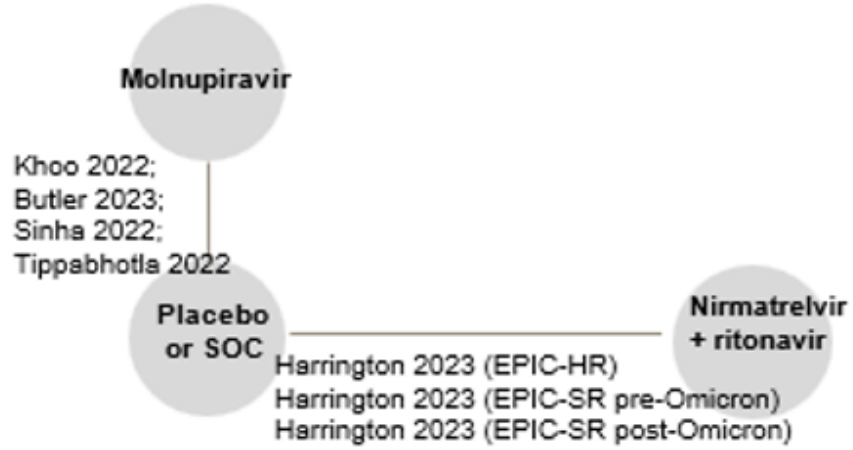
CrI = credible interval

Viral clearance – Day 14 or Day 15

- Six trials comparing an intervention with placebo or usual care (four evaluating molnupiravir and two evaluating nirmatrelvir plus ritonavir) were included in the analysis of reported proportions of patients with viral clearance by Day 14 or Day 15 following randomisation (Figure 4).
    - The total number of patients and the number/proportion of patients with viral clearance by Day 14 or Day 15 in each trial arm are summarised in Table 15.

- Comparing across treatments, patients receiving molnupiravir had a higher chance of viral clearance by Day 14 or Day 15 than those receiving nirmatrelvir plus ritonavir (Table 16 and Table 17). Additionally, compared with placebo, proportions of patients with viral clearance by Day 14 or Day 15 were higher for those receiving molnupiravir and nirmatrelvir plus ritonavir (Table 18).

Figure 4. Network for viral clearance by Day 14 or Day 15



SOC = standard of care
Source: RCT SLR (see Appendix D.1)

Table 15. Event rates for the analysis of viral clearance by Day 14 or Day 15

Trial name / Author and year	Treatment	Outcome	Sample Size	Event Rate (%)
Butler 2022	Placebo	134	241	55.60
	Molnupiravir	96	203	47.29
Harrington 2023 (EPIC-HR)	Placebo	815	948	85.97
	Nirmatrelvir plus ritonavir	835	942	88.64
Harrington 2023 (EPIC-SR post-Omicron)	Placebo	94	104	90.38
	Nirmatrelvir plus ritonavir	99	108	91.67
Harrington 2023 (EPIC-SR pre-Omicron)	Placebo	425	496	85.69
	Nirmatrelvir plus ritonavir	456	511	89.24
Khoo 2022	Placebo	73	90	81.11
	Molnupiravir	77	90	85.56
Sinha 2022	Placebo	543	610	89.02
	Molnupiravir	566	608	93.09
Tippabhotla	Placebo	507	610	83.11
	Molnupiravir	568	610	93.11

Table 16. Median odds ratio of viral clearance by Day 14 or Day 15 comparing each pair of treatments

	Placebo	Molnupiravir	Nirmatrelvir plus ritonavir
Placebo	1	1.49 (1.21, 1.84)	1.30 (1.05, 1.62)
Molnupiravir	0.67 (0.54, 0.83)	1	0.87 (0.65, 1.18)
Nirmatrelvir plus ritonavir	0.77 (0.62, 0.95)	1.14 (0.85, 1.55)	1

Table 17. Median risk ratio of viral clearance by Day 14 or Day 15 comparing each pair of treatments

	Placebo	Molnupiravir	Nirmatrelvir plus ritonavir
Placebo	1	1.06 (1.03, 1.08)	1.04 (1.01, 1.07)
Molnupiravir	0.95 (0.92, 0.97)	1	0.98 (0.95, 1.02)
Nirmatrelvir plus ritonavir	0.96 (0.94, 0.99)	1.02 (0.98, 1.06)	1

Table 18. Odds ratio and risk ratio of viral clearance by Day 14 or Day 15 of each treatment versus placebo

	Odds ratio vs. placebo			Risk ratio vs. placebo		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI
Molnupiravir	1.50	1.49	(1.21, 1.84)	1.06	1.06	(1.03, 1.08)
Nirmatrelvir plus ritonavir	1.31	1.30	(1.05, 1.62)	1.04	1.04	(1.01, 1.07)

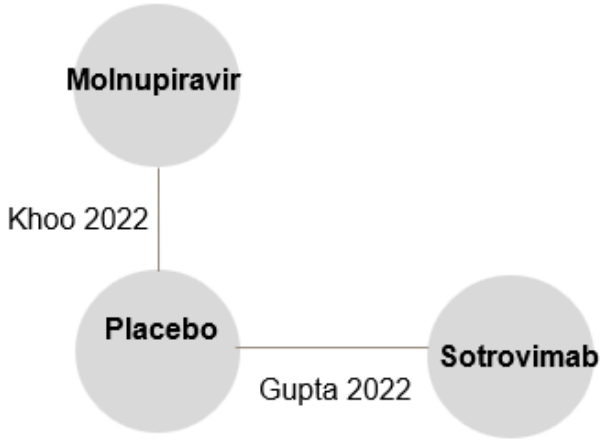
CrI = credible interval

Viral clearance – Day 29

- Two trials comparing an intervention with placebo or usual care (one evaluating molnupiravir and one evaluating sotrovimab) were included in the analysis of reported proportions of patients with viral clearance by Day 29 following randomisation (Figure 5).
    - The total number of patients and the number/proportion of patients with viral clearance by Day 29 in each trial arm are summarised in Table 19.
    - Comparing across treatments, patients receiving molnupiravir had a higher chance of viral clearance by Day 29 than those receiving

sotrovimab (Table 20 and Table 21). Additionally, compared with placebo, proportions of patients with viral clearance by Day 29 were higher for those receiving molnupiravir and sotrovimab (Table 20).

Figure 5. Network for viral clearance by Day 29



Source: RCT SLR (see Appendix D.1)

Table 19. Event rates for the analysis of viral clearance by Day 29

Trial name / Author and year	Treatment	Outcome	Sample Size	Event Rate (%)
Gupta 2022	Placebo	72	77	93.51
	Sotrovimab	64	68	94.12
Khoo 2022	Placebo	79	90	87.78
	Molnupiravir	85	90	94.44

Table 20. Median odds ratio of viral clearance by Day 29 comparing each pair of treatments

	Placebo	Molnupiravir	Sotrovimab
Placebo	1	2.47 (0.84, 8.33)	1.13 (0.28, 4.89)
Molnupiravir	0.41 (0.12, 1.19)	1	0.45 (0.07, 2.82)
Sotrovimab	0.89 (0.20, 3.61)	2.20 (0.35, 13.95)	1

Table 21. Median risk ratio of viral clearance by Day 29 comparing each pair of treatments

	Placebo	Molnupiravir	Sotrovimab
Placebo	1	1.06 (0.98, 1.12)	1.01 (0.79, 1.10)
Molnupiravir	0.95 (0.89, 1.02)	1	0.96 (0.74, 1.06)
Sotrovimab	0.99 (0.91, 1.26)	1.05 (0.94, 1.35)	1

Table 22. Odds ratio and risk ratio of viral clearance by Day 29 of each treatment versus placebo

	Odds ratio vs. placebo			Risk ratio vs. placebo		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI
Molnupiravir	3.00	2.47	(0.84, 8.33)	1.06	1.06	(0.98, 1.12)
Sotrovimab	1.49	1.13	(0.28, 4.89)	0.99	1.01	(0.79, 1.10)

CrI = credible interval

c) The EAG note that the studies by Sinha 2022, Tippabhotla 2022 and Schilling 2023 (included in CS Appendix Tables 19 and 20) were conducted in India and tropical countries and we are uncertain about their generalisability to the UK NHS. Please consider conducting a NMA sensitivity analysis excluding these studies.

MSD note that the study by Schilling 2023 is not included in any network presented in the CS. The studies by Sinha 2022 and Tippabhotla 2022 are included solely in the networks evaluating viral clearance at various timepoints. In the case of viral clearance by day 10, Sinha 2022 and Tippabhotla 2022 are the only studies informing the network branch for molnupiravir versus placebo or standard of care, and removal of these studies would lead to standard pair-wise analysis for each branch of the network. In the networks of viral clearance by day 5 and by day 14/15, the molnupiravir versus placebo or standard of care branch in each network is informed by Butler 2023 (PANORAMIC; N=25,783), which enrolled a considerably larger cohort than Sinha 2022 (N=1,218) and Tippabhotla 2022 (N=1,220) combined and, thus, MSD consider that removing Sinha 2022 and Tippabhotla 2022 from the network would have minimal impact on the overall estimate of comparative clinical effectiveness.

d) Please clarify whether any real-world evidence (RWE) studies report viral outcomes relevant to the NICE scope that could be included in NMAs. If feasible, please provide RWE NMAs for viral outcomes.

As per the final NICE scope, the virological outcomes considered for analyses were viral shedding and viral load. Only one RWE study (Minoia 2023[2]) reported viral shedding and no studies reported on viral load, hence it was not feasible to conduct any analysis of virological outcomes.

A2. The NICE scope and company's Decision Problem (CS Table 1) specify respiratory support as an outcome of interest. However, although the requirement for respiratory support was considered feasible to include in NMAs (CS Appendix Table 18) no results are provided in the CS.

a) Please summarise the results for the requirement for respiratory support outcome from the MOVe-OUT trial.

It should be noted that the requirements for respiratory support were included in the trial based scenarios for the overall population and subgroups for the cost-effectiveness analysis portion of this submission. Respiratory outcomes were included in the "hospitalised" health state by distributing the patients between the General ward, or the ICU with mechanical ventilation, to model costs and QALYs using the pooled percentage data WHO 11-point scale from MOVe-OUT to estimate the proportional distributions of patients to the highest hospital setting (see section B.3.3.1.2). Respiratory support outcomes from MOVe-OUT are as follows:

- MSD MOVe-OUT CSR. 2022 (Data on File): The proportion of participants by Day 29 with oxygen therapy was lower in the molnupiravir group (5.9%) than the placebo group (9.0%).[3] This included the use of non-invasive mechanical ventilation (molnupiravir [0.3%], placebo [1.0%]) and invasive mechanical ventilation (molnupiravir [0.6%], placebo [1.6%]).[3]

- The above results were published in Johnson et al 2022: The proportion of participants who required a respiratory intervention by Day 29 in the molnupiravir and placebo arms was 5.9% and 9.0%, respectively. The

proportion of participants in the molnupiravir and placebo arms requiring each type respiratory intervention were:[4]

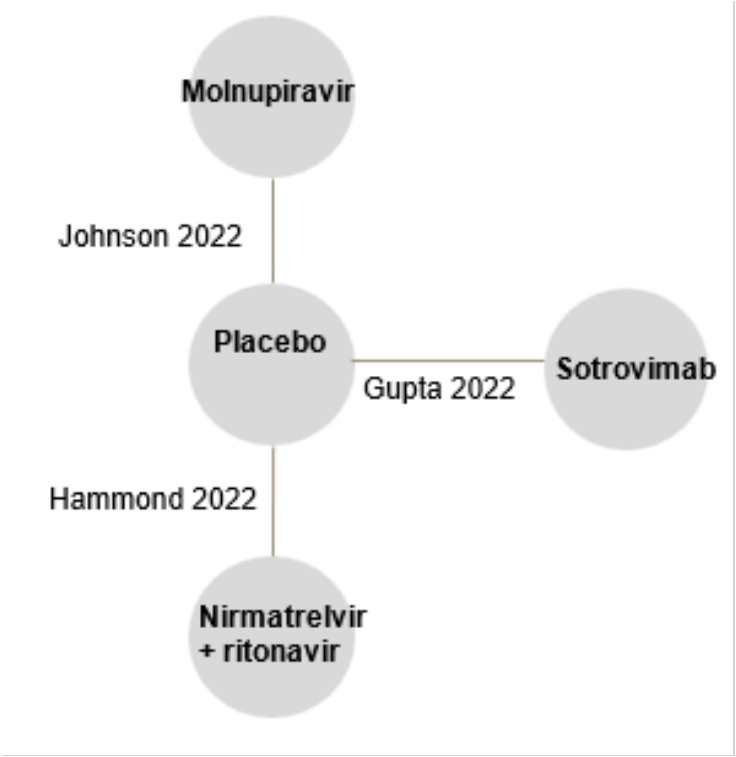
- Oxygen therapy with conventional oxygen: 4.4% versus 5.7% (relative risk reduction 23.6% [95% CI, −20.7% to 51.6%])
- High flow heated and humidified device: 0.8% versus 1.1% (relative risk reduction 26.1% [95% (CI, −112% to 74.2%])
- Non-invasive mechanical ventilation: 0.1% versus 0.6% (relative risk reduction 75.4% [95% CI, −120% to 97.2%])
- Invasive mechanical ventilation: 0.6% versus 1.6% (relative risk reduction 64.1% [CI, −12.1% to 88.5%])

b) Please provide the results of the NMAs of the RCTs for the requirement for respiratory support.

Three trials comparing an intervention with placebo or usual care (one evaluating molnupiravir, one evaluating nirmatrelvir plus ritonavir and one evaluating sotrovimab) were included in the analysis of requirement for respiratory support through Day 28 or Day 29 after randomisation (Figure 6).

- The total number of patients and the number/proportion of patients with requirement for respiratory support in each trial arm are summarised in Table 23.
- Comparing across treatments, patients receiving molnupiravir had a higher chance of respiratory support by Day 28 or Day 29 than those receiving nirmatrelvir plus ritonavir or sotrovimab. However, compared with placebo, proportions of patients with requirement for respiratory support by Day 28 or Day 29 were lower for those receiving molnupiravir, nirmatrelvir plus ritonavir, or sotrovimab (Table 24).

Figure 6. Network for requirement for respiratory support



Source: RCT SLR (see Appendix D.1)

Table 23. Event rates for the analysis of requirement for respiratory support

Trial name / Author and year	Treatment	Outcome	Sample Size	Event Rate (%)
Gupta 2022	Placebo	28	529	5.29
	Sotrovimab	7	528	1.33
Hammond 2022	Placebo	54	1126	4.80
	Nirmatrelvir + Ritonavir	9	1120	0.80
Johnson 2023	Placebo	63	699	9.01
	Molnupiravir	42	709	5.92

Table 24. Odds ratio and risk ratio of requirement for respiratory support of each treatment versus placebo

	Odds ratio vs. placebo			Risk ratio vs. placebo		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI

Molnupiravir	0.65	0.63	(0.42, 0.94)	0.66	0.65	(0.43, 0.95)
Nirmatrelvir + Ritonavir	0.16	0.16	(0.07, 0.31)	0.17	0.16	(0.07, 0.32)
Sotrovimab	0.25	0.23	(0.09, 0.52)	0.26	0.24	(0.10, 0.53)

CrI = credible interval

c) Please clarify whether any real-world evidence (RWE) studies report respiratory support outcomes relevant to the NICE scope that could be included in NMAs. If feasible, please provide RWE NMAs for these outcomes.

Although four RWE studies (Mazzitelli 2023; Paraskevis 2023; Petrakis 2023 and Bajema 2023) evaluated the impact of treatment on the need for respiratory support, no analysis were deemed feasible due to differences in the timing of the outcome assessments and outcome definition heterogeneity.[5-8]

- Bajema 2023 evaluated the impact of molnupiravir and nirmatrelvir + ritonavir on the need for mechanical ventilation at 30 days follow up.[8] The study results showed some inconsistencies in the effectiveness of nirmatrelvir/ritonavir and molnupiravir, as comparisons between the two treatment regimens showed little practical difference (RR 1.33, 95% CI: 0.26, 6.94), but nirmatrelvir/ritonavir showed significant improvements over no treatment (RR 0.28, 95% CI: 0.13, 0.58) whereas molnupiravir did not (RR 0.93, 95% CI: 0.47, 1.83).[8]

- At 35-days follow up, Paraskevis, 2023 assessed the rate of intubation, or ICU admission, without death.[6] Intubation or ICU admission rates were similar in the nirmatrelvir/ritonavir cohort (10%) and the matched cohort of nirmatrelvir/ritonavir 'nonrecipients' (12%).[6] Intubation or ICU admission rates were slightly higher in the molnupiravir recipients (42%) compared to the matched cohort of molnupiravir 'nonrecipients' (33%).[6]

- Mazzitelli, 2023 evaluated the impact of remdesivir on progression to oxygen requirement, the timepoint at which this outcome was assessed was not clearly stated however the total follow up duration was 3 months.[5] Remdesivir was associated with a lower risk of progression to oxygen requirement compared with no treatment (aOR 0.034, 95% CI: 0.008, 0.144).[5]

- Finally, Petrakis, 2023 reported 60-day intubation rates were lower in patients treated with nirmatrelvir/ritonavir compared to the matched cohort of untreated patients (0% vs. 3%, p= 0.034).[7]

Given the differences in the reporting of respiratory outcomes from the RWE studies no formal evidence synthesis was conducted.

Study identification and selection

A3. Please explain (i) the selection process that led to 15 trials being selected from 116 that were identified and subjected to data extraction (CS Appendix Figure 1); (ii) why 14 trials rather than 15 were then subjected to feasibility assessment (CS section B.2.9.1); and (iii) what the reasons were for excluding three trials at the feasibility assessment step (CS section B.2.9.1).

(i) As noted in the CS and Appendices (Section D.1.1.3), the SLR of RCTs was carried out for a global project and included interventions not of interest to the decision problem as set out in the final scope issued by NICE. Subsequently, studies carried through to the feasibility assessment for incorporation into an NMA were those that met the inclusion criteria for the SLR of clinical effectiveness and that evaluated one of the following interventions: molnupiravir; nirmatrelvir + ritonavir; remdesivir; and sotrovimab.

(ii) The table detailing the studies evaluated in the feasibility assessment (Appendix D, Table 9) includes 15 rows of trial names and trial numbers. However, there are only 14 unique studies. The PLATCOV component study reported by Schilling 2023 is listed twice in Table 9 (Appendix D). The PLATCOV study is an adaptive platform trial that encompassed multiple studies evaluating various COVID-19 treatments. Two studies using the PLATCOV platform were included in the feasibility assessment for the NMA: 1) a two-arm trial that compared remdesivir vs no study drug and reported by Jittamala 2023; and 2) a three-arm trial comparing molnupiravir vs nirmatrelvir + ritonavir vs no study drug that was reported by Schilling 2023. For the purposes of the NMA and feasibility assessment, the component study reported by Schilling 2023 had entries in the table as study evaluating molnupiravir trial and as a study assessing

nirmatrelvir+ritonavir trial, thus appearing twice in the table. Whereas, the study by Jittamala 2023 only appeared once as a remdesivir trial.

In subsequent tables presented in the sections detailing the feasibility assessment and results for the NMA, to avoid the issue of redundancy, the PLATCOV trial by Schilling 2023 was listed once under molnupiravir. As a result, subsequent tables show 14 unique studies (2 of which are both PLATCOV component studies, but one by Schilling 2023 and the other by Jittamala 2023) in 14 columns.

(iii) Reasons for exclusion of the three trials were:

- Jittamala 2023: The only outcome of interest reported by Jittamala 2023 was viral load change. However, because the reported metric differed from that reported in other trials the study could not be included in the NMA and was, therefore, excluded.
- Schilling 2023: The study reported two outcomes of interest — all-cause hospitalization and viral load change. However, for all-cause hospitalization, the study reported no event in any treatment arm, and, thus, could not be included in the NMA. Considering viral load change, the reported metric differed from that reported in other trials, rendering it infeasible to be included in the NMA. Therefore, the PLATCOV study by Schilling 2023 was excluded.
- DAWN RCT: The study was excluded because the study was terminated early and had a small sample size.

For the reasons listed above, 11 out of the 14 trials were deemed feasible to be included the NMA.

A4. CS section B.2.8 states that "the SLR identified another RCT". However, the CS does not specify which trial this is. Please (i) provide the reference citation for this RCT (and the PDF if not already provided to the EAG); (ii) explain whether this RCT has been included or excluded from the NMAs; and (iii) if it has been excluded, please explain why.

MSD apologise for the lack of clarity in the introduction to Section B.2.8. PANORAMIC is the study referred to in the sentence, "In the course of this

submission, the SLR identified another RCT reporting the efficacy of molnupiravir in the treatment of mild to moderate COVID-19 in patients at risk of developing severe illness in the UK setting". All studies evaluating molnupiravir that met the prespecified inclusion criteria for the SLR of RCTs are listed in Table 7 (Appendix D), and those deemed feasible to be included in an NMA are listed in Table 9 (Appendix D). Section B.2.8 outlines MSD's reasons for not carrying out a standard pair-wise analysis of studies comparing molnupiravir versus placebo or standard of care.

A5. In CS Appendix Figure 15 the stated reasons for excluding eight RWE studies are imprecise and potentially subjective. For instance, the exclusion of Qian 2023 "due to population heterogeneity" is difficult to interpret without further clarification on the nature and extent of the heterogeneity. The EAG are also uncertain how "incompatible study design" is interpreted and what would be considered a "high" proportion of patients receiving concomitant treatments. To resolve these ambiguities, please clarify precisely why each of these eight studies was excluded.

- Study quality concerns: Bruno, 2022[9] and Martin-Blondel, 2023[10] only reported unadjusted comparative data for the outcomes of interest and so the data were considered at risk of confounding and unsuitable for inclusion in the ITC/NMA. Petrakis 2023[7] reported limited information on patient matching criteria therefore it was not clear whether the study sufficiently accounted for differences in baseline risk and other potentially confounding factors. Note that other studies of this nature were excluded at an earlier stage and were not considered for any analyses; concerns pertaining to these three studies were only identified when conducting the in-depth feasibility assessment.

- Common comparators: Details on concomitant medications were infrequently reported however, one study (Minoia, 2023[2]) reported 13.4% of patients using tixagevimab/cilgavimab prophylaxis across its two treatment groups (molnupiravir and nirmatrelvir/ritonavir), as well as 10.9% receiving concomitant neutralizing monoclonal antibodies, and 8.5% receiving concomitant sotrovimab. It was therefore decided that Minoia 2023 was not suitable for inclusion in any analyses.

- Lack of common outcomes: In Del Borgo, 2023[11] the only outcome analysed in the multivariate regression analysis was a composite endpoint which included the incidence of pneumonia, acute respiratory distress syndrome, COVID-19-related and non-COVID-19-related death; this composite outcome was not reported in any other study. Most studies analysed hospitalisation and mortality rates between 28-to-35 days follow up, whereas two studies (Mazzitelli, 2023[5] and Lin, 2023[12]) only reported mortality rates at 90-day follow-up, which was judged to be too different as a follow-up time for inclusion in the broader analyses. In addition, these two studies were not suitable for averaging with each other as Mazzitelli 2023 evaluated COVID-specific mortality whereas Lin 2023 investigated all-cause mortality. The other outcomes reported by Lin 2023 and Mazzitelli 2023 were deemed unsuitable for analysis due to heterogenous outcome definitions.

- Population heterogeneity: The majority of the studies included in the SLR evaluated patients with any risk factor for progression to severe disease; a few studies specifically focused on older patients. However, there were two outlier studies that recruited patients with specific comorbid conditions: Qian 2023[13] investigated patients with autoimmune rheumatic disease and Zheng 2022[14] investigated patients receiving kidney replacement therapy. Both studies were deemed unsuitable for inclusion in the base case analysis as there was uncertainty as to whether risk in these populations was equivalent to the general higher-risk population. Several studies reported subgroup analyses of patients with chronic kidney disease therefore, Zheng 2022 was deemed eligible for inclusion in a sensitivity analysis. However, none of the studies reported subgroup data for patients with autoimmune disease, therefore Qian 2023 was excluded from all analyses.

RCTs

A6. Please clarify how many people in the usual care arm of the PANORAMIC trial received molnupiravir.

It is reported in the Butler publication of the PANORAMIC trial that given that molnupiravir was considered an option for the usual care of COVID-19 at the time, it

could have been received by people in the usual care arm. However, the number of patients in receipt of molnupiravir in the usual care arm is not reported in this publication or its appendices. The only COVID-19 treatments reported in the baseline characteristics for the usual care arm were inhaled corticosteroids (1% of patients), and monoclonal antibodies (<1% of patients). MSD do not have access to the data outside that in the public domain.

Risk of bias assessments for studies included in NMAs

A7. PRIORITY QUESTION. CS Table 12 lists the company's risk of bias judgements for the RCTs but without any rationale provided for the judgements.

a) Please provide a brief rationale for each of the "low risk", "some concerns" and "high risk" judgements that are listed in CS Table 12.

Please see embedded spreadsheet for justifications of level of bias assigned to each RCT, as determined based on the ROB-2 tool. MSD note that, as the sponsor of MOVe-OUT, we had access to the CSR for MOVe-OUT and, therefore, greater detail on trial methodology than would typically be available in a peer-reviewed publication.


ID6340 Molnupiravir COVID 19 Response t

b) Please explore the sensitivity of the NMA results for each outcome to the inclusion of RCTs judged to be at high risk of bias or those having some concerns.

MSD acknowledge that it would be good practice to carry out sensitivity analyses excluding studies deemed to be at high risk of bias. However, due to time constraints, and MSD's preference for RWE as the evidence base to inform the decision problem, MSD have not performed NMAs excluding RCTs at high risk of bias.

A8. PRIORITY QUESTION. CS Table 13 lists the company's risk of bias judgements for the RWE studies but without any rationale provided for the judgements. The CS states that the NICE checklist was used. However, the source of the checklist questions reported in CS Appendix Table 40 is not reported and the checklist questions appear incomplete, e.g. there is no explicit consideration of missing data bias. Given the observational designs of the RWE studies (case-control and cohort

studies), it seems improbable that so few RWE studies had risk of bias concerns (3/30 in CS Table 13), whereas half of the RCTs had risk of bias concerns (7/14 in CS Table 12). We consider the ROBINS-I tool [1] more appropriate for assessing the risk of bias in observational RWE studies. We note that three published systematic reviews [2-4] between them have assessed 15 out of the 22 included RWE studies using ROBINS-I and all those studies were judged to have at least at moderate, in some cases serious, risks of bias.

a) Please conduct a risk of bias assessment for each of the RWE studies using the ROBINS-I tool and provide a brief explanation for each risk of bias judgement made.

   As discussed, due to time constraints MSD was not able to provide a re-assessment of RWE studies using the ROBINS-I versus the originally used NICE checklist. Instead, it was agreed that MSD would provide more discussion and justification on any systematic error present across the studies, which is discussed in part b.

b) Please explore the sensitivity of the NMA results for each outcome to the inclusion of studies judged to be at high risk of bias according to the ROBINS-I tool.

   - Quality assessment was performed using the assessment criteria outlined in the 2015 STA/HST User Guide:[15]
     - This checklist includes only one signalling question related to the potential impact of missing data: “Was the follow up of patients complete?” As detailed in CS Appendix Table 40, no issues were identified in relation to patient follow up hence there were no quality concerns regarding the potential impact of missing data.
   - Care was taken to ensure at feasibility assessment stage that methods of matching and details of adjustments and sensitivity analyses were extracted and assessed. Only those studies which were considered to have adequately matched patient cohorts for all potentially confounding factors, or performed adequate adjustment for differences in baseline risk, were considered for inclusion in the analyses.
   - Three studies were rated as having high concerns due to inadequately accounting for differences in baseline risk. Both Bruno, 2022 and Martin-

Blondel, 2023 only reported unadjusted comparative data for the outcomes of interest to this review and so the data were considered at risk of confounding and unsuitable for inclusion in the ITC/NMA.[9, 10] Petrakis 2023 reported limited information on patient matching criteria therefore it was not clear whether the study sufficiently accounted for differences in baseline risk and other potentially confounding factors.[7] These three studies were therefore excluded from all analyses.

- There were some concerns regarding the potential impact of confounding factors in two further studies. However, these were deemed to be of minor consequence.[11, 16] Although Manciulli, 2023 used inverse probability weighting (IPTW) to match cohorts based on risk, the outcomes of interest to this SLR were reported only as adjusted analyses for the unmatched cohort. The study does not clearly state which variables were used as covariates in the Cox regression analyses, but it is assumed that confounding is unlikely to bias the results, as the study reported that baseline covariates were well balanced between the four treatment groups both before and after IPTW matching.[16] Finally, in Del Borgo, 2023 the only concern was that the multivariate analysis did not account for BMI, but all other relevant variables were considered therefore this study was not considered of great concern .[11] Both Manciulli, 2023 and Del Borgo, 2023 were deemed eligible for inclusion in the analyses.
- Although no other concerns were identified in the original risk of bias assessment, it is noted that Paraskevis, 2023 does not provide details on the prevalence of comorbidities in the control cohorts. None of the other studies included in the analyses were identified as having 'critical' concerns by the other published SLRs though notably not all included studies were critiqued in the other SLRs.

Treatment effect modifiers in NMAs

A9. For each NMA outcome comparison please explain what the treatment effect modifiers are and whether any imbalances in these remained, after any statistical

adjustment in the RCTs and RWE studies, that could violate the NMA similarity assumption.

RCTs

Potential effect modifiers of COVID-19 treatment in the outpatient setting primarily include the established risk factors that impact COVID-19 prognosis, such as patient demographics, comorbidities, COVID-19 disease characteristics (e.g., severity, time from symptom onset to treatment), vaccination status, previous infections, use of background/concomitant treatments, SARS-CoV-2 viral load, and SARS-CoV-2 variants.

Across the included studies, the distributions of the risk factors listed above were not reported consistently for each trial population, and the treatment effects by level of the identified risk factors were not reported in all trials. As a result, it is not feasible to directly conduct subgroup analyses to understand the potential effect modifications and their impacts on NMA results. Therefore, to identify which of the risk factors can modify treatment effects of molnupiravir and other comparators on study outcomes, a targeted literature review was conducted. RCTs, observational cohort studies, and relevant systematic literature review/meta-analyses that evaluated effect modifications of treatment effects of molnupiravir, nirmatrelvir + ritonavir, remdesivir, and sotrovimab in the outpatient setting were reviewed. Note that in the existing literature, the evaluations of effect modification were not comprehensive, that is, not every outcome of interest or every potential effect modifier considered above has been evaluated.

Based on the current literature, the magnitudes of effect modifications of COVID-19 treatments in the outpatient setting are in general small. In brief:

- Modifications of the effects of molnupiravir vs placebo SOC on all-cause hospitalization or death by SARS-CoV-2 serology status,[1, 17] SARS-CoV-2 viral load level,[17] and immunocompromised status;[4]
- Treatment effects of molnupiravir can be slightly stronger among patients with negative SARS-CoV-2 serology status,[1, 17] with higher viral load level,[17] and being immunocompromised;[4]

- Modifications of the effects of nirmatrelvir + ritonavir on COVID-19 related hospitalization or death by age and SARS-CoV-2 serology status;[18]
- Treatment effects of nirmatrelvir + ritonavir can be stronger among patients aged 65 years or older, and among patients with negative SARS-CoV-2 serology status;[18]
- Modifications of the effects of sotrovimab on all-cause mortality, all-cause hospitalization, and all-cause hospitalization or death by SARS-CoV-2 variants;[19]
- Treatment effects of sotrovimab can be slightly stronger when Delta was the dominant circulating variant (2021) than during later time period.[19]

The magnitudes of the impact of the potential treatment effect modifiers on the results of NMA depend on two aspects: 1) the magnitude of the effect modifications (e.g., how different the treatment effects are between older vs younger populations); 2) the magnitude of the across-trial differences in the distributions of the effect modifiers (e.g., how different the proportions of the older vs younger population are across trials). Considering magnitude of effect modifications, because the magnitude of potential effect modifications was relatively small based on the literature, their impacts on the NMA results should be small.

Considering across-trial differences in distribution of effect modifiers:

- SARS-CoV-2 variants: most of the trials included in the NMA were conducted by mid-2022 (during the Delta and early Omicron era), during which sotrovimab still had strong treatment effect. One of the sotrovimab trials (MONET)[20] evaluating sotrovimab vs nirmatrelvir + ritonavir was conducted between Mar 2022 and Nov 2022 when Omicron BA.4/5 had emerged; if the treatment effect of sotrovimab decreased during this time period as indicated by the literature, its efficacy against nirmatrelvir + ritonavir would have been stronger had it been evaluated during an earlier time period.
- Age: The mean age of patients ranged from 30 to 57 years across trials. The mean age of the nirmatrelvir + ritonavir trial (EPIC-HR)[18] was 46 years, which

lies in the middle of the range. In addition, majority of the trials enrolled middle-aged patients. Thus, the effect modification by age for nirmatrelvir + ritonavir efficacy is not expected to have a large impact on the NMA results.

- SARS-CoV-2 serology status: status was not reported for most trials included in the NMA. Given that serology status reflects vaccination status and/or prior infections, trials conducted during the early pandemic period could have enrolled higher proportions of patients with negative serology status. However, as most of the trials in the NMA were conducted by mid-2022, cross-trial differences in the distributions of SARS-CoV-2 serology status are expected to be relatively small.

- SARS-CoV-2 viral load level and immunocompromised status were not reported by most of the trials and cannot be readily assessed.

Overall, based on the current literature, there are some indications on the presence of effect modifications of the COVID-19 treatments in the outpatient setting, but there evidence is not strong. Given that the magnitudes of these effect modifications are expected to be small and the distributions of most potential effect modifiers were comparable across trials included in this NMA, the potential effect modifications identified from the literature would have small impacts on the results of NMA.

RWE

Visual inspection of the subgroup data reported in RWE studies identified age, vaccination status and the presence of symptomatic disease at baseline, as potential effect modifiers. The literature reported inconclusive evidence on the impact of comorbidities on treatment effect; however, clinical experts advised that comorbidities and multi-comorbidity presence may be expected to modify treatment effects.

Only RWE studies which were considered to have adequately accounted for any differences between patient cohorts were considered for inclusion in the NMA specifically, studies were required to have conducted propensity matching or to have performed suitable regression analyses to match patient cohorts or evaluate the

outcomes of interest. There were therefore minimal concerns regarding treatment effect modifiers within each individual study included in the NMA base-case network.

There were however differences across studies and these were explored in sensitivity analyses that are described below. The majority of the studies evaluated patients with any risk factor for progression to severe disease; a few studies specifically focused on older patients. Two outlier studies which recruited patients with specific comorbid conditions were excluded from the base case analyses: Qian 2023 investigated patients with autoimmune rheumatic disease and Zheng 2022 investigated patients receiving kidney replacement therapy. A sensitivity analyses was conducted for patients with chronic kidney disease however, there was insufficient data to perform a sensitivity analysis of patients with autoimmune rheumatic disease. The RWE studies were heterogenous with regard to age, therefore various sensitivity analyses were performed limiting the evidence base to studies investigating older patient populations (i.e., ≥60 years and ≥70 years). With respect to vaccination status, the only study identified as an outlier was Kabore, 2023 in which 56% of patients were unvaccinated (patients with 0 or 1 dose). A sensitivity analyses was conducted in which this study was excluded from the analysis. Finally, few studies reported on the proportion of patients with symptomatic disease. Three studies reported that 100% of patients were symptomatic and one further study reported that ≥70% of patients were symptomatic. One matched cohort study (Butt 2023b) reported lower rates of symptomatic disease and a discrepancy between the treatment group (42%) and the control arm (23%). In a second matched cohort study (Butt 2023a), the proportion of patients with symptomatic disease in the treatment arm (82%) was comparable to the other studies, however, the rate of symptomatic disease was much lower in the controls arm (65%). Both studies were excluded from the base case analysis and only included in a sensitivity analysis.

Network meta-analyses of RCTs

A10. PRIORITY QUESTION. CS Figure 12 and CS Table 37 report incorrectly that the PANORAMIC trial (Butler 2022) has a placebo arm. Given that the comparator in

PANORAMIC is usual care, not placebo, how can this trial be connected in the network in CS Figure 12?

MSD acknowledge that the comparator arm in PANORAMIC is usual care and recognise that inclusion of PANORAMIC introduces bias into the network. The NMA presented in Figure 12 of the CS is the network for severe AEs. As the outcome relates to adverse effects, any trial reporting severe AEs and deemed feasible to be included in the NMA was included in the network; please see the report shared in response to A11.

A11. CS sections 2.9.1.1 to 2.9.1.8 each state that "Further discussion on results of the NMA analysis for this outcome can be found in Appendix D.1". Similarly, CS Tables 18 to 35, CS Tables 37 to 41, and CS Figures 6 to 13 state "SOURCE: RCT SLR (see Appendix D.1)". However, CS Appendix D.1 does not report any NMA results. Please clarify where the "further discussion" is located and provide the source of the results data for these Tables and Figures.

To provide further details on the NMA of RCTs, MSD shares in confidence the full report for the project – please see the embedded file.

A12. The RCT publications by Sinha 2022, Tippabhotla 2022 and Schilling 2023 report hospitalisation and/or mortality up to day 28 but these RCTs have not been included in the NMAs for these outcomes. Please explain why these RCTs are considered relevant for the viral outcomes NMAs (see Question A1) but not for the hospitalisation or mortality NMAs.

For all-cause mortality, Sinha 2022 and Tippabhotla 2022 were not included in the NMA because there is no event in either active treatment or placebo arms. Schilling 2023 did not report all-cause mortality.

For all-cause hospitalization, the outcome definitions in Sinha 2022 and Tippabhotla 2022 are different from other trials, making them infeasible to be included in the NMA: both studies restricted hospitalizations with "respiratory rate of >24 breaths per

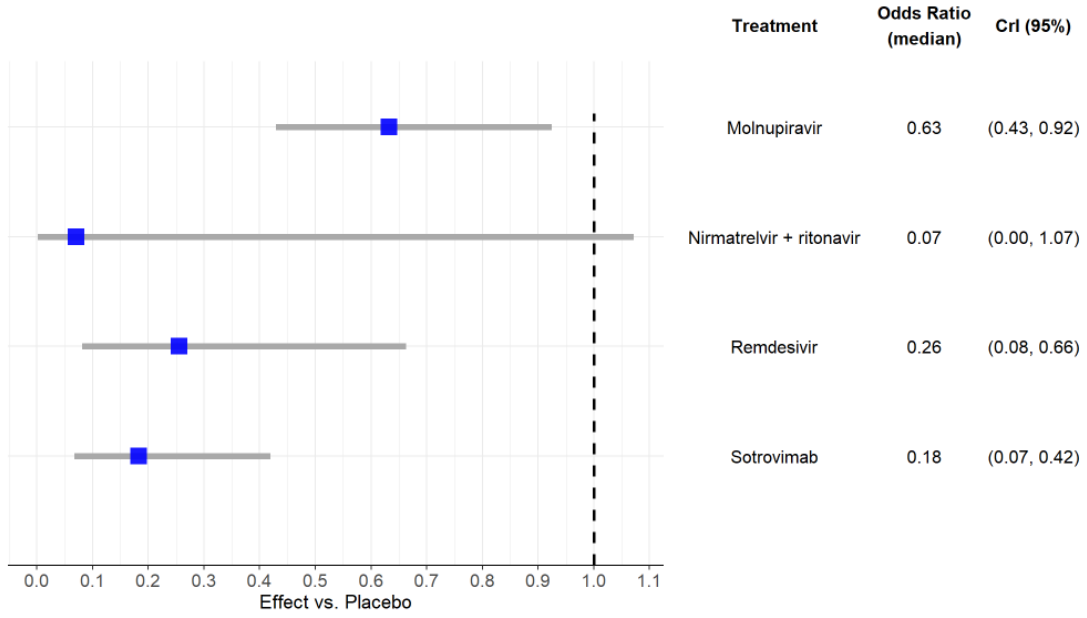
minute and SpO_2 ≤93% in room air and requiring oxygen supplementation", while other trials did not have such restrictions. Schilling 2023 was not included because it reported no event in either active treatment or placebo arms.

Due to the same reasons above, Sinha 2022, Tippabhotla 2022, and Schilling 2023 were not included for the analysis of all-cause hospitalization or death.

A13. CS section B.2.9.2 reporting the RWE NMA results includes forest plots for each outcome, but no forest plots are provided in CS section B.2.9.1 for the RCT NMA results. Please provide the forest plots for the RCT NMA results reported in CS section B.2.9.1.

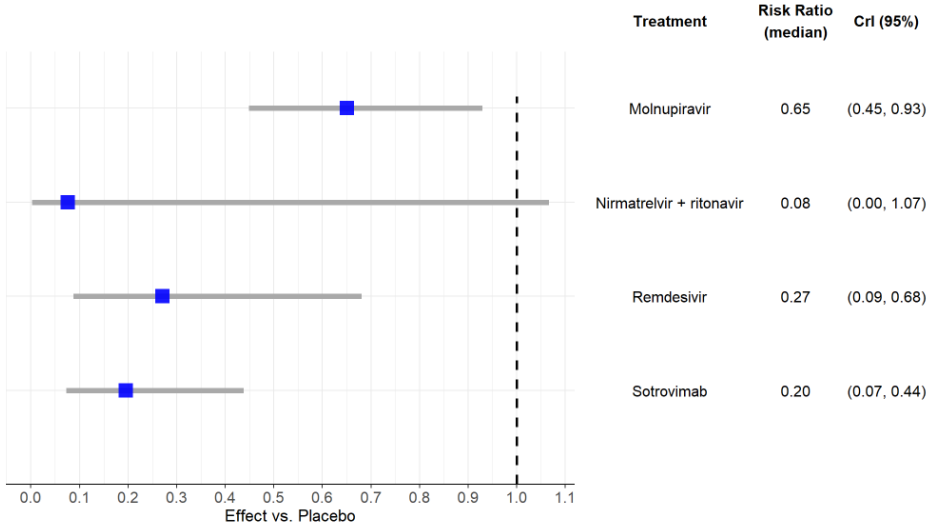
Forest plots for NMAs reported in Section B.2.9.1 are presented below.

Figure 7. Forest plot of median odds ratio of each treatment placebo for the outcome of all-cause hospitalisation or death



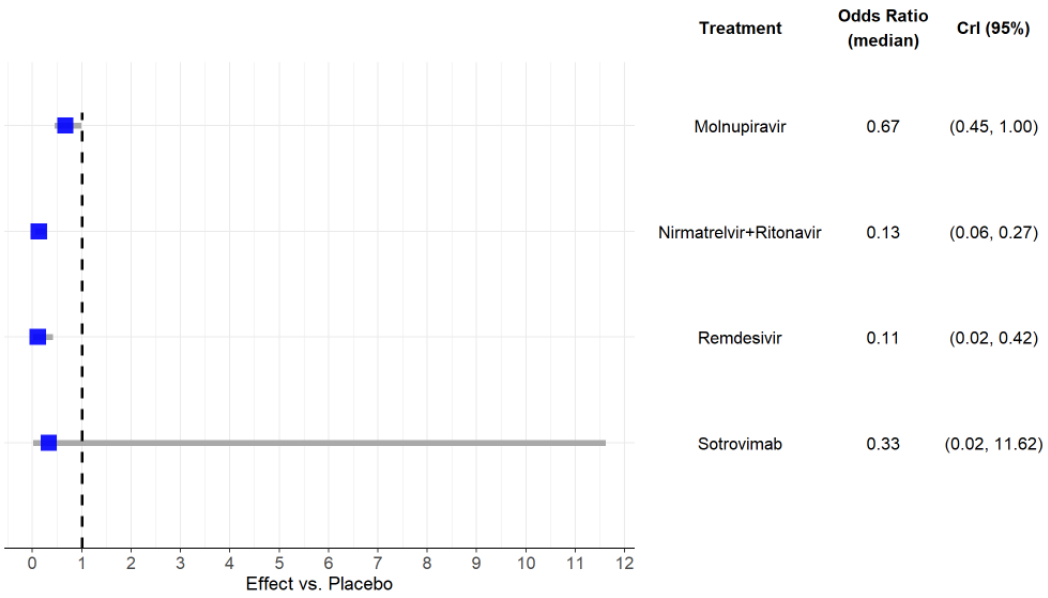
CrI = credible interval

Figure 8. Forest plot of median risk ratio of each treatment placebo for the outcome of all-cause hospitalisation or death



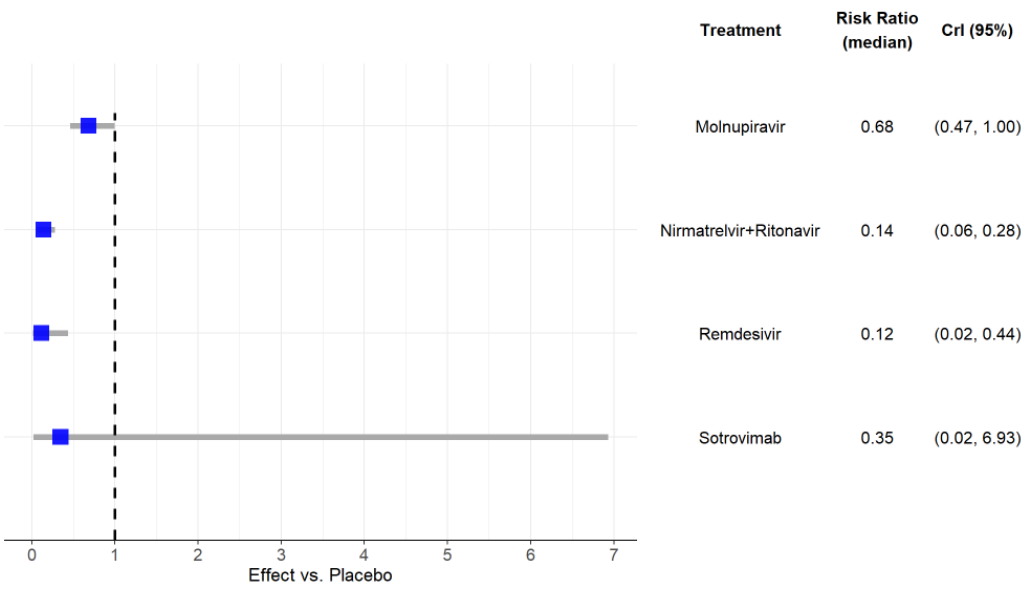
CrI = credible interval

Figure 9. Forest plot of median odds ratio of each treatment placebo for the outcome of COVID-19-related hospitalisation or death



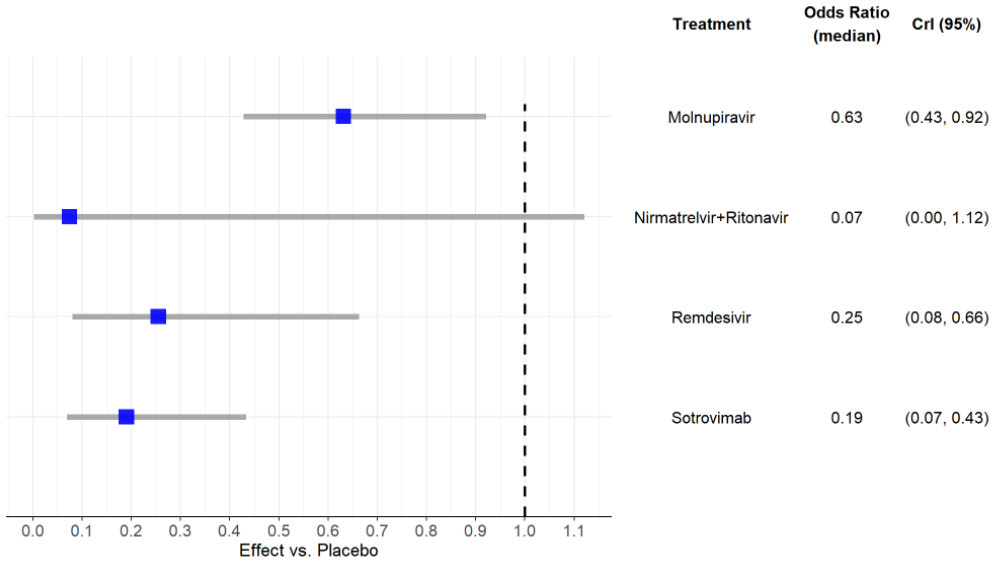
CrI = credible interval

Figure 10. Forest plot of median risk ratio of each treatment placebo for the outcome of COVID-19-related hospitalisation or death



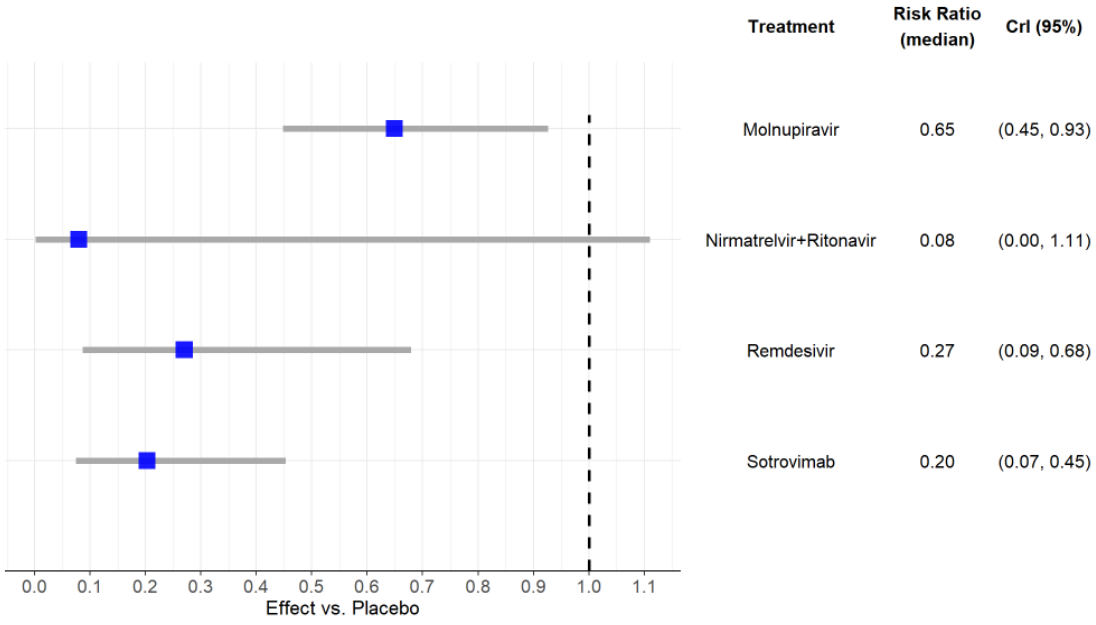
CrI = credible interval

Figure 11. Forest plot of median odds ratio of each treatment placebo for the outcome of all-cause hospitalisation



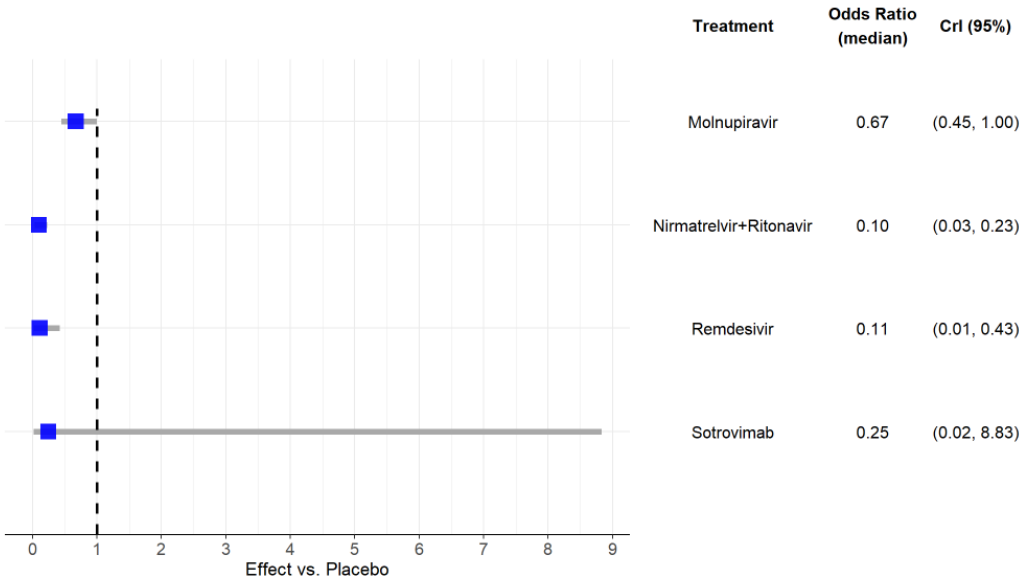
CrI = credible interval

Figure 12. Forest plot of median risk ratio of each treatment placebo for the outcome of all-cause hospitalisation



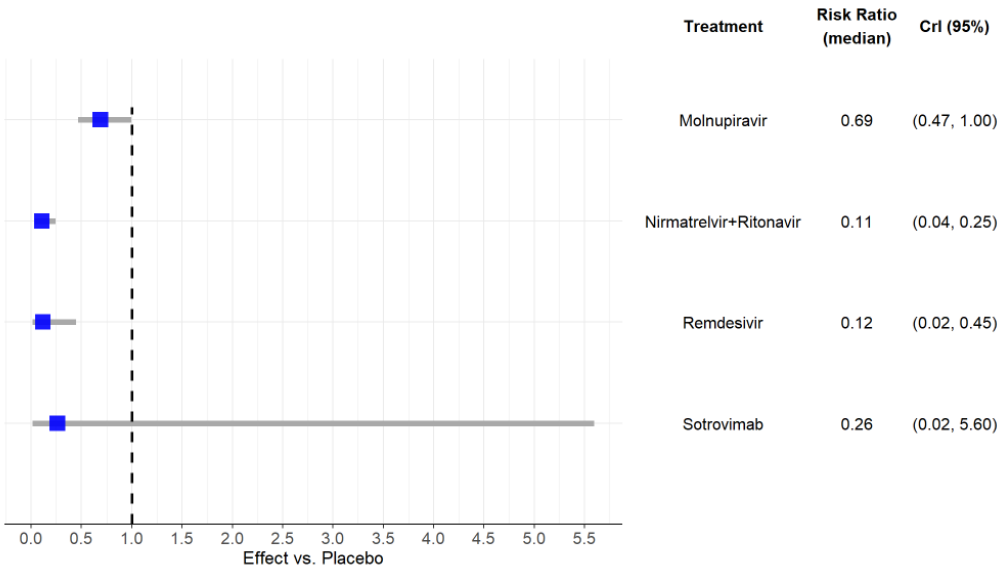
CrI = credible interval

Figure 13. Forest plot of median odds ratio of each treatment placebo for the outcome of COVID-19-related hospitalisation



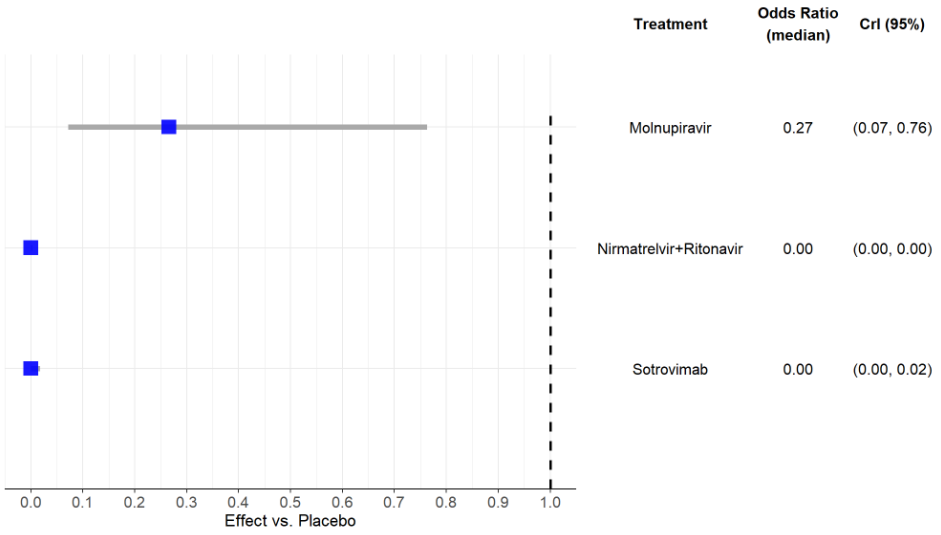
CrI = credible interval

Figure 14. Forest plot of median risk ratio of each treatment placebo for the outcome of COVID-19-related hospitalisation



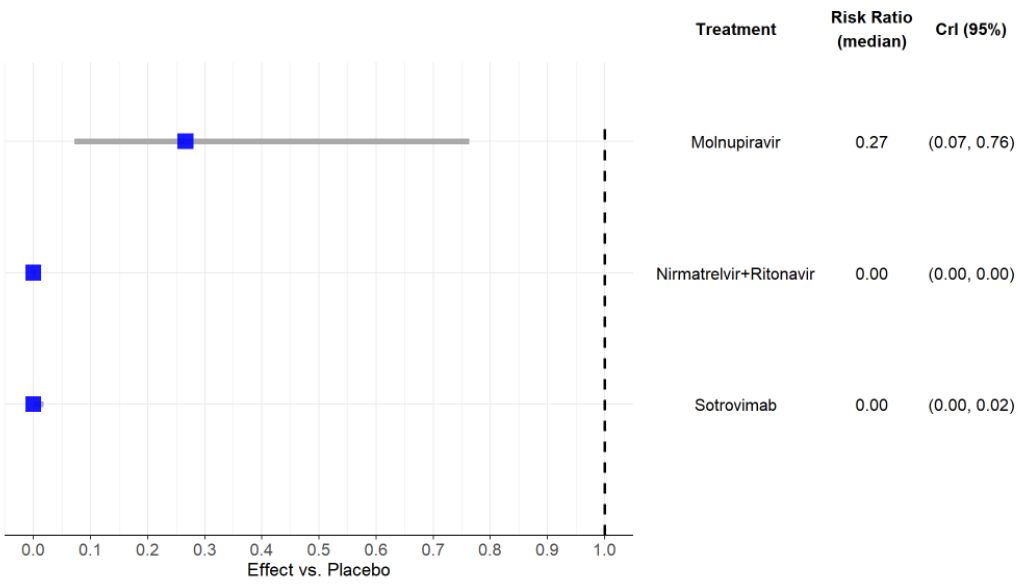
CrI = credible interval

Figure 15. Forest plot of median odds ratio of each treatment placebo for the outcome of all-cause mortality



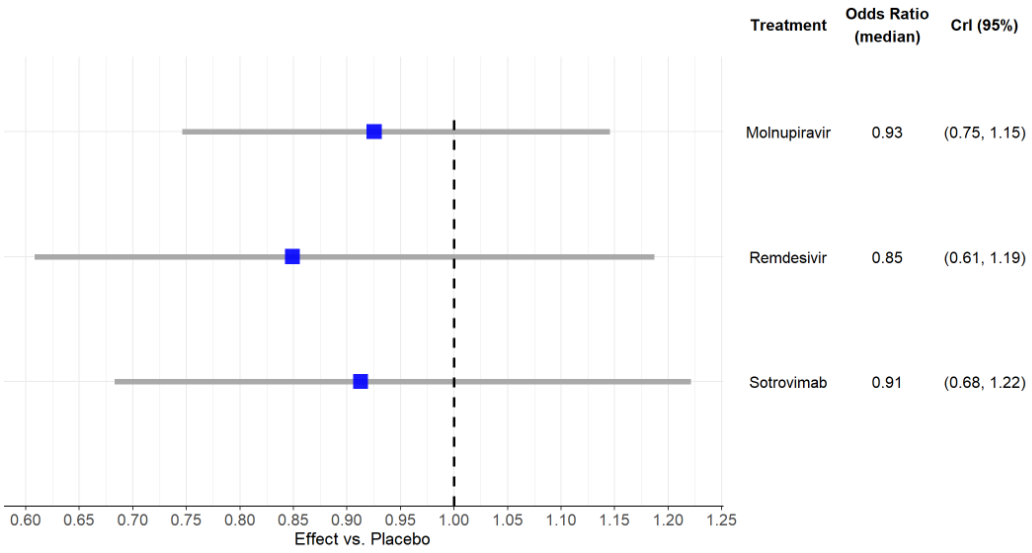
CrI = credible interval

Figure 16. Forest plot of median risk ratio of each treatment placebo for the outcome of all-cause mortality



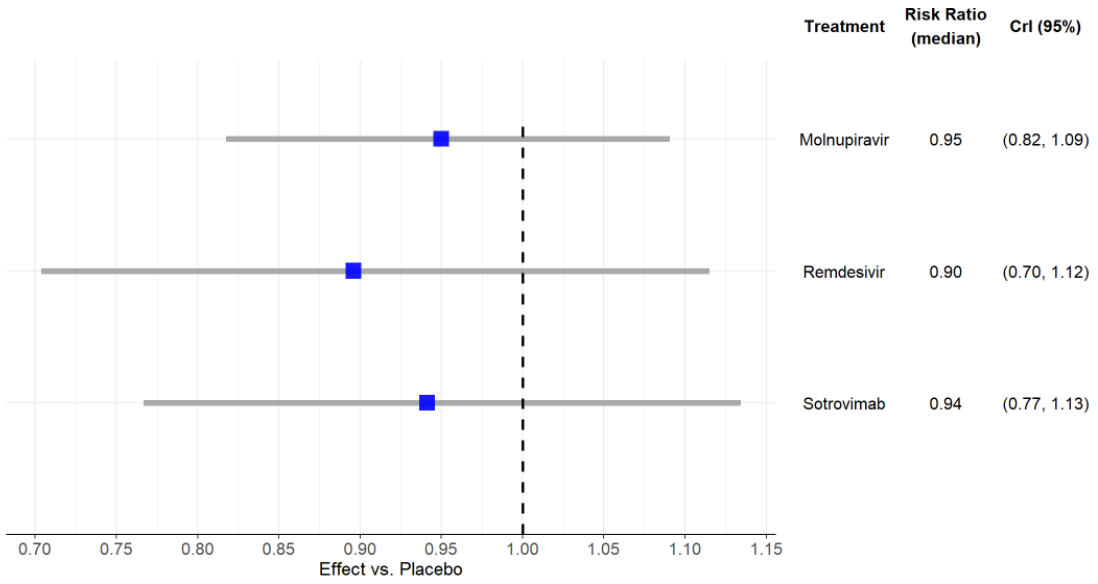
CrI = credible interval

Figure 17. Forest plot of median odds ratio of each treatment placebo for the outcome of any adverse effect



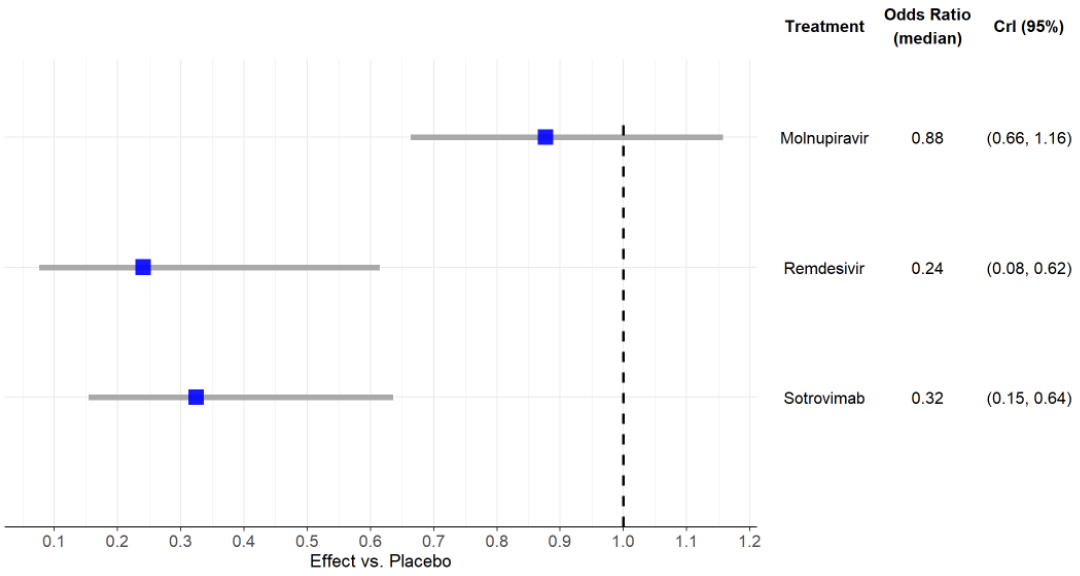
CrI = credible interval

Figure 18. Forest plot of median risk ratio of each treatment placebo for the outcome of any adverse effect



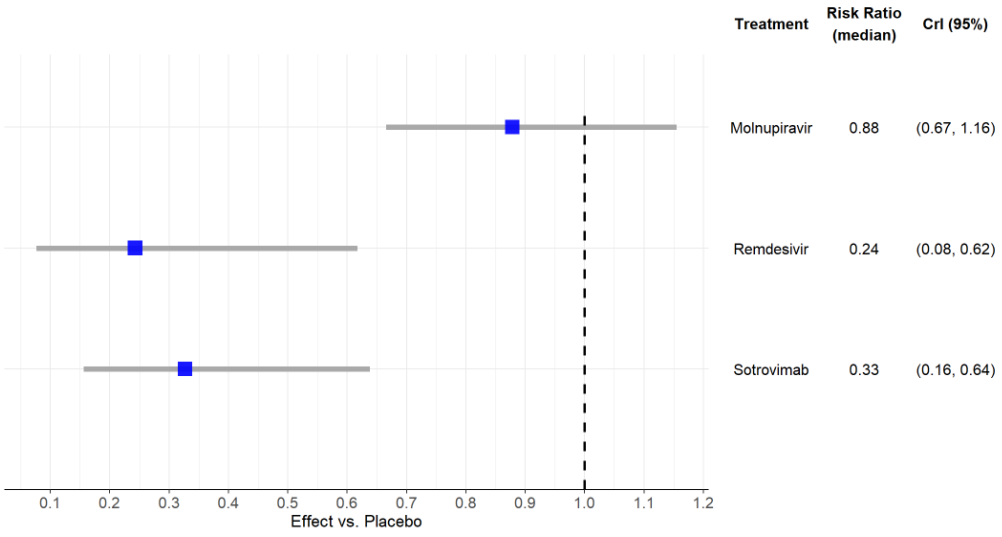
CrI = credible interval

Figure 19. Forest plot of median odds ratio of each treatment placebo for the outcome of severe adverse effects



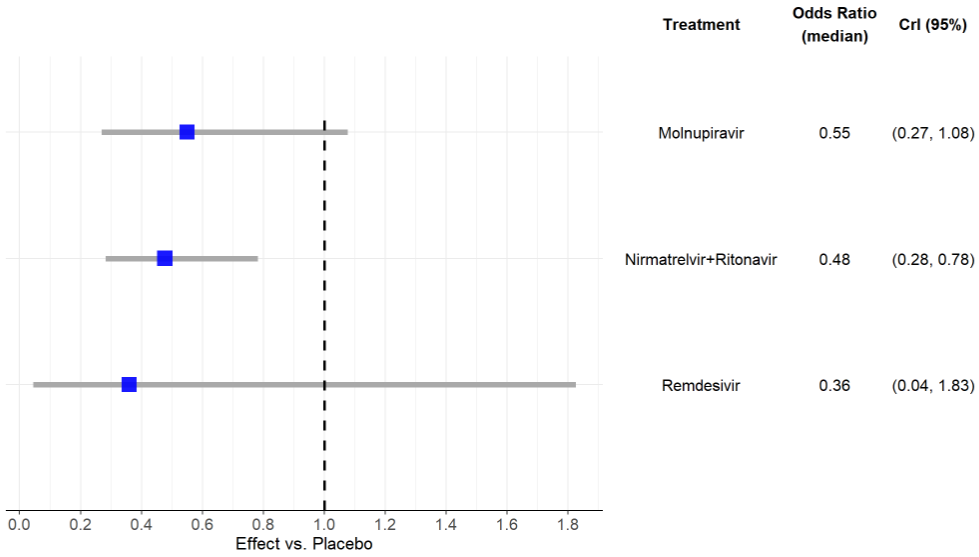
CrI = credible interval

Figure 20. Forest plot of median risk ratio of each treatment placebo for the outcome of severe adverse effects



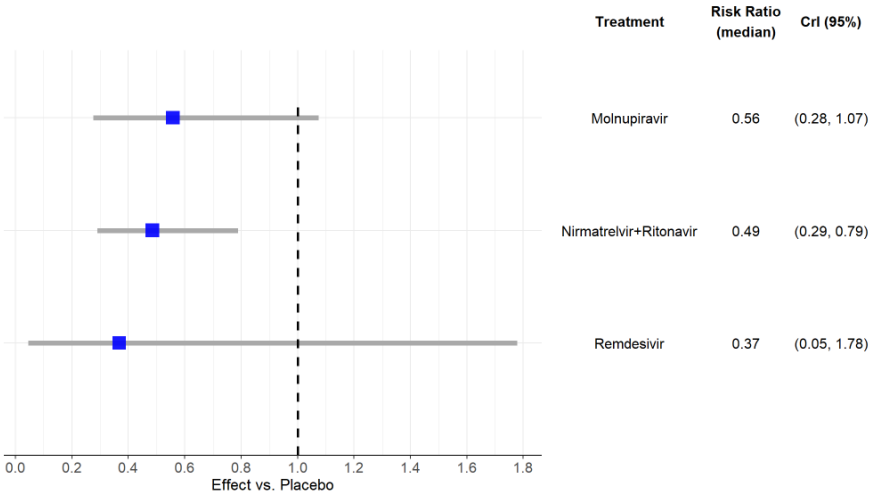
CrI = credible interval

Figure 21. Forest plot of median odds ratio of each treatment placebo for the outcome of treatment discontinuation due to adverse effects



CrI = credible interval

Figure 22. Forest plot of median risk ratio of each treatment placebo for the outcome of treatment discontinuation due to adverse effects



CrI = credible interval

Network meta-analyses of RWE studies

A14. For the outcome "COVID-19 related hospitalisation or death" (CS section B.2.9.2.2) the network diagram in CS Figure 17 and the list of included studies in CS Table 43 do not match the network implied by the forest plot in CS Figure 19 (results

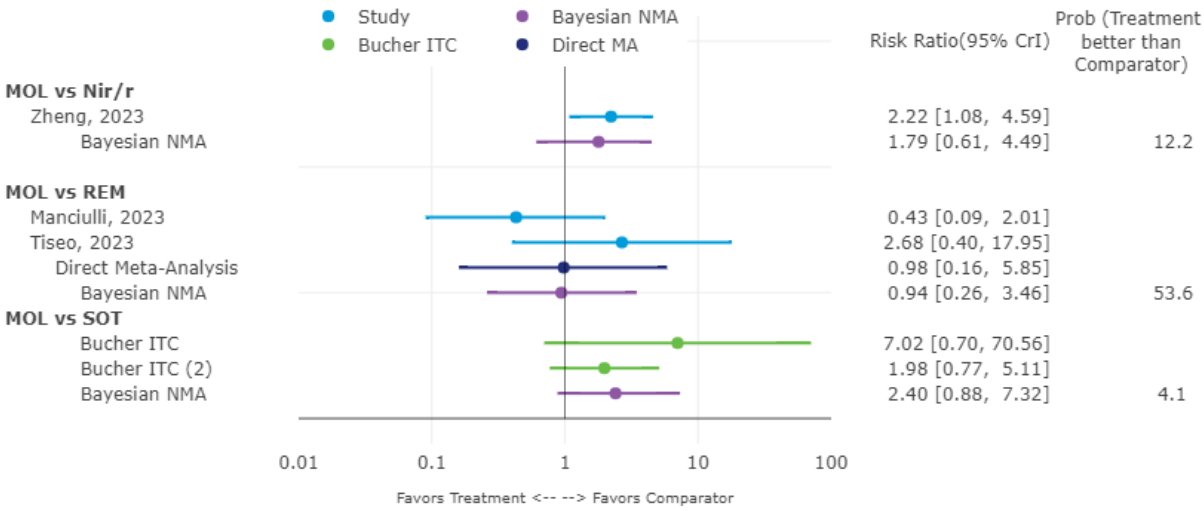
are provided for Arbel 2023, Cegolon 2023, and Cowman 2023, but these studies are not shown as included in the network).

a) Please explain this discrepancy.

Figure 17 and Table 43 show the correct network of studies reporting on the composite outcome of COVID-19-related hospitalisation or death. Figures 18 and 19 of the original submission are the results of a sensitivity analyses and should be replaced by the figures shown below in this response document.

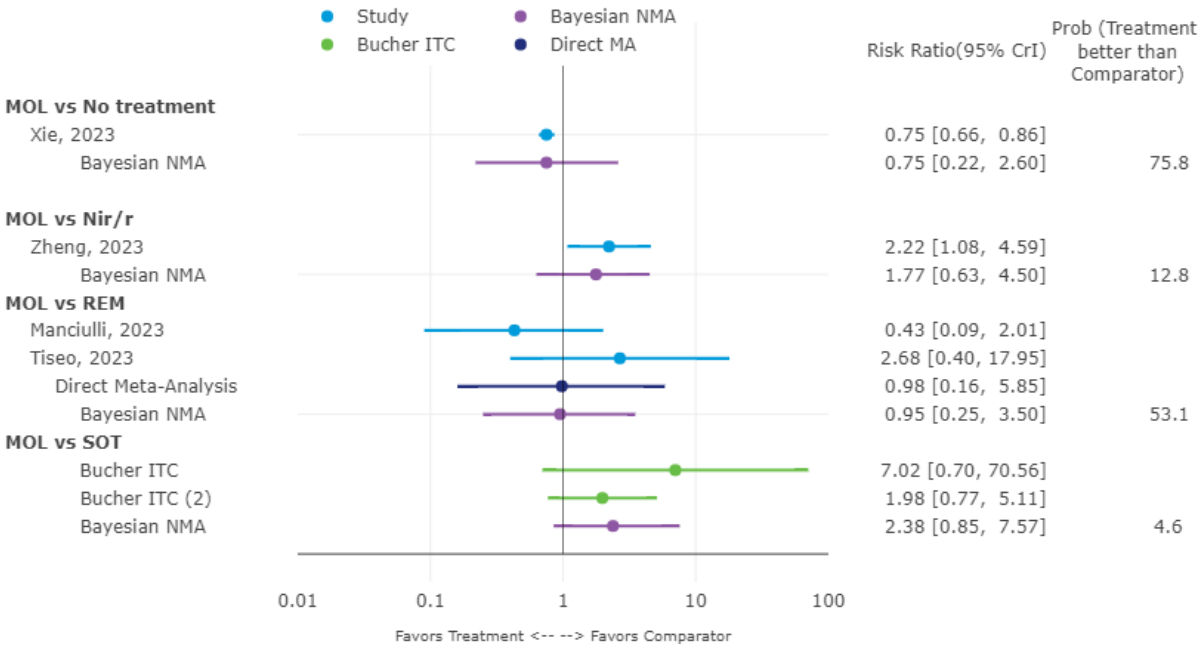
The sensitivity analyses were conducted based on the assumption that the relative effectiveness of treatment in preventing COVID-19-related hospitalisations or COVID-19-related death could be estimated by leveraging two sets of outcome data: 1) the composite outcome of COVID-19-related hospitalisations or COVID-19-related death, and 2) COVID-19-related hospitalisation. The rationale for combining these outcomes in a single sensitivity analysis was that death is generally preceded by hospitalisation, however ultimately it was decided that these results would not be presented in the submission as these analyses were likely to introduce more uncertainty. Figure 18 and 19 in the submission show the results of this sensitivity analysis which also includes studies reporting only on COVID-19-related hospitalisation; Figure 23 and Figure 24 below should have been presented in place of Figures 18 and 19, respectively.

Figure 23. Active treatment evidence network NMA results COVID-19 related hospitalisation or death (random effects)



CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir; SOT = sotrovimab

Figure 24. Active treatment/control evidence network NMA results COVID-19 related hospitalisation or death (random effects)



CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir; SOT = sotrovimab

b) The study by Cegolon 2023 included molnupiravir, nirmatrelvir + ritonavir, sotrovimab and no treatment (CS Appendix Table 36) but only the comparison of "Mol vs "No treatment" is included in CS Figure 19 for this study. Please explain this.

As noted above (question 14A response), Figure 19 in the CS is incorrect and should be replaced by Figure 24. Irrespective of this error, the forest plots throughout the report show the effectiveness of molnupiravir versus each active comparator and control, displaying both the direct evidence reported in the literature and the results of a frequentist direct meta-analysis (pooled estimates of direct evidence) and Bayesian NMA for each comparison. The NMA leverages the full network of evidence on the relative effectiveness of active treatments (i.e., sotrovimab vs. nirmatrelvir/ritonavir vs. remdesivir) and comparisons of sotrovimab, nirmatrelvir/ritonavir, remdesivir relative to no treatment. However, the figures only show comparisons for molnupiravir versus comparators/controls and do not show the data inputs, and outputs, for sotrovimab / nirmatrelvir+ritonavir / remdesivir versus comparators.

c) The study by Arbel 2023 is included in CS Figures 19, 23, and 25 and in CS Appendix Figure 17 for the comparison "MOL vs No Nir/r or Mol". However, Table

1 in the Arbel 2023 publication specifies that the comparison was between molnupiravir-treated and untreated patients, whilst CS Appendix Table 36 states that the "intervention(s)" were molnupiravir versus no treatment. Should the Arbel 2023 study therefore have been included for the comparison "Mol vs No treatment" instead?

In several of the RWE studies control groups were described as 'untreated' however, authors noted in the discussion that some patients in the control group may have received active treatment other than the study intervention. This limitation was not described in Arbel 2023 however, the study only states that 'patients treated with ritonavir-boosted nirmatrelvir or monoclonal antibodies were all excluded from the study,' with no mention of excluding remdesivir recipients. Arbel 2023 was conducted in Israel in 2022; remdesivir was licensed for use in Israel in 2020 so it was considered possible that some patients in the control may have received remdesivir. The same judgement was reached for Najjar-Debbiny 2023a (also conducted in Israel in 2022) which stated that nirmatrelvir/ritonavir recipients were excluded, and monoclonal antibodies were not available, but did not mention the exclusion of remdesivir recipients. Thus, we could not assume the control arm in Arbel 2023 was 'no treatment'.

A15. PRIORITY QUESTION. CS section B.2.9.2 states that "the NMA of RWE studies contains two control nodes, one labelled "no treatment" in which the patients in the control group were considered to be untreated, and one labelled "no nirmatrelvir + ritonavir or molnupiravir" in which control patients did not receive either of the oral antivirals but may have received other active interventions". The implications of this unconventional network structure for interpretation of the NMA results are unclear.

a) Please conduct sensitivity analyses that exclude the "no nirmatrelvir + ritonavir or molnupiravir" node from the "active treatment/control evidence network" and provide the updated forest plots for CS Figures 16, 19, 22, 25, and 27.

Three studies (Kabore 2023, Arbel 2023, and Schwartz 2023) deemed eligible for inclusion in the base case analyses were connected to the network via the 'no molnupiravir / no nirmatrelvir + ritonavir' control node. Table 25 and the forest plots

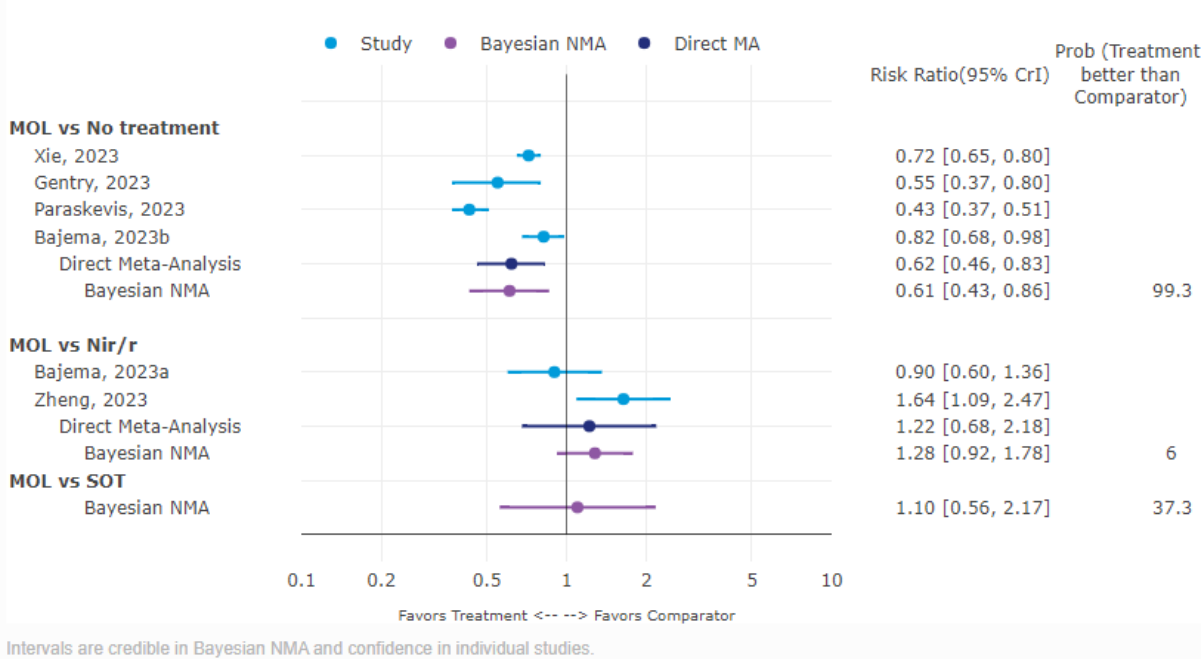
below show the NMA results after removing these studies from the networks. Results were generally consistent with the base case analyses. However, the original analysis of COVID-19-related hospitalisation was based on only five studies and the removal of two studies from the network had a notable impact on results; the sensitivity analysis showed more favourable results for molnupiravir relative to comparators for this outcome. None of these studies reported COVID-19 hospitalisation or death therefore no sensitivity analysis is shown for this outcome.

Table 25. RWE NMA Results: Sensitivity analysis excluding the "no nirmatrelvir + ritonavir or molnupiravir" node

Outcome	Intervention vs. Comparator	Original analyses RR (95% CrI)	Sensitivity analysis excluding the "no nirmatrelvir + ritonavir or molnupiravir" node RR (95% CrI)
All cause hospitalisation or death	Molnupiravir vs. no treatment	0.61 (0.43, 0.86)	0.61 (0.43, 0.86)
	Molnupiravir vs. nirmatrelvir + ritonavir	1.28 (0.91, 1.79)	1.28 (0.92, 1.78)
	Molnupiravir vs. sotrovimab	1.10 (0.55, 2.23)	1.10 (0.56, 2.17)
All-cause hospitalisation	Molnupiravir vs. no treatment	0.79 (0.66, 0.92)	0.79 (0.65, 0.93)
	Molnupiravir vs. nirmatrelvir + ritonavir	1.19 (0.98, 1.43)	1.19 (0.98, 1.43)
	Molnupiravir vs. remdesivir	1.65 (0.35, 8.63)	1.71 (0.33, 8.12)
COVID-19-related hospitalisation	Molnupiravir vs. no treatment	0.85 (0.49, 1.53)	0.22 (0.05, 0.87)
	Molnupiravir vs. nirmatrelvir + ritonavir	1.58 (0.98, 2.54)	0.39 (0.10, 1.57)
	Molnupiravir vs. sotrovimab	1.64 (0.19, 13.04)	0.51 (0.05, 5.61)
All-cause death	Molnupiravir vs. no treatment	0.31 (0.21, 0.46)	0.31 (0.20, 0.46)
	Molnupiravir vs. nirmatrelvir + ritonavir	1.44 (1.00, 2.10)	1.44 (0.99, 2.12)

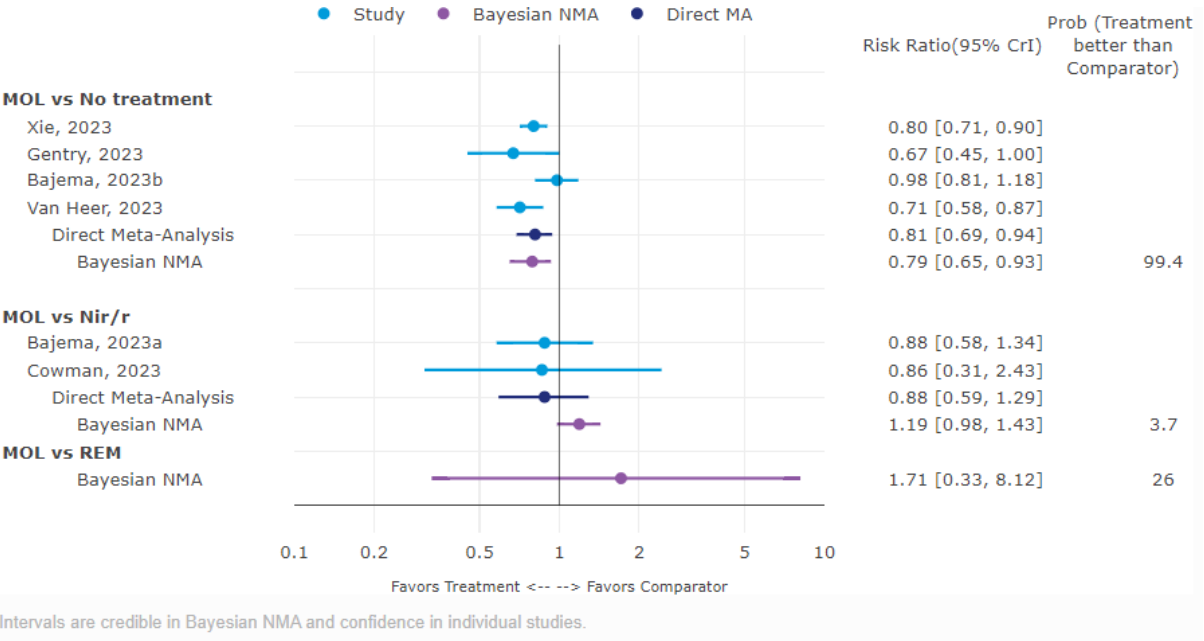
CrI = credible interval; NMA = network meta-analysis; RWE = real-world evidence

Figure 25. NMA results all-cause hospitalisation or death (random effects) – sensitivity analyses with 'no molnupiravir / no nirmatrelvir + ritonavir' node removed.



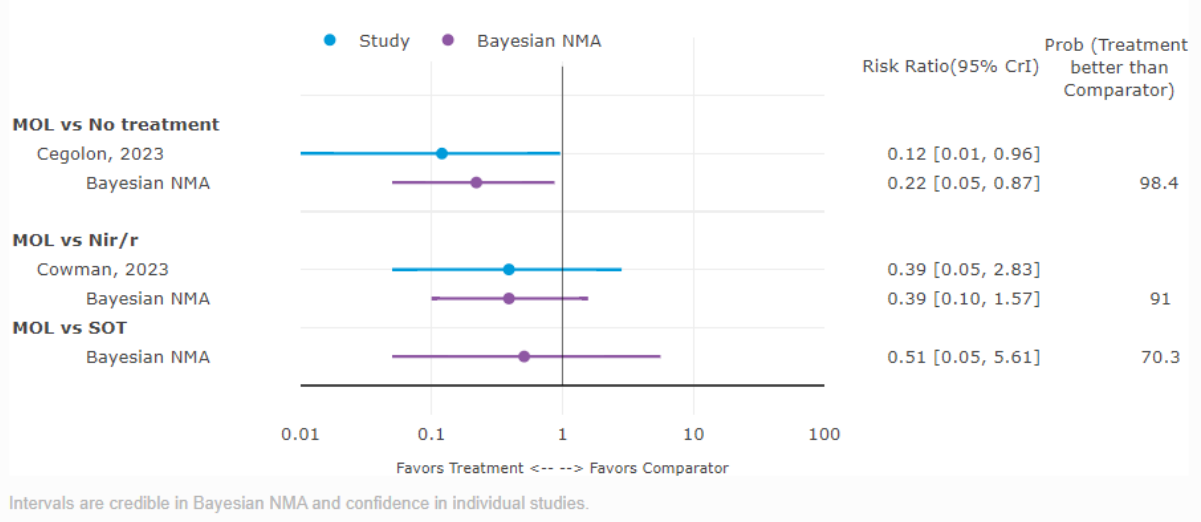
Kabore 2023 removed from the analysis.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir; SOT = sotrovimab

Figure 26. NMA results all-cause hospitalisation (random effects) – sensitivity analyses with 'no molnupiravir / no nirmatrelvir + ritonavir' node removed.



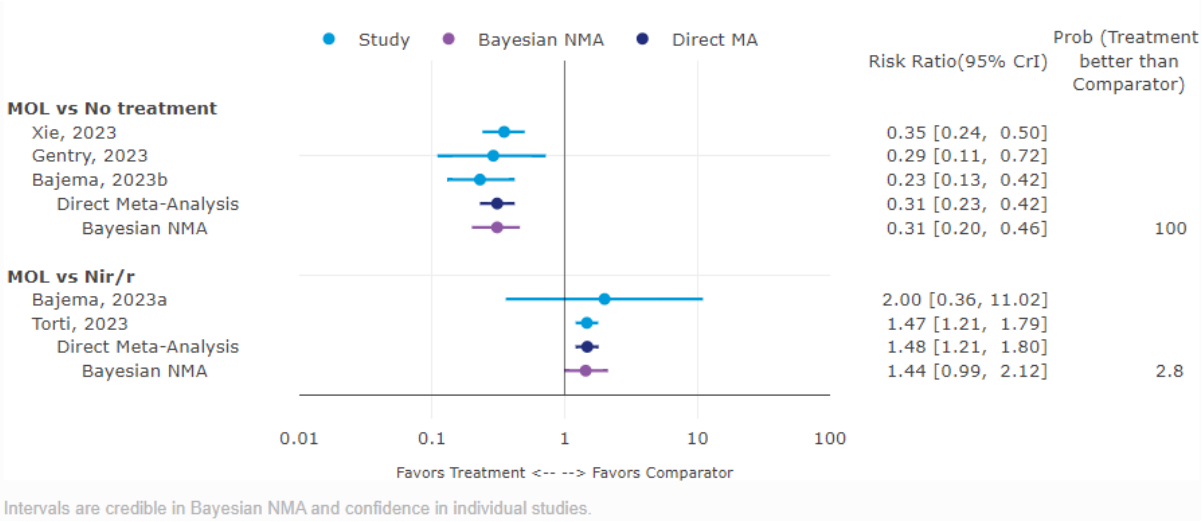
Kabore 2023 removed from the analysis.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir

Figure 27. NMA results COVID-19-related hospitalisation (fixed effects) – sensitivity analyses with 'no molnupiravir / no nirmatrelvir + ritonavir' node removed.



Arbel 2023 and Kabore 2023 removed from the analysis.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; SOT = sotrovimab

Figure 28. NMA results all-cause death (random effects) – sensitivity analyses with 'no molnupiravir / no nirmatrelvir + ritonavir' node removed.



Schwartz 2023 removed from the analysis.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis

b) CS Figure 17 depicts the network for the outcome "COVID-19 related hospitalisation or death" and does not include a "no nirmatrelvir + ritonavir or molnupiravir" node. However, the corresponding NMA results in CS Figure 19 indicate that this node was present. Please explain this discrepancy.

CS Figure 17 depicts the correct network of evidence for this outcome. The CS Figure 19 should be replaced by Figure 24 above, further detail is provided in response to question A14 above.

A16. PRIORITY QUESTION. CS section B.2.9 briefly mentions that Bayesian NMAs were conducted. However, the forest plots reported for the NMAs of RWE studies in CS section B.2.9.2 show that three types of ITC were performed: "Bayesian NMA", "direct NMA" and "Bucher ITC". CS section B.2.9.2 also consistently refers to the "base case NMA results derived from the active treatment network".

a) Please clearly define the "base case" NMA method for each outcome – is this the "Bayesian NMA"?

The use of 'base case' is intended to differentiate between the main analyses and the subgroup and sensitivity analyses which were conducted. The base case results indeed refer to the Bayesian NMA results.

b) Please explain the rationale for conducting the Bucher ITCs and clarify why they are reported for some outcomes but not others. Why are three different "Bucher ITC" analyses reported for the MOL vs SOT comparison in CS Figure 19 whereas for all other outcomes there is a maximum of one Bucher ITC per comparison?

The direct MA results are derived from the pooling of effectiveness estimates for each study evaluating a specific pair of comparators (or one treatment versus no treatment); the direct MAs do not leverage the indirect evidence derived from the network, but are provided for reference; the primary analysis strategy is Bayesian NMA. Similarly, the Bucher ITC results are only provided for reference, as sometimes they can be useful as a signal for potential inconsistency. The Bucher ITCs are only reported when there is common comparator between two treatments. When more than one Bucher ITC is reported, this indicates that there is more than one common comparator between the two treatments and the results of the indirect comparisons vs each common comparator is reported. The results of the Bayesian NMA should be prioritised over the Bucher ITC(s).

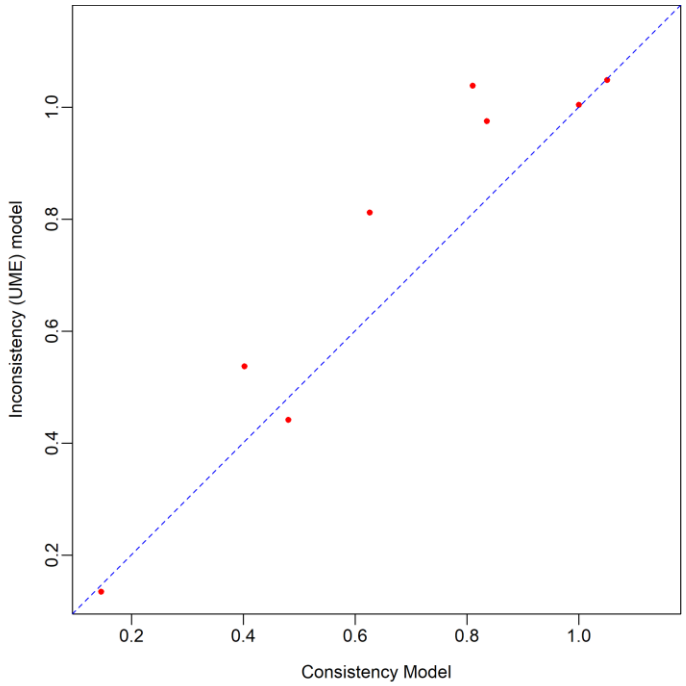
c) CS Appendix D.2.1.7 states that "Comparisons between the posterior means of the residual deviance and deviance information criterion (DIC) statistics of the consistency and inconsistency models are provided" but this information is not reported. Please explain the location of this information and provide a structured assessment of consistency for those outcomes where both direct and indirect comparisons are available.

Inconsistency was explored using the GeMTC package. A fixed-effects model was used to maximize the power to detect signals. Study-level deviance scores (standardized, by dividing by the number of contrasts) were plotted for consistency and inconsistency (unrelated mean effects – "UME") models; high deviance scores for the consistency model (as a rule of thumb, >3) are a function of heterogeneity, inconsistency, or both, while high scores for the UME model imply heterogeneity greater than would be expected by chance, as indirect information is not leveraged in the UME model. No inconsistency was found across outcomes (defined here as a difference of 3 or more between UME and consistency-model deviance scores) but, as expected, deviance scores for some studies were high in both UME and consistency models, signaling the significant statistical heterogeneity described in the submission.

Additional comparisons were conducted using random-effects models, which essentially examine whether there are any signals of inconsistency above and beyond what would be expected given the estimate of random-effects variation. Because this variation is, in part, a function of inconsistency, the power to detect inconsistency with such a model can be low, and indeed, no signals were found in RE comparisons (i.e., all deviance scores fell very close to the reference line).

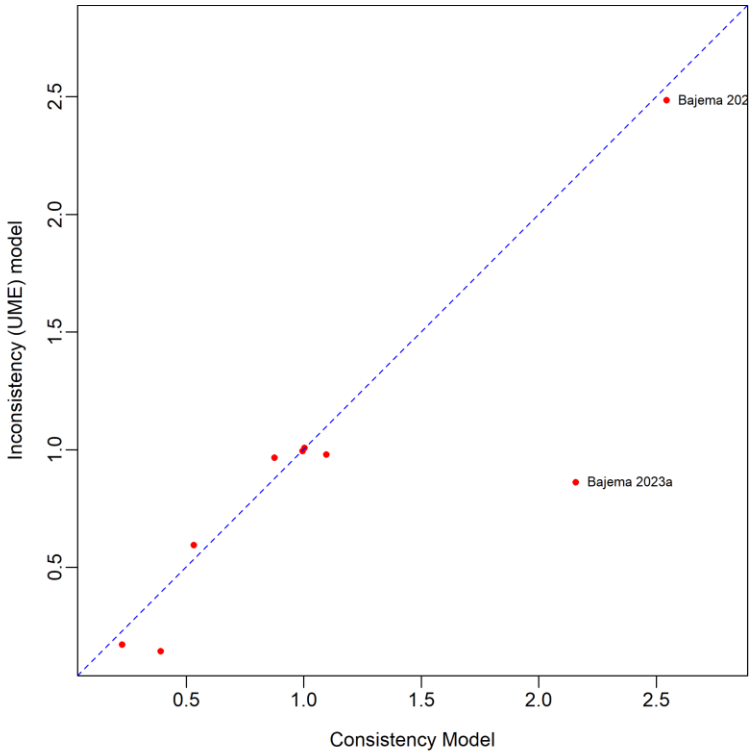
All-cause Death

There is no evidence of inconsistency in this outcome as the UME and consistency models produce similar DICs (11.8 vs 10.0). Contributions of the deviance of the individual data points in both models are similar and close to the line of equality.



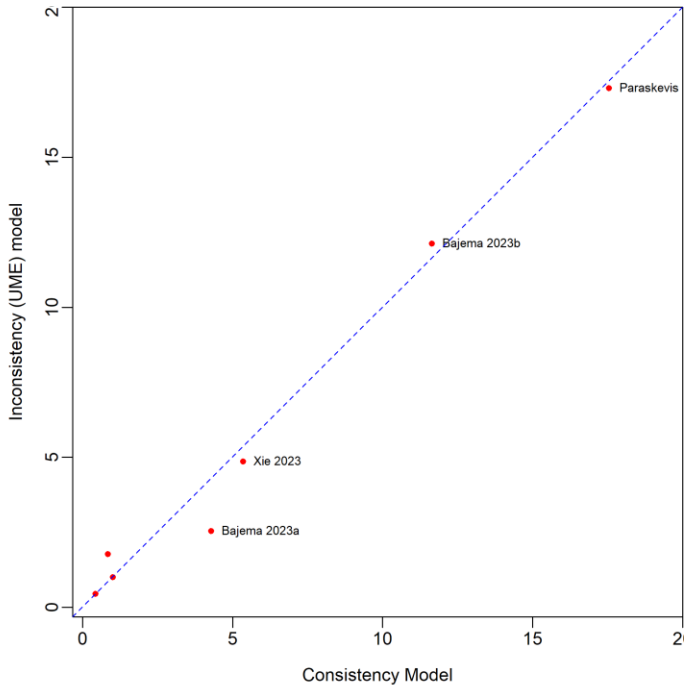
All cause Hospitalisation

There is no evidence of inconsistency in this outcome as the UME and consistency models produce similar DICs (17.6 vs 18.3). Contributions of the deviance of the individual data points in both models are similar and close to the line of equality, with the possible exception of the direct evidence from Bajema 2023.



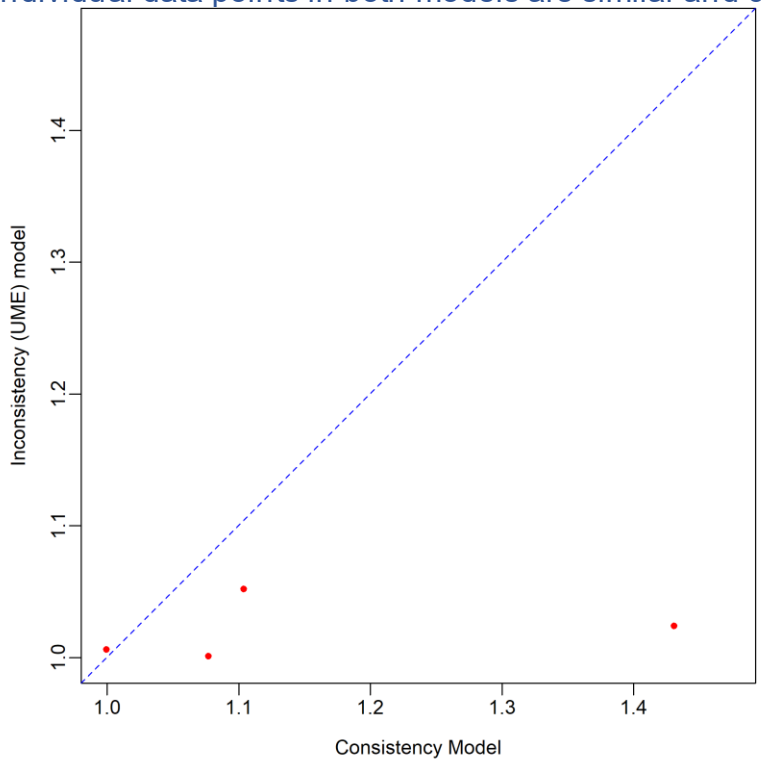
All Cause hospitalisation or death

There is no evidence of inconsistency in this outcome as the UME and consistency models produce similar DICs (17.6 vs 18.3). Contributions of the deviance of the individual data points in both models are similar and close to the line of equality, with the possible exception of the direct evidence from Bajema 2023.



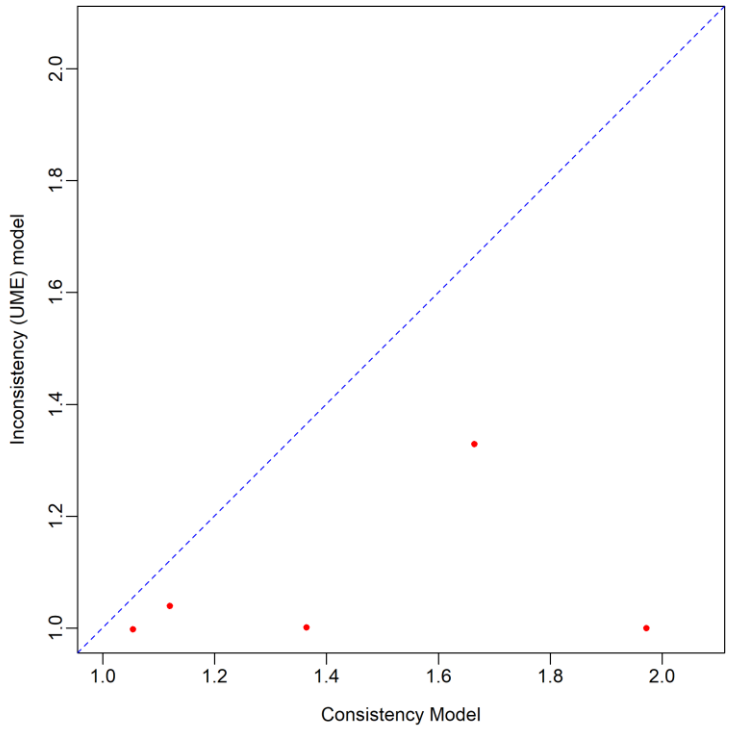
COVID-related hospitalisation or death

There is no evidence of inconsistency in this outcome as the UME and consistency models produce similar DICs (14.2 vs 13.6). Contributions of the deviance of the individual data points in both models are similar and close to the line of equality.



COVID-related hospitalisation

There is no evidence of inconsistency in this outcome as the UME and consistency models produce similar DICs (14.0 vs 14.5). Contributions of the deviance of the individual data points in both models are similar and close to the line of equality.



A17. CS sections 2.9.2.1 to 2.9.2.5 each state that "Further discussion on results of the NMA analysis for this outcome can be found in Appendix D.2". Similarly, CS Tables 42 to 46, and CS Figures 14 to 27 state "SOURCE: RWE SLR (see Appendix D.2)". However, CS Appendix D.2 does not report any NMA results. Please clarify where the "further discussion" is located and provide the source of the results data for these Tables and Figures.

Sensitivity and subgroup analyses results for all outcomes are presented below in response to question A18 (Table 26 to Table 30).

A18. CS section B.2.9.4.2 gives a general overview of the limitations of the studies included in NMAs. For clarity and transparency of interpretation, as well as helping the EAG understand the study selection process:

a) Please provide a table showing which studies each of the stated limitations apply to and what the action taken for each limitation was (e.g. was the study excluded from the analysis due to the limitation(s), or included in the analysis despite the limitation(s) due to lack of alternative options).

b) Could sensitivity analyses be conducted to explore the impact of any of these limitations?

Please see the below responses on each point including tabulated results of analyses for the base-case, sub-group and sensitivity analyses explored in the RWE NMA.

Limitation	Action
Vaccination rates not considered comparable to UK setting (i.e., studies conducted in Asia and Mexico)	Analyses restricted to studies conducted in the North America, Europe, Australia, and Israel. Studies conducted in Asia and Mexico excluded from the analyses: (Chang, 2023; Hirai, 2023; Inaba, 2023; Kim, 2023; Kwok, 2023; Low, 2023; Lui, 2023; Rajme-Lopez, 2022; Park, 2023; Park, 2023; Saheb Sharif-Askari, 2022; Wai, 2023; Wang, 2023; Wee, 2023; Wong, 2022; Wong, 2023; Yip, 2023)[21-36]
Generalisability to current UK clinical practice given the heterogeneity in SARS-CoV-2 variants studied across the different time periods	Studies conducted between 2021 and early 2022 evaluating treatment effectiveness against variants preceding Omicron or early Omicron variants (BA.1 and BA.2) were excluded: Aggarwal, 2023; Cheng, 2022; Evans, 2023; Goodwin, 2023; Hedvat, 2022; Henderson, 2023; Huang, 2022; Nevola, 2023; Patel, 2022; Piccicacco, 2022; Razonable, 2019; Zheng, 2022b; Zhou, 2022)[37-49] [48, 49] Salmanton-García 2023[50] was conducted from October 2021 to January 2023 however there was disparity in the timing of treatment received in the two treatment groups. A higher proportion of the molnupiravir recipients were treated between October 2021 and June 2022 when Omicron BA.1 and BA.2 were the dominant SARS-CoV-2 variants whereas a greater proportion of patients received nirmatrelvir/ritonavir from July 2022 through March 2023 after the emergence of

	newer Omicron variants. This study was also excluded from any analyses.
Potential impact of confounding factors	Studies that performed no adjustment for prognostic factors, those in which adjustment was considered in adequate, and those reporting insufficient detail on patient matching/ adjustments were excluded from the analyses: Bruno, 2022a; Bruno, 2022b; Drysdale, 2023; Gentile, 2022; Gleeson, 2022; Kauer, 2023; Lahouati, 2023; Petrakis, 2023; Martin-Blondel, 2023; Pinargote-Celorio, 2023; Radcliffe, 2022; Ranganath, 2023; Rinaldi, 2023; Salerno, 2022; Scotto, 2023; Shah, 2022; Spiliopoulou, 2023; Vicente-Valor 2023; Villamarin, 2022.[7, 9, 10, 51-66]
Control groups were often poorly described	Studies in which the control group were clearly described as untreated and those in which there was ambiguity as to whether patients in the control may have received treatment other than the study intervention (no molnupiravir and no nirmatrelvir/ritonavir) were considered separate comparators in the NMA.
Population heterogeneity with regard to potential effect modifiers (i.e., age, vaccination status, comorbidities, and symptomatic disease at baseline)	Age: Subgroup analyses were conducted limiting the patient populations to those aged ≥60 and 70 years, the results of these analyses are shown below. Comorbidities: Studies focusing on patients with specific comorbid conditions were excluded from the base case. Where feasible, subgroup analyses were conducted to explore the impact of comorbid conditions (i.e., cancer, cardiovascular disease, kidney disease, obesity, diabetes, and immunocompromised patients) on treatment effectiveness. The results are shown below. Vaccination status: A sensitivity analyses was conducted excluding one trial (Kabor 2023[67]) in which vaccination rates were much lower than the other included studies. Symptomatic disease at baseline: Two studies (Butt 2023a[68] and Butt 2023b[69]) were considered outliers and excluded from the base case due to disparity in the occurrence of symptomatic disease at baseline between the treatment and control arms; a sensitivity analyses was conducted in which these two studies were included in the analyses.

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UK = United Kingdom

Table 26. Sensitivity and subgroup analysis for all-cause hospitalisation or death

		Effect Size, RR (95% CrI)				
		Mol vs. no treatment	Mol vs. no Nir/r or Mol	Mol vs. Nir/r	Mol vs. REM	Mol vs. SOT
Base case	Active treatment evidence network			1.22 (0.50, 2.99)		1.07 (0.33, 3.55)
	Active treatment/control evidence network	0.61 (0.43, 0.86)	0.41 (0.19, 0.89)	1.28 (0.91, 1.79)		1.10 (0.55, 2.23)
Sensitivity analyses	Vaccinated patients	0.61 (0.43, 0.86)		1.28 (0.92, 1.78)		1.10 (0.56, 2.17)
	Symptomatic disease	0.65 (0.45, 0.93)	0.64 (0.36, 1.20)	1.36 (0.97, 1.90)		1.15 (0.56, 2.39)
Subgroup analyses	Patients aged ≥60 years	0.58 (0.40, 0.84)	1.04 (0.60, 1.77)	1.36 (0.91, 1.99)		
	Cancer*	0.69 (0.55, 0.86)		1.27 (0.94, 1.75)		
	CVD*	0.86 (0.74, 0.99)		1.75 (1.40, 2.19)		
	Kidney disease*	0.82 (0.66, 1.02)		1.79 (1.26, 2.53)		1.60 (1.17, 2.18)
	Diabetes*	0.70 (0.59, 0.82)		1.37 (1.06, 1.78)		
	Patients aged ≥70 years					
	Immunocompromised					
	Obesity					

The RE model was used as base-case except in instances there is only one study per comparison, or only one instance of two studies for a comparison. An asterisk (*) indicates that results are derived from an FE model. Sensitivity analysis of vaccination status includes all base case-eligible studies except Kabore 2023 which is considered an outlier with regards to vaccination status. Sensitivity analysis of symptomatic disease includes outliers with regards to symptomatic disease distribution across treatment arms (Butt 2023a and Butt 2023b) in addition to base-case eligible trials. Subgroup analyses leverage data from studies which exclusively recruited older patients or patients with specific comorbidities and those studies reporting subgroup analyses for the respective populations of interest.

Table 27. Sensitivity and subgroup analysis for COVID-19-related hospitalisation or death

		Effect Size, RR (95% CrI)				
		Mol vs. no treatment	Mol vs. no Nir/r or Mol	Mol vs. Nir/r	Mol vs. REM	Mol vs. SOT
Base case	Active treatment evidence network			1.79 (0.61, 4.49)	0.94 (0.26, 3.46)	2.40 (0.88, 7.32)
	Active treatment/control evidence network	0.75 (0.22, 2.60)		1.77 (0.63, 4.50)	0.95 (0.25, 3.50)	2.38 (0.85, 7.57)
Sensitivity analyses	Vaccinated patients					
	Symptomatic disease					
Subgroup analyses	Patients aged ≥60 years					
	Cancer					
	CVD					
	Kidney disease*					2.76 (1.53, 4.99)
	Diabetes					
	Patients aged ≥70 years					
	Immunocompromised					
	Obesity*			10.72 (1.71, 68.03)		3.70 (1.00, 13.80)

The RE model was used as base-case except in instances there is only one study per comparison, or only one instance of two studies for a comparison. An asterisk (*) indicates that results are derived from an FE model. The sensitivity analysis which excluded one outlier with regard to vaccination status (Kabore 2023) was futile as this outcome was not reported by Kabore 2023. The sensitivity analysis which included two outliers with regard to symptomatic disease (Butt 2023a and Butt 2023b) was futile as this outcome was not reported by either study. Subgroup analyses leverage data from studies which exclusively

recruited older patients or patients with specific comorbidities and those studies reporting subgroup analyses for the respective populations of interest.

Table 28. Sensitivity and subgroup analysis for all-cause hospitalisation

		Effect Size, RR (95% CrI)				
		Mol vs. no treatment	Mol vs. no Nir/r or Mol	Mol vs. Nir/r	Mol vs. REM	Mol vs. SOT
Base case	Active treatment evidence network			1.01 (0.53, 1.81)	1.40 (0.21, 9.45)	
	Active treatment/control evidence network	0.79 (0.66, 0.92)	0.37 (0.25, 0.53)	1.19 (0.98, 1.43)	1.65 (0.35, 8.63)	
Sensitivity analyses	Vaccinated patients	0.79 (0.65, 0.93)		1.19 (0.98, 1.43)	1.71 (0.33, 8.12)	
	Symptomatic disease					
Subgroup analyses	Patients aged ≥60 years	0.68 (0.42, 1.04)	0.99 (0.45, 2.16)	1.32 (0.82, 2.07)		
	Cancer					
	CVD					
	Kidney disease					
	Diabetes					
	Patients aged ≥70 years *	0.71 (0.58, 0.88)	0.89 (0.61, 1.27)	1.18 (0.85, 1.64)		
	Immunocompromised					
	Obesity					

The RE model was used as base-case except in instances there is only one study per comparison, or only one instance of two studies for a comparison. An asterisk (*) indicates that results are derived from an FE model. Sensitivity analysis of vaccination status includes all base case-eligible studies except Kabore 2023 which is considered an outlier with regard to vaccination status. The sensitivity analysis which included two outliers with regard to symptomatic disease (Butt 2023a and Butt 2023b) was futile as this outcome was not reported by either study. Subgroup analyses leverage data from studies which exclusively recruited older patients or patients with specific comorbidities and those studies reporting subgroup analyses for the respective populations of interest.

Table 29. Sensitivity and subgroup analysis for COVID-19-related hospitalisation

		Effect Size, RR (95% CrI)				
		Mol vs. no treatment	Mol vs. no Nir/r or Mol	Mol vs. Nir/r	Mol vs. REM	Mol vs. SOT
Base case	Active treatment evidence network*			0.50 (0.11, 2.26)		0.43 (0.03, 5.29)
	Active treatment/control evidence network*	0.85 (0.49, 1.53)	0.46 (0.30, 0.73)	1.58 (0.98, 2.54)		1.64 (0.19, 13.04)
Sensitivity analyses	Vaccinated patients*	0.22 (0.05, 0.88)	0.55 (0.34, 0.89)	0.39 (0.10, 1.55)		0.52 (0.05, 5.55)
	Symptomatic disease*					
Subgroup analyses	Patients aged ≥60 years*		0.55 (0.34, 0.88)	0.75 (0.45, 1.27)		
	Cancer					
	CVD					
	Kidney disease					
	Diabetes					
	Patients aged ≥70 years					
	Immunocompromised					
	Obesity					

The RE model was used as base-case except in instances there is only one study per comparison, or only one instance of two studies for a comparison. An asterisk (*) indicates that results are derived from an FE model. Sensitivity analysis of vaccination status includes all base case-eligible studies except Kabore 2023 which is considered an outlier with regard to vaccination status. The sensitivity analysis which included two outliers with regard to symptomatic disease (Butt 2023a and Butt 2023b) was futile as this outcome was not reported by either study. Subgroup analyses leverage data from studies which exclusively

recruited older patients or patients with specific comorbidities and those studies reporting subgroup analyses for the respective populations of interest.

Table 30. Sensitivity and subgroup analysis for all-cause death

		Effect Size, RR (95% CrI)				
		Mol vs. no treatment	Mol vs. no Nir/r or Mol	Mol vs. Nir/r	Mol vs. REM	Mol vs. SOT
Base case	Active treatment evidence network*			1.48 (1.22, 1.79)		
	Active treatment/control evidence network	0.31 (0.21, 0.46)	0.70 (0.36, 1.42)	1.44 (1.00, 2.10)		
Sensitivity analyses	Vaccinated patients					
	Symptomatic disease					
Subgroup analyses	Patients aged ≥60 years*	0.24 (0.10, 0.56)	0.66 (0.50, 0.86)	1.34 (1.09, 1.66)		
	Cancer					
	CVD					
	Kidney disease					
	Diabetes					
	Patients aged ≥70 years					
	Immunocompromised					
	Obesity					

The RE model was used as base-case except in instances there is only one study per comparison, or only one instance of two studies for a comparison. An asterisk (*) indicates that results are derived from an FE model. The sensitivity analysis which excluded one outlier with regard to vaccination status (Kabore 2023) was futile as this outcome was not reported by Kabore 2023. The sensitivity analysis which included two outliers with regard to symptomatic disease (Butt 2023a and Butt 2023b) was futile as this outcome was not reported by either study. Subgroup analyses leverage data from studies which exclusively recruited older patients or patients with specific comorbidities and those studies reporting subgroup analyses for the respective populations of interest.

A19. Three of the RWE studies included in the NMAs (Cowman 2023, Gentry 2023, Xie 2023) were conducted using the same electronic health record system (Veterans Health Administration). Please clarify whether there is any data overlap between these studies and if so, how this was accounted for in the NMAs.

Cowman 2023 did not use the VHA system; however, both Gentry 2023 and Xie 2023 did use the system. The accrual period for Gentry 2023 was Jan 1 through Feb 6 (2022) for all veterans aged 65 years and older; the accrual period for Xie was Jan 5 through Sep 30 (2022) for veterans 60 and older or with a different risk factor for progression (e.g., BMI>30, chronic lung disease, diabetes, etc.). Gentry 2023 used a multivariate logistic regression in analyses, while Xie 2023 used a 10:1 propensity score matching technique to create the comparator cohort. Finally, and perhaps most importantly, Gentry included a comparison to nirmatrelvir/ritonavir and Xie 2023 did not. Because of the differences in inclusion criteria (wider for Xie 2023), accrual period (wider for Xie 2023), methodological techniques, and comparators (more for Gentry 2023), it was judged best to include both studies in analyses. We note that for

all cause hospitalization, the result for Gentry 2023 (risk ratio of 0.55) is very close to the Bayesian estimate (risk ratio of 0.61) and so exclusion of Gentry would have a miniscule impact on the final estimate.

Section B: Clarification on cost-effectiveness data

Comparators

B1. The NICE scope includes remdesivir as a comparator (subject to NICE evaluation). Please conduct a scenario analysis in the economic model to include remdesivir as a comparator.

MSD acknowledge the inclusion of remdesivir in the final scope. Nonetheless, we have provided a very detailed justification as to why remdesivir should not be considered as a direct comparator to Molnupiravir considering its current use in the NHS, its marketing authorisation and NICE guidance.

It should be noted that whilst earlier NHS commissioning policies put in place before the MTA commenced did not preclude the use of Remdesivir in the outpatient setting for mild-moderate COVID-19. However, due to supply issues its use was at the time extremely limited.

The commissioning policy from NHS England was updated to specify the use of Remdesivir in hospitalised only patients. It has subsequently been superseded by the NICE final guidance on Remdesivir (TA971) which specifies the technology as an in-hospital treatment only (TA971). Remdesivir is recommended by NICE for the treatment of COVID-19 in hospital and therefore does not form part of the outpatient treatment pathway, in contrast to Molnupiravir which can be used in the community also. As such the technologies are not fully interchangeable for the overall population under consideration for ID6340 and therefore formal inclusion of this comparator in the model engine alongside nirmatrelvir plus ritonavir, sotrovimab and no-treatment (depending on the cohort of interest) would be spurious.

MSD have acknowledged that there are instances whereby Remdesivir could be considered a direct comparator for patients admitted to hospital for reasons other than COVID-19 and subsequently diagnosed as incidental COVID-19 cases. Clinical

experts informed MSD that in fact remdesivir is occasionally used in the treatment of patients with incidental COVID-19 acquired whilst in hospital for reasons not related to COVID-19. However, healthcare professionals who treat these patients with incidental COVID-19 indicate that the treatment pathway for those on a general ward not requiring supplemental oxygen is the same as in the outpatient setting (i.e. nirmatrelvir plus ritonavir or sotrovimab). [70] The experts do however indicate that on occasion, remdesivir, which was recently recommended by NICE for COVID-19 treatment in-hospital only (TA971), may be also be used in incidental COVID-19, if deemed by the clinician to be the most appropriate treatment.[70] As there is a small hypothetical crossover in populations which is driven by incidental COVID-19 cases alone, but remdesivir is not considered a strict and direct comparator of interest in this submission.

For incidental COVID-19 cases whereby no oxygenation is necessary, remdesivir could be used in parallel with other active treatments. However, MSD are not aware of any studies reporting outcomes for incidental COVID-19 cases treated with therapeutics. Since incidental cases are already in hospital for other reasons, the only subsequent clinical outcomes that can be experienced by patients (and are relevant for the HTA) are those of mortality or recovery and subsequent discharge. As such, introducing remdesivir formally in the model would require the extrapolation of outpatient derived efficacy data to the hospital setting i.e. disaggregating the hospitalisation and mortality composite outcome for all treatments which is limited by data availability and subsequent tracking of mortality alone within the model. This would start to resemble formal treatment sequencing with no robust data to substantiate this.

For the purposes of this submission and for the main population of interest in ID6340 (community/outpatients), the assumption is that remdesivir is a “treatment escalation” as it may be used for hospitalised patients with some oxygenation needs (a population stipulated in by TA971). Under these circumstances, patients accessing would need to have “failed” beforehand a community/outpatient prescribed treatment and subsequently experienced a hospitalisation outcome.

The simplifications made for modelling purposes specific to incidental COVID-19 do not have any negative effects on the treatment pathways patients may experience in the real word. For example a patient treated with Molnupiravir or “no treatment” in the community/outpatients, if hospitalised, would experience the treatment effects for remdesivir once in the medical ward. On the contrary, a patient would never be treated with remdesivir in the community outpatients and then proceed to receive yet again remdesivir once in the medical ward.

The current model attempts to avoid unnecessary complexity by assuming that previously community treated patients, if hospitalised for COVID-19, experience a COVID-19 treatment escalation. Since any patient progressing may access remdesivir regardless of the prior treatment received, this does not have an impact on the cost-effectiveness as we would not expect the use of remdesivir to vary between treatment arms.

For incidental COVID-19 case effectiveness, the outpatient data for remdesivir may be used to infer the relative clinical effectiveness of all alternative treatment options there is no study reporting on the effects of treatments for incidental COVID-19 acquired in hospital to enable a more granular modelling.

Given data limitations, MSD consider formal modelling of remdesivir in the outpatients to be inappropriate. Instead, its inclusion in the networks of evidence for comparative clinical effectiveness in outpatients can be used to inform decision making. For these reasons, MSD have not formally modelled remdesivir as a comparator.

Model input parameters

B2. Please explain why the baseline characteristics reported in CS Table 70 (including mean age and proportion female) have not been obtained from the same source.

The mean age from PANORAMIC was selected as the population included in this study was thought to be more representative of the overall at-risk population included in the NICE scope due to the broader definition of high-risk compared

MOVe-OUT trial. The mean weight is only used in the model to calculate tocilizumab costs so most appropriate to use the value from the Resource Impact template as used in TA878.

B3. PRIORITY QUESTION. Please explain how the company calculated the cost of remdesivir reported in CS Table 70 (£1445) from the BNF reported price of £340 for 100mg.

The price of remdesivir is £340 for 100mg (BNF). A course of remdesivir for an adult is a loading dose of 200mg on day one, with a maintenance dose of 100mg daily for at least 5 days and up to 10 days in total (3 days in total if not in receipt of supplementary oxygen).

The representative price of a course of remdesivir was calculated by using 7.5 days as an 'average' duration of treatment (mid-point between 5 and 10 days), and costing for 200mg on day one, and 100mg each subsequent day. However, in our analysis, the cost of £340 was wrongly attributed to 200mg. We acknowledge this error and have updated the calculation using the mid-point of 3 days (not on oxygen) and 10 days (maximum course length, on oxygen) = 6.5 days and then costing as above (with cost of £340 per 100mg) = £340 x 2 for day one plus £340 per day for subsequent 5.5 days = £2,550. See confidential appendix with updated results.

B4. PRIORITY QUESTION. The EAG are unable to derive the cost of long-term sequelae reported in CS Table 70 from the study by Vos-Vromans et al. 2017.

a) Please explain how this was derived from the source.

The value used was based on the £2,267 value used in TA971 and inflated to 2024 using PSSRU inflation rates.

b) In TA971, it is stated that a new source (The Optimum Health Clinic Foundation. Counting the Cost Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. London: The Optimum Health Clinic Foundation; 2017) to inform long-term sequelae was preferable compared to Vos-Vroman et al. 2017. Please explain why this source is not appropriate for the company's base case and please

consider providing a scenario analysis using it to inform long-term sequalae costs.

We have a different interpretation of the conclusions of TA971. From the draft guidance document, we understood that the committee accepted the Vos-Vromans costs as the chronic fatigue symptom estimate suggested by the company was thought to underestimate the true cost. See section 3.28 p42 which states 'During the first draft guidance consultation, a consultee said that the AG's base-case long-COVID cost underestimates the true burden of long-COVID. They provided an alternative higher cost from Vos-Vromans et al. (2017). The AG accepted this new evidence and inflated the cost to £2,267 per year (to reflect 2021/2022). The committee agreed with the updated base-case value.' Therefore in line with the committee decision in TA971 we used the £2,267 per year.

B5. PRIORITY QUESTION. The EAG are unable to identify the sources of several model input parameters which are reported in the CS and used in the company's model (**Table 31**). Please clarify how these values were derived from the corresponding sources, by stating where they could be found in the source and, if applicable, the calculations needed to derive the model input value.

Please see the below responses on each point (Table 31).

Table 31. EAG queries on sources of model input parameters

Model parameters	Location in company submission	Location in company's model	Source	Describe how the values for the input parameters were derived (provide detail where they are in the corresponding source and any calculations needed)
Clinical effectiveness				
Baseline characteristics				
Mean weight	CS Doc B Table 70	Setting!E51	Assumption TA878 RIA	This is based on the value for mean weight used in the resource impact template excel for tocilizumab. This only affects the hospitalised % of the model and is kept constant across all treatment arms regardless of outpatient treatment for mild/moderate COVID-19 received.
Disease characteristics				
Length of stay	CS Doc B Table 70	DiseaseParam!F 42, F44	Yang et al. 2023 Table 2	This was described in CS p144 Mean length of stay in general ward was calculated

Model parameters	Location in company submission	Location in company's model	Source	Describe how the values for the input parameters were derived (provide detail where they are in the corresponding source and any calculations needed)
				as overall mean length of stay less the product of the proportion of patients in critical care and length of stay in critical care
Outpatient visits	CS Doc B Table 58	DiseaseParam!F98-F100	NICE TA971	No outpatient visits were mentioned in TA917 therefore it was assumed no outpatient visits would be included
Adverse events				
Molnupiravir and no treatment				
Headache	CS Doc B Table 64	AE!D8:H15	MOVe-OUT trial	The original source was MOVeOUT CSR figure 14-3-3 which reports 0% headache for no treatment, however reinspection of MOVeOUT CSR table 14.3-2 shows this is an error in the value used for no treatment, it has been corrected to 0.1%
Diarrhoea	CS Doc B Table 64	AE!D8:H15	MOVe-OUT trial	The original source was MOVeOUT CSR figure 14-3-3 which does not include diarrhoea however on reinspection MOVeOUT CSR table 14.3-7 does contain values for this AE. There is an error in the values used and have been updated to 2.3% for molnupiravir and 3.2% for placebo
Nirmatrelvir plus ritonavir				
Headache	CS Doc B Table 64	AE!D8:H15	Paxlovid SmPC	Taken from EPAR https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf "The most common adverse reactions reported during treatment with Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) were dysgeusia (4.6%), diarrhoea (3.0%), headache (1.2%) and vomiting (1.2%)."
Diarrhoea	CS Doc B Table 64	AE!D8:H15	Paxlovid SmPC	
Dysgeusia	CS Doc B Table 64	AE!D8:H15	Paxlovid SmPC	
Vomiting	CS Doc B Table 64	AE!D8:H15	Paxlovid SmPC	
Sotrovimab				
Nausea	CS Doc B Table 64	AE!D8:H15	Xevudy SmPC	These values were actually derived from the COMET-ICE trial reporting Gupta A, Gonzalez-Rojas Y, Juarez E,
Headache	CS Doc B Table 64	AE!D8:H15	Xevudy SmPC	

Model parameters	Location in company submission	Location in company's model	Source	Describe how the values for the input parameters were derived (provide detail where they are in the corresponding source and any calculations needed)
Diarrhoea	CS Doc B Table 64	AE!D8:H15	Xevudy SmPC	Crespo Casal M, Moya J, Rodrigues Falci D, Sarkis E, Solis J, Zheng H, Scott N, Cathcart AL, Parra S, Sager JE, Austin D, Peppercorn A, Alexander E, Yeh WW, Brinson C, Aldinger M, Shapiro AE; COMET-ICE Investigators. Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2022 Apr 5;327(13):1236-1246. doi: 10.1001/jama.2022.2832. PMID: 35285853; PMCID: PMC8922199.
Utilities				
Symptomatic	CS Doc B Table 70	QoL!D10:E15	Vignette study (Ntais et al. 2023)	8 heath states were defined in the Vignette study. Pooled utility of state 2 (mild Covid-19, outpatient) and state 3 (moderate covid-19, outpatient) was used as utility for symptomatic patients in the model.
Long-term sequelae	CS Doc B Table 70	QoL!D10:E15	Vignette study (Ntais et al. 2023)	Health state utility of state 8 (the patient had Covid-19 and is suffering from health issues as a result) was use as utility for long term sequalae in the model
Resource use and costs				
Outpatient management	CS Doc B Table 70	CostInputs!F7	NHS reference costs 2022	This was an error in the model – the value has been updated to £165 based on Weighted average cost of 340 and 341 Respiratory Medicine Service and Respiratory Physiology Service unit cost
A&E visit	CS Doc B Table 70	CostInputs!F8	NHS reference costs 2022	This was an error in the mode – the value has been updated in the model to £1,640 based on XC07Z Adult Critical Care, 0 Organs supported

Model parameters	Location in company submission	Location in company's model	Source	Describe how the values for the input parameters were derived (provide detail where they are in the corresponding source and any calculations needed)
Cost of hospitalisation (both general ward and intensive care unit)	CS Doc B Table 70	CostInputs!F9,F11	NHS reference costs 2022	The cost of general ward and ICU was incorrectly weighted, using the activity number as the weighting the cost of ICU is £2,143.52 (hence ICU with mechanical ventilation is £3,362.52) and general ward is £385.19
MOVe-OUT trial data				
Overall population				
Distribution of patients with COVID-19 in different hospital settings	CS Doc B Table 53	NA	MOVe-OUT trial	MSD 2021 BARDS subgroup analysis efficacy ICER v2 Table 1.2-7 Treatment arms were pooled and WHO 11-Point Scale category 4 and 5 were combined to calculate the proportion in general ward, category 6 was used for the proportion in high dependency unit and category 7–9 was used for the proportion in ICU with mechanical ventilation.
Mortality rate by highest hospital setting - General ward	CS Doc B Table 56	NA	MOVe-OUT trial	MSD 2021 BARDS subgroup analysis efficacy ICER v2 Table 1.2-7 Treatment arms were pooled and WHO 11-Point Scale category 4 and 5 were combined to calculate the proportion in general ward, category 6 was used for the proportion in high dependency unit and category 7–9 was used for the proportion in ICU with mechanical ventilation.
Patients aged > 70 years				
All-cause hospitalisation rate	Appendix E CS Table 41	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-14
COVID-19 related hospitalisation rate	Appendix E CS Table 41	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-14
Proportion by highest hospital setting	Appendix E CS Table 41	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis descriptive summaries v5 Table 3-51 Treatment arms were pooled and WHO 11-Point Scale category 4 and 5 were combined to calculate the

Model parameters	Location in company submission	Location in company's model	Source	Describe how the values for the input parameters were derived (provide detail where they are in the corresponding source and any calculations needed)
				proportion in general ward, category 6 was used for the proportion in high dependency unit and category 7–9 was used for the proportion in ICU with mechanical ventilation.
Overall mortality in hospital	Appendix E CS Table 41	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-67
Mortality rate by highest hospital setting	Appendix E CS Table 41	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-67 Treatment arms were pooled and WHO 11-Point Scale category 4 and 5 were combined to calculate the proportion in general ward, category 6 was used for the proportion in high dependency unit and category 7–9 was used for the proportion in ICU with mechanical ventilation.
HR all-cause hospitalisation	Appendix E CS Table 43	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-14
HR COVID-19 related hospitalisation	Appendix E CS Table 43	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-14
Patients contraindicated to nirmatrelvir plus ritonavir				
All-cause hospitalisation rate	Appendix E CS Table 45	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-48
COVID-19 related hospitalisation rate	Appendix E CS Table 45	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-96
Proportion by highest hospital setting	Appendix E CS Table 45	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis descriptive summaries v5 Table 3-63 Treatment arms were pooled and WHO 11-Point Scale category 4 and 5 were combined to calculate the proportion in general ward, category 6 was used for the proportion in high dependency unit and category 7–9 was used for the proportion in ICU with mechanical ventilation.

Model parameters	Location in company submission	Location in company's model	Source	Describe how the values for the input parameters were derived (provide detail where they are in the corresponding source and any calculations needed)
Overall mortality in hospital	Appendix E CS Table 45	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-99
HR all-cause hospitalisation	Appendix E CS Table 46	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-48
HR COVID-19 related hospitalisation	Appendix E CS Table 46	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-96
Patients immunocompromised				
All-cause hospitalisation rate	Appendix E CS Table 47	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-43
COVID-19 related hospitalisation rate	Appendix E CS Table 47	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-91
Proportion by highest hospital setting	Appendix E CS Table 47	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis descriptive summaries v5 Table 3-61 Treatment arms were pooled and WHO 11-Point Scale category 4 and 5 were combined to calculate the proportion in general ward, category 6 was used for the proportion in high dependency unit and category 7–9 was used for the proportion in ICU with mechanical ventilation.
Overall mortality in hospital	Appendix E CS Table 47	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-94
HR all-cause hospitalisation	Appendix E CS Table 49	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-43
HR COVID-19 related hospitalisation	Appendix E CS Table 49	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-91
Patients with chronic kidney disease				
All-cause hospitalisation rate	Appendix E CS Table 50	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-23
COVID-19 related hospitalisation rate	Appendix E CS Table 50	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-71
Proportion by highest hospital setting	Appendix E CS Table 50	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis descriptive summaries v5 Table 3-53 Treatment arms were pooled and WHO 11-Point Scale category 4 and 5 were

Model parameters	Location in company submission	Location in company's model	Source	Describe how the values for the input parameters were derived (provide detail where they are in the corresponding source and any calculations needed)
				combined to calculate the proportion in general ward, category 6 was used for the proportion in high dependency unit and category 7–9 was used for the proportion in ICU with mechanical ventilation.
Overall mortality in hospital	Appendix E CS Table 50	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-74
HR all-cause hospitalisation	Appendix E CS Table 52	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-23
HR COVID-19 related hospitalisation	Appendix E CS Table 52	NA	MOVe-OUT trial	MSD 2024 BARDS subgroup analysis efficacy v5 Table 3-71

B6. PRIORITY QUESTION. Different input values are reported in the company submission and in the company's model for several input parameters (Table 32). Please clarify which of the values should be considered in the company's base case.

Please see the below responses on each point (Table 32).

Table 32. EAG queries on discrepancies between reported model input parameters

Model parameters	Location in company submission	Location in company's model	Source	Which of the values (company submission or model) should be considered in the company's base case?
Clinical effectiveness				
Disease characteristics				
Outpatient duration of symptoms	CS Doc B Table 70	DiseaseParam!F93	PANORAMIC trial	Table 70 in the submission matches the value used in the model, in the cell referenced here – 9 days, taken from the PANORAMIC trial (Butler et al)
Resource use and costs				
Adverse events	CS Doc B Table 69	CostInputs!E25:E29	eMIT	Error in the price of paracetamol in the model – currently reported as £0.55 vs £0.27 in the submission. £0.27 is the correct price in eMIT
Subgroups				
Patients immunocompromised				

Model parameters	Location in company submission	Location in company's model	Source	Which of the values (company submission or model) should be considered in the company's base case?
Overall mortality	Appendix E CS Table 48	DiseaseParam!F 80:F82	INFORM Evans et al. 2023 Table 3	The value reported in the submission document and in NICE TA971 (24.98%) should be used in the model base case. Please note that the erroneous value of 25.64% is coded into the base case reset macro and it is necessary to manually enter 24.98 into cells G80:G82 in the DiseaseParam sheet in the model.
Patients with chronic kidney disease				
COVID-19 related hospitalisation rate	Appendix E CS Table 51	DiseaseParam!F 14	DISCOVER-NOW	Values reported in the submission report are correct. 4.4% is used in the base case.

B7. The EAG note that COVID-19 pneumonia was included in the model for sotrovimab although this is not mentioned in the CS. Please clarify whether this adverse event should be considered in the company's base case and, if so, please explain the source of COVID-19 pneumonia incidence.

MSD note that adverse events have a limited impact on the ICERs generated due to their mild nature and generally short duration, since most of these would resolve during the acute phase once patients recover from mild/moderate COVID-19.

For this reason, MSD have not included AE related disutilities in the model but attempted to capture some costs to reflect the endemic setting alongside AE frequencies.

MSD acknowledge the limited reporting of AEs across pivotal publications and limitations of including crude AE rates which were not formally synthesised to adjust for discrepancies in placebo arms. However, our aim was to include the most commonly reported AEs from the SmPCs or EPARs where available to ensure some consistency with the NICE methods of health technology evaluation. In an endemic setting patient preferences may also change where multiple comparators exist.

The EAG is correct to point that the model did include COVID-19 pneumonia for Sotrovimab. This was subsequently accidently omitted from the main submission. The source of COVID-19 pneumonia is the UK MHRA EPAR Table 21.(71)

MSD propose that COVID-19 pneumonia is included the model for completeness of the evidence base (as % of patients experiencing this). However, like the rest of AEs in this submission, this adverse event is not formally costed or has any additional disutility applied, as it would be assumed that patients experiencing COVID-19 pneumonia would also experience a hospitalisation event and once hospitalised for COVID-19 pneumonia, subsequent costs associated with this the management of this AE would therefore be captured in the associated HRGs (alongside any additional treatments for severe disease).

To provide further clarity, the PAXLOVID AEs were sourced from the EMA EPAR (table 2[72]), which are slightly lower compared with those reported in the MHRA EPAR.[73]

Whilst MSD acknowledge the limitations associated with AE inclusion in this submission, we have attempted to capture these in a way that does not introduce uncertainty, but retains key qualitative elements for consideration by appraisal committee.

Utilities

B8. PRIORITY QUESTION. Please provide evidence and a rationale for using a vignette study to inform utilities rather than using published EQ-5D studies as specified in the NICE reference case.

a) Please discuss whether alternative sources might be appropriate to inform utilities in the current appraisal.

b) Please consider providing a scenario analysis with utilities from previous relevant technology appraisals (e.g. TA878 and TA971).

In TA971 FAD it was stated that COVD-19 specific utility values were preferred and suggested using vignette studies, hence these were used in the company base case. “During consultation, stakeholders critiqued the use of utility decrements from a non-

COVID-19 population. An alternative approach for a utility study was proposed. The approach was to use COVID-19 severity-specific vignettes with EQ-5D-3L questionnaires completed by the UK general population."

An alternative utility scenario has been set up in the model, based upon the values from TA878/971 supplemented with alternative values identified from the literature, where more recent appropriate studies were identified in the SLR conducted by MSD. However MSD would like to take the opportunity to note some strengths and limitations of the alternative sources of utility data used within TA878/971 versus the vignette study as a single source of utilities.

The vignette study conducted by MSD in the UK and is used in the base case as it was designed to directly inform the economic modelling. It has been presented at a conference, and was recently submitted for publication in a peer-reviewed journal. This represents a large UK-based study, with a sample generalisable to the UK population.

The utilities systematic literature review carried out for this submission identified several other potential sources of health utilities but these were often reported as secondary outcomes, may not be representative of the population at risk of severe COVID-19 disease, and rarely reported utility values for all relevant health states to address the decision problem. With the exception of the current vignette study no single source of utility estimates suitable for the model structure developed were identified. Therefore, using alternative sources of utility data would involve combining utility values generated by different studies, methodologies and at different times, in potentially different populations which could lead to inherent flaws and inconsistencies.

It should be noted that utility sources reported in TA878 and TA971 are not condition-specific and do not fully meet the NICE reference case (other than being generated using the EQ-5D). In terms of hierarchy in HRQoL methods, proxy condition utility values rank last within the NICE health technology evaluation manual (Figure 4.1). Given the scrutiny of these sources the FAD states that alternative options should be explored in the future including vignette studies. Whilst vignette studies are also not fully compliant with the NICE reference case, the vignette study

in this instance was conducted at the time where COVID-19 was circulating and collected public preferences for COVID-19 specific health states, with 11.8% of responders explicitly stating that they had a previous COVID-19 infection, 0.6% stating they had a current COVID-19 infection and 67.8% reporting that a close friend of family member had had a COVID-19 infection. This means that the vignette study is a more robust source of utility data given the limitations of the current alternatives.

MSD conducted a review of the original publications used by Rafia et al 2022 for in-hospital utility decrements (original research by Hollman et al 2013[74]). We note that decrements applied in TA878/971 were estimated from a Spanish study sample using Influenza as proxy condition. These were age-adjusted by Rafia et al and applied in the UK assuming full generalisability. The publication provides no information on the level of oxygenation and its invasiveness (if any). As such MSD cannot ascertain to what level any of the disutilities used in the MTA could be robust for decision making. We also understand that the inpatient utility decrement is subject to a single measurement at the point of admission and as such this decrement does not capture patient deterioration. The public values some health states worse than “dead” i.e. utility score of less than 0 when unconscious (necessity with mechanical ventilation, as observed in the results of the vignette study). As such assuming a utility of 0 for those hospitalised and with mechanical ventilation (as in TA878/971) contradicts the literature.

It should be noted that TA878 and TA971 use a decrement derived from Wilcox et al 2017[75] as a source of utility for the hospitalised patients not requiring oxygenation. This has been sourced from patients with recurrent *Clostridium difficile* bacterial infection, and cannot be argued as a true proxy. Whist the study is UK specific, the sample size is very small (n=30) and the transferability of these estimates to COVID in the general medical ward is questionable.

Scenario analysis tested for response to the EAG

As requested, an alternative scenario for utilities was considered, based upon the values used in the original multiple technology appraisal, TA878 and TA971.

Mild/moderate COVID-19:

Whilst previous appraisals have assumed no utility decrement associated with mild/moderate COVID, the results of the vignette study strongly argues against this, with respondents reporting a health profile associated with a utility score of 0.302. Therefore, an alternative utility value of 0.57 from Sandmann et al (2022) representing the worst day of acute COVID-19 was used in the scenario analysis. This publication was obtained from the SLR results.

Hospitalised COVID-19:

The MTA and subsequent technology appraisals (TA878 and TA971) used utility decrements from Rafia et al (2022) for hospitalised states. As requested by the EAG, these are used in this scenario analysis, but are associated with a number of limitations and additional necessary assumptions:

- Rafia et al (2022) reports utility values by oxygen requirement, whereas the health states in our model are based on hospital location (general medical ward, high dependency unit and intensive care unit). Therefore it was necessary to make an assumption regarding oxygen therapy use: we assumed that 50% of the patients in GMW were in receipt of oxygen (LFO/HFO/NIV) and 50% were not, and all patients in HDU were in receipt of oxygen (LFO/HFO/NIV).

- The utility decrements used in Rafia et al (2022) are based on values for *Clostridium difficile* for the hospitalised without oxygen state, and influenza for the hospitalised with oxygen supplementation (LFO/HFO/NIV) state. There is therefore an implicit assumption that the impact of hospitalisation with these other common infections upon patients' quality of life is the same as COVID-19 which cannot be validated.

- The vignette study yielded absolute utility values, whereas Rafia et al (2022) reports utility decrements. These utility decrements were therefore applied to the age-adjusted baseline HRQoL according to the average starting age in the model.

- Rafia et al (2022) includes a utility decrement for the first 52 weeks after discharge from hospital. This is not compatible with our model, therefore the impact of COVID-19 upon HRQoL will be underestimated in this scenario analysis.

Long COVID:

The MTA used a utility value from a study by Evans et al (2022), which was conducted early in the pandemic (2020-2021) and reports utility value of 0.69 (IQR: 0.52 – 0.80) for long COVID non-recovered responders as one of several secondary outcomes at a 5 month timepoint. We have sourced an alternative value from the utilities SLR from Carlile et al 2023, reporting 0.49 utility score for this health state. Alternative sources indicate that the utility value reported by Evans et al 2022 is a likely upper estimate outlier (with multiple sources reporting values between 0.49 and 0.54), which can be validated versus the lower IQR value of 0.52 reported by the authors. It should be noted that Carlile et al 2023 is the most recent and largest UK-based long COVID HRQoL study identified by our SLR, which used the OpenSAFELY population and had patient-reported outcomes as its primary outcome.

Table 33. Summary of scenario analysis

Health state	Vignette study	TA878 and TA971	Scenario analysis
Mild/moderate acute COVID-19	0.302	No utility decrement	0.57
Co-morbidities		–0.116 (decrement)	
Hospitalised – no oxygen		–0.36 (decrement)	
Hospitalised – LFO/HFO/NIV		–0.58 (decrement)	
Hospitalised - GMW	-0.181		–0.586 (decrement) (0.116 + 50%*0.36 + 50%*0.58)
Hospitalised - HDU	-0.114		–0.696 (decrement) (0.116 + 0.58)
Hospitalised – ICU with MV	-0.376	0	0
Long COVID-19	0.209	0.69	0.49

COVID-19 = coronavirus disease 2019; GMW = general medical ward; HDU = high dependency unit; ICU = intensive care unit

Table 34. Results of scenario analysis

Comparison	Base case ICER	Utility scenario analysis ICER

Molnupiravir vs no treatment	*****	*****

ICER = incremental cost-effectiveness ratio

Although the alternative values tested leads to an increase in the ICERs for molnupiravir compared with comparator treatments or no treatment, this scenario was considered less methodologically robust for the following reasons:

- Health state utility values were taken from multiple sources, with different populations, time scales and methodologies and not all are condition specific or fully complaint with the NICE reference case needs.
- Health state utility values do not necessarily account for the underlying co-morbidities in the population of interest in the present appraisal.
- Utility values for hospitalised COVID from Rafia et al (2022) were based upon values for *Clostridium difficile* and Influenza, both of which are arguably inappropriate as proxies. In particular, the applicability of utility data for an enteric pathogen such as *Clostridium difficile* to the respiratory infection COVID-19 is questionable. At the time of conducting the MTA, these may have represented the best available data, however, at this stage alternative studies have been designed and carried out specifically in COVID-19, in a relevant population and these should be used preferentially.
- Assumptions were necessary to convert utility decrements based on oxygen requirements from Rafia et al (2022), to absolute utility values based on hospital location for the model.
- Lack of model functionality to include the utility decrement for 52 weeks following discharge from Rafia et al (2022), resulting in an overall underestimate of the impact of COVID-19 upon HRQoL.

Whilst we acknowledge that all sources of utilities have inherent limitations, MSD conducted a utility vignette study as proposed in the TA971 FAD. Although the vignette study also only partly meets the NICE reference case, using a single source of utility estimates for modelling removes methodological inconsistencies in datasets. The vignette study was carried out in 2021-2022, in a population with experience of

COVID-19 infection directly or indirectly and as such is more likely to reflect the true population preferences for health states associated with the disease. MSD therefore consider this as the preferred source to provide robust utility inputs for the STA to inform the base case analysis and subsequent decision making.

B9. Please justify why the company did not include a utility value for readmission after long-term sequelae. Please consider providing a scenario analysis to explore this.

MSD do not use readmission as a separate outcome in the model as readmission cost/utility are included in the cost and utility assumed for long-term sequalae applied. Therefore, MSD cannot do a scenario on this without separating out the cost/utility associated with readmission only from the input which is not feasible.

Model validation

B10. To cross-validate the model results, please provide a comparison of the model results from the current appraisal against the results from TA878 and TA971.

Model comparisons and validations are warranted by the limited data reported across TA878/971, community/antiviral treatments are modelled using a decision tree for the first 30 days, followed by a Markov model (this submission) or a Partition Survival Model (TA878/971). Nonetheless, we provide some additional context below.

In the original CS we presented a comparison with the MTA results which showed similarity in total incremental QALYs, although due to differences in model structure and lack of reporting of Lys, a comparison of other outcomes is not plausible. We conducted an analysis comparing the company model results to those recently published for PANORAMIC in-trial modelling.[76] Using a 6-month time horizon in the company model generates total QALYs of 0.3674 for molnupiravir and 0.3610 resulting in incremental QALYs of 0.006. These values are comparable with those from the PANORAMIC model which reported 0.416 for molnupiravir and 0.4080 for usual care with incremental QALYS of 0.0055. This demonstrates the validity of the values derived from the company model.

MSD went on to conduct a comparison of total discounted QALYs over a lifetime

between the current STA model and comparators other than Molnupiravir (November 2022 Committee papers ACM2: Table 21 EAG report). It should be noted that results were not reported in the most recent EAG report for Molnupiravir at the time and there was a significant change in QALYs between July 2022 report and Nov 2022 report due to changes in model inputs carried out by the EAG. The table below presents these findings including some additional extractions for Molnupiravir using the most recent model provided at the time (MTA AG model v6.0 16012023). Upon model review and comparison of mean efficacy outputs MSD noticed discrepancies between MTA reported values (Table 21) and model outputs (presented below). The EAG MTA model does not output LYs for further comparisons. It should be noted that MSD has no ownership of the MTA model and during the appraisal process a number of modelling errors were identified by stakeholders which may explain the discrepancies presented below.

Table 35. Summary of comparisons in modelled outcomes between TA878/971 and current model

Intervention	TA878 – November 2022 report (mean efficacy)	TA878 in MTA model – extracted by MSD	Current model – for the overall population
	Total QALYs discounted		
No treatment	13.42	*****	12.873
Molnupiravir	Not reported – extracted by MSD using the final MTA model shared by NICE at the time: *****	*****	*****
Nirmatrelvir/ritonavir	13.56	*****	*****
Sotrovimab	13.56	*****	*****

Although cost-effectiveness estimate comparisons between trial analyses and modelling activities are heavily caveated due to different methodologies, when the time horizon of the current model is limited to 6 months with a subsequent update on drug list price the cost-effectiveness conclusions are broadly consistent. This includes comparisons for the overall population and for those at higher risk (NHS-priority categories and post-hoc subgroup analyses) versus the 70+ subgroup ICERs outputted by the model. This work demonstrates that modelled estimates (and ICERs when key inputs such as administration costs and effect estimates and baseline hospitalisation rates are corrected) are broadly comparable between TA878/971 and the current model both in the short term and in the long term with

minor deviations arising from differences in model inputs and methodology.

Scenario analysis

B11. PRIORITY QUESTION. The EAG are unable to replicate the company's results presented in the following tables reported in CS section B.3.11.3:

- CS Table 74: Trial based scenario- mortality by highest level of care
- CS Table 75: Trial based scenario- overall mortality
- CS Table 76: Alternative scenario
- CS Table 78: Trial-based scenario results for patients aged > 70 years
- CS Table 80: Trial-based scenario results for patients contraindicated to nirmatrelvir plus ritonavir
- CS Table 82: Trial-based scenario results for the immunocompromised subgroup
- CS Table 83: Base case results for patients with chronic kidney disease

These can be run by changing the subgroup selection to CKD in the settings tab

- CS Table 84: Trial-based scenario results for patients with chronic kidney disease

All scenarios can be run from the 'Scenarios' tab in the excel model. The scenarios are laid out by column and the scenarios that have 'yes' selected in row 11 will be run when the button 'Run selected scenarios" is selected. This will then generate a separate excel file with a copy of the results sheet for each of the selected scenarios.

See the table below for the names of the scenarios in the scenario tab that corresponds to each scenario.

Values used for each scenario can be found on the reset tab, the named range used for each parameter varied is shown in the table below.

Please could you clarify and tabulate the following for each of the above tables:

1. Which parameters in the model were varied for the respective scenarios?
2. What values were inserted for the parameters for each of these respective scenarios?

Please see in the inserted table below the information on the parameters varied for each scenario.

Scenario description in CS	Trial based scenario – mortality by highest level of care	Trial based scenario – overall mortality	Alternative scenario	Trial based scenario for patients aged >70 years	Trial based scenario for patients contraindicated	Trial based scenario for the immunocompromised subgroup	Trial based scenario for patients with chronic kidney disease
Scenario Name in Model	Scenario 1a overall	Scenario 1b overall	Scenario 2 overall	Scenario 1 70 Plus	Scenario 1 DDI	Scenario 1 trial Immunocompromised	Scenario 1 CDK
Parameters varied (named range used in reset sheet for scenario) Value	Hospitalization rate (rstHospTrial) 0.0916	Inpatient mortality (rstInpMort TrialOverall) 0.0917	Hospitalization rate (rstHospDiscover) 0.0282	Hospitalization rate (rstHospTrial70) 0.146	Hospitalization rate (rstHospTrialDDI) 0.1948	Hospitalization rate (rstHospTrialIC) 0.226	Hospitalization rate (rstHospTrialCKD) 0.1163
	Inpatient proportion (rstHospTrial) GW: 0.727 ICU without MV: 0.16 ICU with MV: 0.133		Inpatient Mortality (rstInpMortExpLoc) GW: 0.02 ICU without MV: 0.12 ICU with MV: 0.12	Inpatient proportion (rstHospTrial70) GW: 0.7 ICU without MV: 0.2 ICU with MV: 0.1	Inpatient proportion (rstHospTrialDDI) GW: 0.64 ICU without MV: 0.16 ICU with MV: 0.2	Inpatient proportion (rstHospTrialIC) GW: 0.833 ICU without MV: 0 ICU with MV: 0.167	Inpatient proportion (rstHospTrialCKD) GW: 0.4268 ICU without MV: 0.1429 ICU with MV: 0.4286
	Inpatient Mortality (rstInpMortTrialLoc) GW: 0.0259 ICU without MV: 0.1765 ICU with MV: 0.4167		Treatment effect based on COVID-19 related hospitalization	Inpatient mortality (rstInpMort70) 0.3	Inpatient mortality (rstInpMortDDI) 0.16	Inpatient mortality (rstInpMortIC) 0.333	Inpatient mortality (rstInpMortCKD) 0.14286
				All-cause hospitalization Treatment effect (rstTxEffectDef4) 0.83	COVID-19 specific hospitalization Treatment effect (rstTxEffectDef6) 0.66	All-cause hospitalization Treatment effect (rstTxEffectDef2) 0.37	COVID-19 specific hospitalization Treatment effect (rstTxEffectDef3) 0.45

Section C: Textual clarification and additional points

C1. The caption for CS Table 12 refers to the NICE checklist for the risk of bias assessment, not the Cochrane RoB 2 tool. Please confirm whether this is a typographic error.

This is a typographic error. The Cochrane RoB 2 tool was used to assess the risk of bias in RCT evidence.

C2. Section B.2.9.2.2 of the CS reports the outcome "COVID-19 related hospitalisation or death", citing CS Figure 18 for the results. However, CS Figure 18 is titled "COVID-19 related hospitalisation or death plus COVID-related hospitalisation" and the studies in CS Figure 18 do not match those listed in CS Table 43 for the COVID-19 related hospitalisation or death outcome. The same applies to CS Figure 19. Is this a typographical error? If not a typographical error please provide the correct forest plots for these Figures.

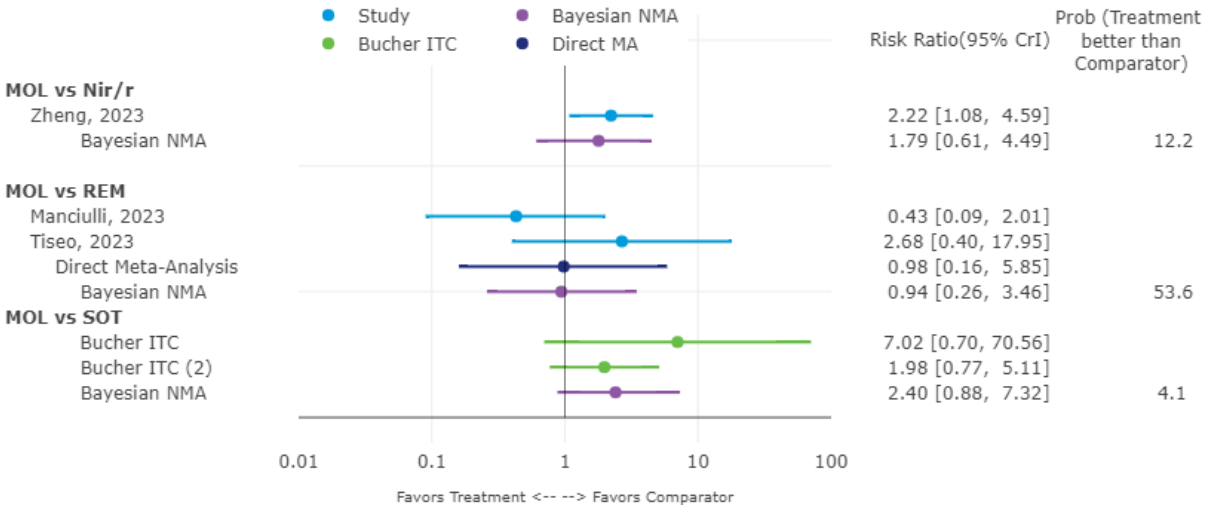
The correct forest plots for COVID-19-related hospitalisation or death RWE outcomes are provided below. The studies listed in the Figure 29 and Figure 30 also now align with those listed in Table 43 in the CS.

- The base case NMA results derived from the active treatment network suggested similar effectiveness of molnupiravir relative to all comparators in reducing the risk of COVID-19 related hospitalisation or death in outpatients with mild-to-moderate COVID (Figure 29). There was little difference in effect between molnupiravir and remdesivir with an RR of 0.94 (95% CrI: 0.26, 3.46). However, the results suggested molnupiravir was inferior to nirmatrelvir/ritonavir (RR 1.79, 95% CrI: 0.61, 4.49) and sotrovimab (RR 2.40, 95% CrI: 0.88, 7.32), although these results were not statistically significant.

- The results derived from the active treatment/control network suggested that molnupiravir reduces the risk of COVID-19 related hospitalisation or death relative to no treatment (RR 0.75, 95% CrI: 0.22, 2.60), although this result was not statistically significant (Figure 30). There appeared to be little difference in the effects of molnupiravir and remdesivir (RR 0.95, 95% CrI: 0.25, 3.50). However, molnupiravir appeared to be associated with a higher

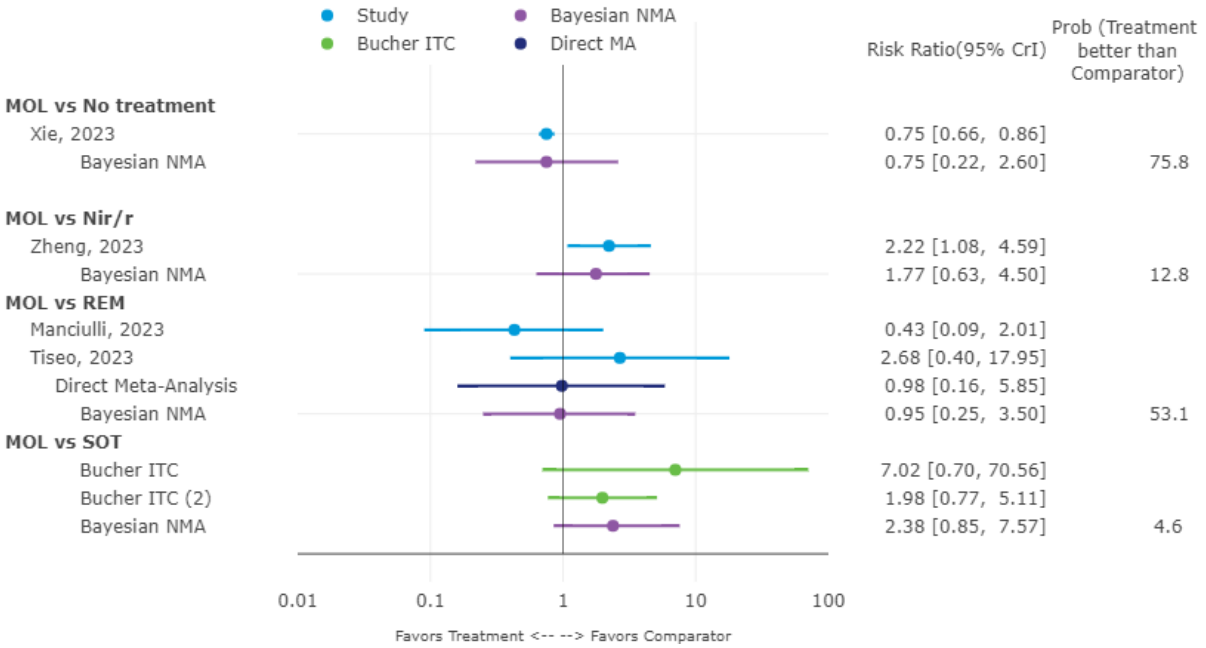
risk of COVID-19–related events compared with nirmatrelvir/ritonavir (RR 1.77, 95% CrI: 0.63, 4.50) and sotrovimab (RR 2.38, 95% CrI: 0.85, 7.57) although these findings were not statistically significant. Comparisons with no nirmatrelvir/ritonavir or no molnupiravir were not possible.

Figure 29. Active treatment evidence network NMA results for COVID-19 related hospitalisation or death (random effects)



Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir; SOT = sotrovimab

Figure 30. Active treatment/control evidence network NMA results for COVID-19 related hospitalisation or death (random effects)



Intervals are credible in Bayesian NMA and confidence intervals from individual studies.
CrI = credible interval; ITC = indirect treatment comparison; MA = meta-analysis; MOL = molnupiravir; Nir/r = nirmatrelvir plus ritonavir; NMA = network meta-analysis; REM = remdesivir; SOT = sotrovimab

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Section D: Confidential Appendix

Updated results

Base case results

Table 36. Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	1,028	16.257	12.873	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	[redacted]
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Covid-19 related hospitalisation used to inform estimates
ICER = incremental cost-effectiveness ratio; LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years

Probabilistic results

Table 37. Probabilistic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	938	16.262	12.903	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; QALYs = quality-adjusted life years

Figure 31. Probabilistic sensitivity analysis results – cost-effectiveness acceptability curve

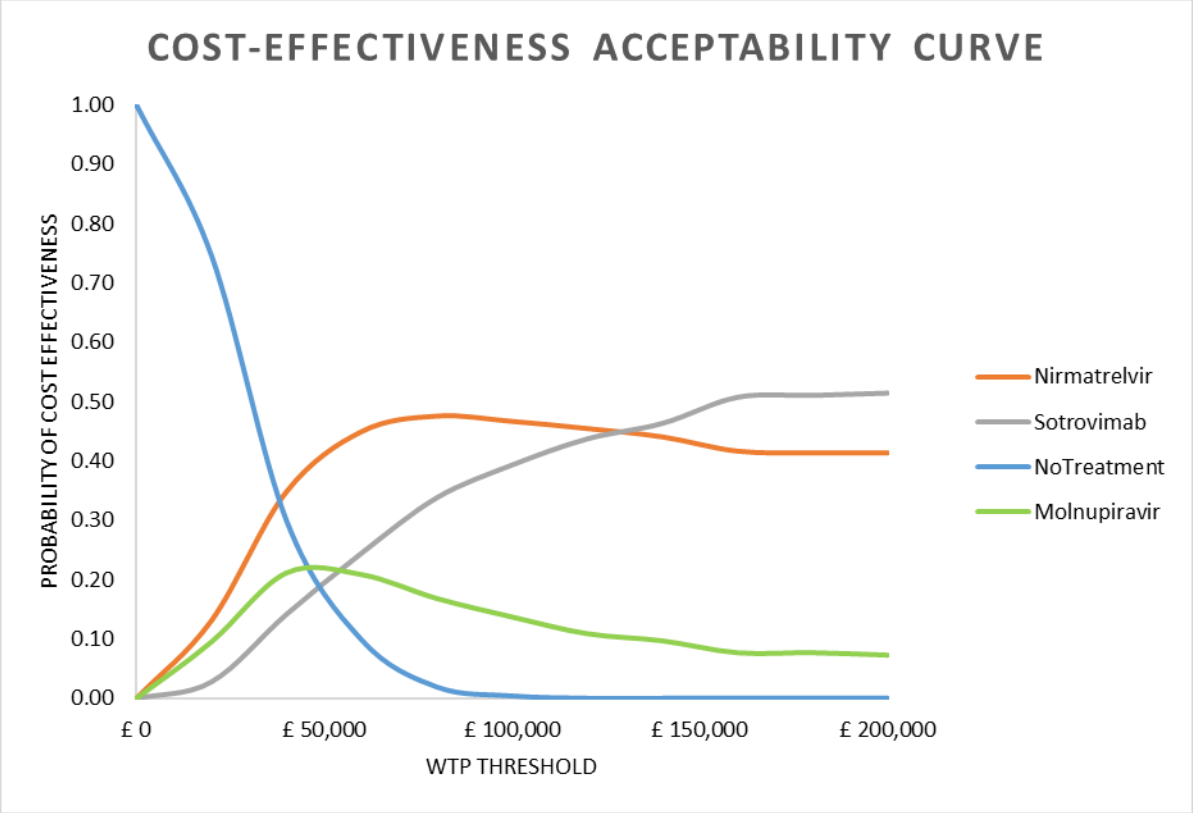

Figure 32. Probabilistic sensitivity analysis results – molnupiravir vs no treatment

Figure 33. Probabilistic sensitivity analysis results – molnupiravir vs nirmatrelvir plus ritonavir

Figure 34. Probabilistic sensitivity analysis results – molnupiravir vs sotrovimab

Deterministic results

Figure 35. Deterministic sensitivity analysis results, net monetary benefit – molnupiravir versus no treatment

NMB = net monetary benefit; qol = quality of life; SMR = standardised mortality ratio

Figure 36. Deterministic sensitivity analysis results, net monetary benefit – molnupiravir versus nirmatrelvir plus ritonavir

NMB = net monetary benefit; qol = quality of life; SMR = standardised mortality ratio

Figure 37. Deterministic sensitivity analysis results, net monetary benefit – molnupiravir versus sotrovimab

NMB = net monetary benefit; qol = quality of life; SMR = standardised mortality ratio

Scenario results

Table 38. Trial-based scenario results- mortality by highest level of care (scenario 1a)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	2,058	16.106	12.703	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	Ext Dominated
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years

Table 39. Trial-based scenario results- overall mortality (scenario 1b)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inv. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	1,021	16.236	12.858	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	[redacted]
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years

Table 40. Alternative scenario results (scenario 2: uses 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	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	877	16.263	12.888	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	Ext Dominated
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years

Table 41. Results for scenario using alternative utility values from the literature (new analysis in response to CQ B6 on utility sources not in original submission)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	1,028	16.257	12.951	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	Ext Dominated
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years

Table 42. Results for scenario using alternative utility values from the literatures and low molnupiravir prescription costs per Png et al 2024 of £9.35 (new analysis not in the original submission)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	1,028	16.257	12.951	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	[redacted]
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years

Subgroup results

Table 43. Base case results for patients aged > 70 years (subgroup selected in Setting tab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	2,313	8.011	5.721	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	[redacted]
Nirmatrelvir plus ritonavir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference

Table 44. Trial-based scenario results for patients aged > 70 years* (scenario 1 70 plus)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	2,824	7.828	5.593	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference
*Owning to data limitations and need of additional assumptions for other comparators, only comparisons of molnupiravir versus no treatment are presented for subgroup-related scenario analyses

Table 45. Base case results for patients contraindicated to nirmatrelvir plus ritonavir (subgroup selected in Setting tab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	1,059	16.254	12.869	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference

Table 46. Trial-based scenario results for patients contraindicated to nirmatrelvir plus ritonavir* (scenario 1 DDI)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	4,267	15.819	12.379	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference
*Owning to data limitations and need of additional assumptions for other comparators, only comparisons of molnupiravir versus no treatment are presented for subgroup-related scenario analyses

Table 47. Base case results the immunocompromised subgroup (subgroup selected in Setting tab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc NHB	Inc. NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	3,780	15.637	12.213	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	Dominated
Nirmatrelvir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference

Table 48. Trial-based scenario results for the immunocompromised subgroup* (scenario 1 Trial immuno)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	3,955	15.624	12.202	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference
*Owning to data limitations and need of additional assumptions for other comparators, only comparisons of molnupiravir versus no treatment are presented for subgroup-related scenario analyses

Table 49. Base case results for patients with chronic kidney disease (subgroup selected in Setting tab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc NHB	Inc NMB	ICER vs baseline (£/QALY)	ICER inc. (£/QALY)
No treatment	1,125	18.737	15.278	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref	[redacted]
Sotrovimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference

Table 50. Trial-based scenario results for patients with chronic kidney disease* (scenario 1 CKD)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. NHB	Inc. NMB (£)	ICER vs baseline (£/QALY)
No treatment	3,492	18.491	15.008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Molnupiravir	[redacted]	[redacted]	[redacted]	Ref	Ref	Ref	Ref	Ref	Ref

ICER = incremental cost-effectiveness ratio; Inc. = incremental LCLE = lower cost and lower effects; LYG = life years gained; MOV = molnupiravir; NHB = net health benefit; QALYs = quality-adjusted life years; ref = reference
*Owning to data limitations and need of additional assumptions for other comparators, only comparisons of molnupiravir versus no treatment are presented for subgroup-related scenario analyses

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Molnupiravir for treating COVID-19 [ID6340]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Clinically Vulnerable Families
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Voluntary patient and family support organisation for people at high risk of severe covid and its sequalae.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	**We have a Facebook support group with 2600 members**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Since “freedom day” we have felt abandoned. We know we are still at high risk of hospitalisation, death or severe sequalae if infected. Some of us have no immunity despite multiple vaccinations. Many of us are immunosuppressed or have conditions that leave us, or our family members ,very vulnerable to covid infections, while the rest of the world behaves as if the pandemic is over

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**There are hardly any available and, even when they are (ie Paxlovid™) , they are extremely difficult to access. Many of us are ineligible for the only available non-hospital treatment**
8. Is there an unmet need for patients with this condition?	Yes – a huge one

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**We would like access to a technology that is effective to enable us is live more normal lives.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We accept that molnupiravir may not be effective when used alone, but may be when used in combination.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with no anti-bodies or who are ineligible for treatment with Paxlovid™ might benefit from access to other effective treatments if they are available

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Most eligible patients are disabled in some way by their pre-existing conditions or by society's current response to us

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Many of us remain at high risk of severe covid infections • We live very restricted lives in our attempts to avoid infection • Few treatments are available if/when we do become infected • Knowledge that we could access other effective treatments would reduce our fears of becoming infected and help open up our lives •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Molnupiravir for treating COVID-19 [ID6340]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Royal College of Pathologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	Please fill in
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No – please confirm
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduce hospitalisations and death related to Covid-19
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Lack of progression to severe Covid-19. Improvement in signs and symptoms of Covid-19
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Variable depending on severity and risk factors – according to NICE rapid guideline: managing Covid-19
9a. Are any clinical guidelines used in the	NICE rapid guideline: managing Covid-19

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care is well defined but there is some varying opinion on whether sotrovimab should be recommended given the potential lack of efficacy with recent circulating SARS-CoV-2 variants.
9c. What impact would the technology have on the current pathway of care?	Would continue as an alternative therapy where nirmatrelvir/ritonavir and remdesivir are contraindicated.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Would continue as an alternative therapy where nirmatrelvir/ritonavir and remdesivir are contraindicated.
10a. How does healthcare resource use differ between the technology and current care?	Nirmatrelvir/ritonavir and molnupiravir both administered orally within 5 days of symptom onset. Remdesivir administered intravenously within 7 days of symptom onsent Sotrovimab – intravenous transfusion
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary or secondary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	No
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	No
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not known

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Similar to nirmatrelvir/ritonavir. Easier to administer than remdesivir or sotrovimab.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No
16a. Is the technology a 'step-change' in the management of the condition?	No

16b. Does the use of the technology address any particular unmet need of the patient population?	Oral option for high risk patients where nirmatrelvir/ritonavir or remdesivir are contraindicated
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Minimal side effects.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Hospitalisation and death
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical	No

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA878 and NICE technology appraisal guidance TA900?	No
21. How do data on real-world experience compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None known
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Oral option for treating Covid-19 in high risk patients where nirmatrelvir/ritonavir or remdesivir are contraindicated • Evidence of reduction in hospitalisations and death related to Covid-19 in unvaccinated individuals • Evidence of faster time to recovery from Covid-19 •

Thank you for your time.

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Single Technology Appraisal

Molnupiravir for treating COVID-19 [ID6340]

Professional organisation submission

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- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	UK Clinical Pharmacy Association (UKCPA)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? Yes or **No** Other (please specify):
5a. Brief description of the organisation (including who funds it).	*UKCPA provides opportunities for networking, collaborations, sharing best practice and inspiring innovation among the clinical pharmacy community. The organisation provides education and community support to pharmacists and pharmacy technicians in the UK and beyond. Funding is provided by membership fees with commercial sponsorship for specific events*
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Aim of treatment is to prevent severe covid-19 illness, resulting in hospitalisation or long-term disability
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in hospitalisation rate of 5%
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the only other oral treatment has significant interaction possibility

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Via Paxlovid treatment or sotrovimab/remdesivir. Sotrovimab has uncertain efficacy due to genomic mutation, both sotrovimab and remdesivir require intravenous treatment making them unavailable in the timespan required
9a. Are any clinical guidelines used in the	Current NICE guidelines, based on WHO guidelines

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined, although interpretation of NICE NG191 criteria for severe risk may vary as to what constitutes significant risk for severe coid-19.
9c. What impact would the technology have on the current pathway of care?	An alternative to oral Paxlovid where this cannot be used due to drug interactions
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	Reduction in the need for IV therapy where oral Paxlovid can be used
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary care when resourcing allows, currently secondary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Negligible

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, current care is complex IV therapy where Paxlovid is unavailable
11a. Do you expect the technology to increase length of life more than current care?	Yes, for the group of patients who cannot use Paxlovid
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, the impact of long covid needs be considered for patients who cannot access IV sotrovimab and cannot use oral Paxlovid
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As above

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Negligible

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The impact of covid-19 on medium to long-term disability e.g. from long covid needs to be considered as part of the QALY calculation
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, only alternative to pharmacokinetically boosted antiviral
16a. Is the technology a 'step-change' in the management of the condition?	No

16b. Does the use of the technology address any particular unmet need of the patient population?	Patients on chemotherapy and other medicines which are adversely impacted by use of ritonavir in Paxlovid
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Negligible side effects

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes although based on different variants of covid-19
18a. If not, how could the results be extrapolated to the UK setting?	n/a
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Hospitalisation – yes Long-term disability – no
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were	No

not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA878 and NICE technology appraisal guidance TA900?	No
21. How do data on real-world experience compare with the trial data?	Anecdotal evidence of similar impact when introduced during the pandemic, uncertain impact now we have less severe variants of the virus

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not to our knowledge
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Only one other oral treatment exists, which is hampered by complex drug interactions • Only IV therapies are available where Paxlovid is contraindicated • Drug interactions are common with many of the high risk factor conditions for which antiviral treatment is indicated • •

Thank you for your time.

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Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Molnupiravir for treating COVID-19 [ID6340]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating COVID-19 and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	David Lowe
2. Name of organisation	1. Royal Free London NHS Foundation Trust 2. University College London 3. British Society for Immunology
3. Job title or position	
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with COVID-19? ☐ A specialist in the clinical evidence base for COVID-19 or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for COVID-19?	1. To prevent progression to hospitalisation in very high risk individuals.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	2. To prevent chronic infection in the highly immunosuppressed and thereby reduce the risk of poor long-term clinical outcomes and evolution of novel variants. 3. To treat those people who already have established chronic infection. 4. To reduce serious complications and mortality in those admitted to hospital.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	In reference to the answer to Question 8: - In Group 1, full recovery with prevention of hospitalisation, death or other serious adverse outcome. - In Group 2, sustained viral clearance. - In Group 3, sustained viral clearance. - In Group 4, full recovery with prevention of death or other serious adverse outcome.
10. In your view, is there an unmet need for patients and healthcare professionals in COVID-19?	The major unmet need is the treatment of chronically infected patients, for whom there are currently no approved antivirals. There is also a need for preventative strategies in those patients who fail to respond to SARS-CoV-2 vaccination but who do not otherwise have an indication for normal human immunoglobulin replacement therapy.
11. How is COVID-19 currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Clinical guidelines exist including NICE TA878 and NG191. The guidelines are relatively well defined but the roles for antivirals are not clearly explained beyond the first 5-7 days of illness. This is of unlikely to have a significant impact on most patients but is important for those who are highly immunosuppressed. The guidelines also do not consider combination therapies. Consequently, there is variation between centres in the management of immunosuppressed patients with persistent symptomatic COVID-19 both in hospital and the community.

• What impact would the technology have on the current pathway of care?	Molnupiravir is already included within the guidelines, generally as a fourth line treatment.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Molnupiravir only has a limited role in the current guidance and I do not anticipate that changing substantially.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Molnupiravir only has a limited role in the current guidance and I do not anticipate that changing substantially.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Molnupiravir would rarely be the preferred first option for treatment of COVID-19. In the general population, molnupiravir does not reduce hospitalisation or death (see PANORAMIC results, PMID: 36566761). There are some modest benefits in terms of time to recovery, contact with healthcare (PMID: 36566761) and persistent symptoms to 6 months (PMID: 39265595) but these are unlikely to justify the cost and need to be balanced against potential unintended consequences eg blunting of boost to SARS-CoV-2 spike antibody from natural infection and greater persistence of often heavily mutated virus to Day 14 (PMID: 38396069).

	There may be a role in eg healthcare workers during a severe outbreak to reduce time off work, but this would hopefully be avoided by vaccination campaigns and molnupiravir would likely to be second choice to eg nirmatrelvir/ritonavir. Highly immunosuppressed patients continue to need treatment either acutely or in those with established chronic infection. However, molnupiravir is mutagenic and the risk of persistence of mutated virus following treatment is even higher in this group. While it is reasonable to keep molnupiravir as a treatment option in these patients (eg where other treatments are contraindicated), research should be done to investigate longer treatment courses or combination therapies and whether these achieve viral clearance.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Molnupiravir has fewer contraindications and interactions than eg nirmatrelvir/ritonavir and is oral which confers advantages versus eg remdesivir and therapeutic monoclonals. It is therefore the easiest licensed COVID-19 treatment to use. However, it cannot be given to pregnant women.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Eligibility should be restricted to those with proven SARS-CoV-2 infection, high risk of poor outcome and where other treatments are contraindicated.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	If molnupiravir (including the use of an extended course or in combination with other therapies) is able to effectively clear infection in immunosuppressed patients, especially those with established chronic infection, this will reduce intra-host evolution and the risk of new variants.

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Even a small reduction in time off work may be beneficial for eg healthcare workers in a severe outbreak, and this is unlikely to be captured by QALY calculation.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	At this stage, molnupiravir cannot be considered innovative. However, it is one of only a few licensed RdRp inhibitors.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are relatively rare and tend to be mild but it is potentially teratogenic.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Most clinical trials on which licensing decisions were based were performed earlier in the pandemic with (a) no widespread vaccination and (b) more virulent SARS-CoV-2 variants. They were also performed in mostly immunocompetent participants. The results from these studies are therefore no longer relevant to the current situation. The most important trial performed in a mostly vaccinated population infected with omicron variants is PANORAMIC. However, the study population of PANORAMIC does not reflect the groups currently approved for antiviral treatment as it was considered unethical to potentially withhold antivirals from the highest risk individuals. I am not aware of any robust prospective trials on the use of molnupiravir (or other COVID-19 therapeutics) in the groups for whom it is currently approved,

	i.e. highly immunosuppressed or otherwise very high-risk individuals. Ideal trial design would include comparison of different therapies, assessment of combination treatment and of extended courses of treatment. The key outcome in immunosuppressed individuals is viral clearance to prevent long-term lung damage and the evolution of novel variants. This differs from current trial outcomes which tend to focus on early hospitalisation and death. Previous applications to run these trials to eg NIHR have been declined.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, but I would recommend considering lower quality evidence in immunosuppressed participants and/or chronic infection, where numbers are relatively low and prospective trials have not been performed.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA878] and TA971?	The most important new evidence for nirmatrelvir-ritonavir is: Hammond J, Fountaine RJ, Yunis C, et al. Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19. *The New England journal of medicine* 2024; **390**(13): 1186-95 The following recent papers may also be relevant: - Hsu CK, Hsu WH, Shiau BW, et al. The effectiveness of novel oral antiviral treatment for non-hospitalized high-risk patients with COVID-19 during predominance of omicron XBB subvariants. *Expert Rev Anti Infect Ther* 2024: 1-8. - Schilling WHK, Jittamala P, Watson JA, et al. Antiviral efficacy of molnupiravir versus ritonavir-boosted nirmatrelvir in patients with early symptomatic COVID-19 (PLATCOV): an open-label, phase 2, randomised, controlled, adaptive trial. *Lancet Infect Dis* 2024; **24**(1): 36-45.

	- Wongnak P, Schilling WHK, Jittamala P, et al. Temporal changes in SARS-CoV-2 clearance kinetics and the optimal design of antiviral pharmacodynamic studies: an individual patient data meta-analysis of a randomised, controlled, adaptive platform study (PLATCOV). *Lancet Infect Dis* 2024; **24**(9): 953-63 - Bai F, Beringheli T, Vitaletti V, et al. Clinical Outcome and 7-Day Virological Clearance in High-Risk Patients with Mild-Moderate COVID-19 Treated with Molnupiravir, Nirmatrelvir/Ritonavir, or Remdesivir. *Infect Dis Ther* 2024; **13**(7): 1589-605 - Butt AA, Yan P, Shaikh OS. Nirmatrelvir/ritonavir or Molnupiravir for treatment of non-hospitalized patients with COVID-19 at risk of disease progression. *PLoS One* 2024; **19**(6): e0298254 - Esmaeili S, Owens K, Wagoner J, Polyak SJ, White JM, Schiffer JT. A unifying model to explain frequent SARS-CoV-2 rebound after nirmatrelvir treatment and limited prophylactic efficacy. *Nature communications* 2024; **15**(1): 5478. I also have the unpublished data from PANORAMIC on nirmaltrelvir-ritonavir (including the virology/immunology substudy) and from LUNAR (looking at virological and clinical outcomes following sotrovimab administration to immunosuppressed patients). I could share these at the meeting if the sponsors consent.
23. How do data on real-world experience compare with the trial data?	As mentioned previously, most of the placebo-controlled, double blind trial data are no longer relevant to the current real-world situation. PANORAMIC is the most relevant trial for current patients but there is a lack of high quality evidence for the highest risk patients.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this	Molnupiravir is contraindicated in pregnant women and females of childbearing potential are required to perform a pregnancy test before taking the medication. There are insufficient data for children.

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Molnupiravir is unlikely to confer significant benefits for most people.

There remains a potential role in the highest risk patients where other treatments are contraindicated.

However, there are insufficient data on highly immunosuppressed individuals and there is a risk of persistence of highly mutated virus following the use of molnupiravir which may facilitate the evolution of novel variants; viral clearance should be investigated in this group, including with prolonged and/or combination treatment.

Most robust randomised, placebo-controlled trial data are no longer relevant to the current clinical situation due to widespread vaccination and changes in dominant viral variants.

Molnupiravir appears to confer modest improvements in time to recovery and long-term symptoms, making it a potential treatment option for eg healthcare workers in the context of a severe outbreak.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Molnupiravir for treating COVID-19 [ID6340]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with COVID-19 or caring for a patient with COVID-19. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with COVID-19

Table 1 About you, COVID-19, current treatments and equality

1. Your name	Robbie Burns
2. Are you (please tick all that apply)	☒ A patient with COVID-19? (Twice) ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with COVID-19? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Cardiothoracic Transplant Patient Group
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	I Chair the Cardiothoracic Transplant Patient Group which includes over 20 stakeholder organisations and numerous patients from across the country. I liaise with heart and lung transplant patients on a daily basis. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with COVID-19? If you are a carer (for someone with COVID-19) please share your experience of caring for them	In February / March 2024, the CTPG undertook an online patient survey relating to COVID-19. The survey scope was only for people (or carers of people) who had received a heart and / or lung transplant. 252 completed surveys were received which represented 6.2% (6.4% lungs & 6.1% hearts) of the 4,080 people living in the UK following a heart and or lung transplant. The patient survey investigated this issue, focusing on people's current lifestyle adjustments to reduce the risk of catching COVID-19. Firstly, the survey asked people the following question, "On a scale of 1-10 how would you describe your lifestyle to avoid catching COVID-19. 10 would be behaving as you did during the height of the COVID-19 pandemic restrictions. 1 would be your behaviour is the same as it would be if COVID-19 didn't exist." A complete spectrum of responses were received, with a mean score of 5.7. Each number received at least 6% of the overall total with the top three being 8 (15.5%), 5 (14.7%), 7 (13.1%). The lowest was 1 with 6.0%. The mean for lung transplant recipients (5.9) was higher than heart recipients (5.6).

	The survey asked specific questions about behaviours to avoid catching COVID-19, as follows, with the positive responses in brackets; Wearing a mask in busy places (46%) Frequent hand washing and / or gelling (73%) Avoiding people who are unwell (89%) Avoiding or reducing my visits to busy indoor places, such as a pub, theatre, cinema, club etc (54%) Reducing my time socialising with friends or family (27%) Sometimes asking people to take a COVID-19 test before I meet them (33%) Trying to only meet people outside (22%) The overwhelming majority of cardiothoracic transplant patients continue to make lifestyle adjustments to avoid catching COVID-19, with over half of patients reporting behaviours closer to full COVID-19 lockdown than acting pre COVID-19 pandemic. Many patients are reporting high levels of anxiety, fear, and depression with poor quality of life. The survey offered an opportunity for respondents to provide a narrative regarding the benefit an effective prophylactic COVID-19 treatment would have on their mental and physical wellbeing. Many took the opportunity to describe their current quality of life due to COVID-19, below are a sample. “Shielding at home is so destroying. I am such an outgoing person and had such a wonderful social life. Now I feel like I’ve been left behind, I do the same thing more or less every day and just feel a prisoner in my own home.” “I am currently treated for depression and anxiety, because of social exclusion from fear of catching COVID, becoming seriously ill or dying and the impact this would have on my loved ones.”

	"I don't think I have the words to adequately describe the mental load of thinking about catching covid again." "Still shielding with no protection after 4 years.Lost everything." Greig et al (2024) (Exploring the attitudes of solid organ transplant recipients towards COVID-19 shielding communications and the language of 'clinically extremely vulnerable': a qualitative study investigating lessons for the future | BMJ Public Health) explored the attitudes of solid organ (including heart) transplant recipients towards COVID -19 shielding and communications. Greig's findings corroborated those of the patient survey; "for these participants, despite the fact both shielding and mask regulations had ended months prior to them being interviewed, the fear and anxiety they continued to feel towards COVID-19 was clear. Again, this fear relates to leaving one's home and coming into contact with others, resulting in many participants continuing to self-impose shielding and mask wearing. Hence, while COVID-19 restrictions may have come to an end, their impact—both in terms of how people feel and in terms of how people act persists"
7a. What do you think of the current treatments and care available for COVID-19 on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The CTPG patient survey asked several questions around the responsiveness of COVID-19 treatments and care, and the overall opinion of the NHS COVID-19 treatment services. The survey first asked whether patients were aware of how they obtained free COVID-19 test kits. This is fundamental to proceeding to treatment as this is the only out of hospital route to confirming COVID-19 infection. Since November 2023 eligible patients in all nations apart from Scotland obtain free COVID-19 test kits from pharmacies. The CTPG survey revealed that 44% of patients were unaware that is how they now obtained test kits, 30% had encountered difficulties with

	obtaining them from pharmacies and the smallest proportion, 26%, had been able to obtain test kits from pharmacies. The CTPG are extremely concerned with this survey result and believe that eligible patients were not informed of the change at an individual level, which had been the case with prior changes to the COVID-19 care pathway. The CTPG survey asked patients who had been infected with COVID-19 since the introduction of community-based treatments (January 2022) and wanted to receive a treatment whether they had received treatment and if it had been within the effectiveness window of 5 days since symptom onset. 78% of people reported that they had received treatment within 5 days, 11% received treatment after 5 days and 11% were unable to receive a treatment due to system failures. Patients in the latter two categories were asked why they were unable to receive treatment in a timely manner. Multiple reasons were provided, with no overarching common point of failure. However, lack of weekend provision and the inability to provide staff for a Sotrovimab infusion were the most frequently mentioned. The CTPG patient survey asked patients and carers what they thought of the NHS funded treatments and care for COVID-19. The survey offered five responses and the breakdown was as follows, excellent (13%), good (33%), average (34%), poor (10%) and very poor (9%). The results reveal a wide range but with a positive rather than negative tendency. People were also offered the opportunity to provide a narrative on why they gave the rating. Many were positive, for example, “Excellent service, within 4 hours of 1st call to say I had COVID i had managed to book to get antivirals”. Some however, were negative, “It’s difficult to access treatments, most staff at 111 haven’t heard of it, GP’s and hospitals have different interpretations and patients are left caught in the middle”. Based on the patient survey and reports from

	multiple patients and patient support groups, the quality and responsiveness of COVID-19 treatment appears to be dependent on the patient's ICS / nation.
8. If there are disadvantages for patients of current NHS treatments for COVID-19 (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The challenges revolve around the ability to access the treatment across the country rather than the treatments themselves. Since the devolution of COVID 19 treatments to ICSs, it has become a lottery.
9a. If there are advantages of molnupiravir over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does molnupiravir help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	No The CTPG understand that previous assessments of Molnupiravir did not show a benefit over Sotrovmiab. Indeed, the CTPG believe they showed the Molnupiravir to be inferior to Sotrovimab at reducing the risk of severe COVID-19 and suffering long term effects. As a patient expert I am probably not the best placed person to assess whether this still holds true. It would be extremely helpful if the clinical experts on the NICE Committee would objectively assess Molnupiravir against Sotrovimab. If Molnupiravir remains inferior to Sotrovimab we see no advantages of the treatment.
10. If there are disadvantages of molnupiravir over current treatments on the NHS please describe these. For example, are there any risks with molnupiravir? If you are concerned about any potential side effects you have heard about, please describe them and explain why	On the basis that Molnupiravir remains inferior to Sotrovimab the CTPG would be extremely concerned that if approved by NICE, ICSs may choose to prescribe Molnupiravir to treat COVID 19 in post-transplant patients in preference to the more effective Sotrovimab.

11. Are there any groups of patients who might benefit more from molnupiravir or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering COVID-19 and molnupiravir? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	On the basis that Molnupiravir remains inferior to Sotrovimab, the CTPG is extremely concerned that in patients where Paxolovid is contraindicated (e.g post-transplant), some ICSs would choose to prescribe the tablet Molnupiravir rather than organise a Sotrovimab infusion. The CTPG believe that if Molnupiravir is approved it will disadvantage some post-transplant patients.
13. Are there any other issues that you would like the committee to consider?	Yes, whilst most eligible patients have been able to receive appropriate treatment in a timely manner, some have not.

	ICS and patient expertise are key factors in this. Knowledgeable patients, able to advocate for themselves are showing local COVID-19 treatment teams, NICE guidance to be able to access treatment. Some local teams have very poor knowledge of the treatments they are prescribing and importantly not prescribing. Examples include, - Prescribing Paxlovid to patients who are contraindicated - Prescribing Molnupiravir instead of Sotrovimab – despite NICE guidance and NHSE Clinical Management Guidelines (3.11) - Refusing treatment for mild COVID-19, stating that it is only used for severe disease.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- If Molnupiravir is inferior to Sotrovimab, the CTPG believe that Molnupiravir approval will disadvantage some patients who have had either a heart and / or lung transplant
- Some patients are not receiving the current recommended NICE treatments for COVID-19 due to poorly organised and clinically ignorant local teams.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Patient expert statement

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Molnupiravir for treating COVID-19 [ID6340]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with COVID-19 or caring for a patient with COVID-19. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **04 October 2024** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with COVID-19

Table 1 About you, COVID-19, current treatments and equality

1. Your name	Susannah Thompson
2. Are you (please tick all that apply)	☒ A patient with COVID-19? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with COVID-19? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Long Covid SOS
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Knowledge of others with Long covid, including those who have taken Molnupiravir for acute covid episodes.

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with COVID-19? **If you are a carer (for someone with COVID-19) please share your experience of caring for them**	My experience of living with Covid-19 is that I contracted it in April 2020 and have never recovered. Prior to contracting Covid-19 I took no medications, was actively and healthy. I had had asthma as a child but not taken inhalers for 20 yrs. When I was first ill with Covid-19 I was sleeping 20hrs or more a day and could only just about make it a few metres walk to the bathroom and would have to wait a couple of hours laying on the floor to have the energy to return to bed. I had oxygen levels that dipped to 92% after any activity i.e. standing up or walking a few steps. At the time I was working as a doctor in the covid response so I did not attend hospital as I could monitor my oxygen levels at home. With hindsight I should have attended to rule out any kind of blood clot etc causing the drop in oxygen levels. I was exhausted and had pain in my joints and limbs which has continued for 4.5 yrs so far. Imagine those horrible pains during the worst episode of flu and having them every single day. Varying intensity and location. At time it will be so excruciating I cannot think of anything else other than needing it to stop or decrease. I try my best to ignore the pain during the day, with distraction, reframing. The pain I get is similar to a lot of people during and following a covid -19 infection Every single day I am in pain it can be some or all of the following types of pain every single day.

	1) Pain in any muscle I have used in the previous 48hrs, typing and dictating this means I will be unable to chew for a couple of days because my mouth muscles will be too fatigued and painful. I will also struggle to use my hands in any way for a week. 2) Pressure, hot poker pain in my joints and pain that makes it feel like they will burst. 3) Pain that feels deep in the bones in my limbs, so bad that I had a dental abscess and it did not compare to the pain I have normally. I say that to make it easier to understand for someone who has not experienced it. If it is severe I have pain medications, I can take, but if I take them too often they upset my breathing and give me ingestion. Every new covid-19 infection comes with a risk of worsening intensity of pain. Ever since my Covid-19 infection my heart rate has gone to fast on standing and sitting up, or on eating. My average heart rate was 100 bpm on a 48hr constant ECG. I get chest pains on standing or sitting for too long for which I take medications to slow my heart rate and raise my blood pressure and also dilate blood vessels to the heart. I use a wheelchair inside and outside my house due to the fatigue, pain and PoTs (postural tachycardia syndrome) . I have a stair lift because I am unable to climb the stairs. I have lost my cognitive function; I get easily overwhelmed by noise and light and struggle to follow a conversation. I can answer questions, but I often have word finding difficulty, or am slow in my speech, and commonly forget things in the middle of conversations. I need to take regular breaks and sleep and rest a lot. I can plan to do an activity, i.e. join an online meeting but I will need 2-3 days afterwards to recover and rest otherwise I will dip and get worse again.

	I have reached a steady state but if I do more then I get worse. In august 2023 I did not rest as much as I should, and it's been over 12 months and I am not back to what I thought was my baseline. Sometimes I have flares of symptoms when the duvet is too heavy, I can't even lift it to get out of bed, it's like I am a prison in my body those times. The most recent one 2 months ago I was unable to eat for 5 days. There is a fear of getting further infections and getting worse. The pain and having to lay on the floor for a couple of hours to be able to return to bed are the worst parts of those. If I get symptoms of covid-19 acute infection I would love the opportunity to be given an antiviral to prevent worsening of my symptoms because it appears it's very likely each time, I get worse, I don't recover to the point I was at previously. I have been in close contact with multiple people who have long covid, i.e. never recovered from their Covid-19 infection. I am unable to have covid-19 vaccinations because I had an allergic reaction to the vaccine, and I had a significant worsening of symptoms in Feb 2021 triggered by the vaccine.
7a. What do you think of the current treatments and care available for COVID-19 on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I think this is a difficult question because there is no evidence that those of us with "long covid" have cleared the infection. It could be like chicken pox, hepatitis C etc and live in our bodies meaning we are currently infected with it and a trial of antiviral medication could potentially improve symptoms or even cure the condition. The current treatment for Covid-19 acute infections seems to vary greatly depending on the area, it is unclear to most people who might be at risk how to get

	treatment and is quite common to take days after contacting a specialist team etc to get a return phone call and eventually antivirals for those who meet the current criteria. There is a big question that is important and needs to be answered around those with long covid. Lots of those with long covid now sadly meet the criteria because their covid infection has left them with autoimmune diseases and heart disease amongst others. For a number of these this was on their second, 3rd, or even 5th covid infection, they already had long covid, but a subsequent infection left them with even more damage. **There is a good argument if people with long covid are considered at risk, because their bodies have been proved to be damaged by the virus then treatment for acute covid-19 infection could reduce morbidity and improve quality of life.** I know personally several people with long covid who had managed to return to work, like myself, I returned in a wheelchair initially, who then after a subsequent infection were no longer able to work. There are some treatments for long covid, but I think this is getting outside of the scope, but I would be happy to comment on them if useful.
8. If there are disadvantages for patients of current NHS treatments for **COVID-19 (for example, how they are given or taken, side effects of treatment, and any others) please describe these**	Vaccines are used as a preventative measure but there are also side effects from vaccines – some people allergic etc. some given long covid symptoms from vaccine. Current treatments for acute covid-19 Access to treatments is variable, post code lottery, difficulty with lack of testing, lack of knowledge how to access antivirals especially out of hours/weekends etc. Then for those that require hospitalisation, there is the fear of catching other illnesses, being teased for wearing mask asking for ventilation etc.

9a. If there are advantages of molnupiravir over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does molnupiravir help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Unexplored advantage of if it could treat long covid caused by persistent virus. Advantage to patients who have been showed to be at risk of covid, saving lives, would be nice to think reduced morbidity but seems unknown. Specifically people with Long covid who I have spoken to and have taken molnupiravir report that their acute covid infection lasted less than the times they did not take molnupiravir and that they also found an increase in their baseline, i.e. reduction of long covid symptoms. Compared to worsening of long covid symptoms persisting after acute infection when not given molnupiravir or anything for an acute covid infection. Potential treatment of long terms symptoms and reduction of worsening/relapse by repeated infection, prevention of morbidity and mortality from ongoing covid-19 infection Being accessible at home would be a big advantage to someone who is housebound as friend or family could collect the medication/it could be delivered and there is no risk associated with travel and being in a hospital environment.
10. If there are disadvantages of molnupiravir over current treatments on the NHS please describe these. For example, are there any risks with molnupiravir? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I've not heard of any, other than difficulty accessing and lack of long covid as an "at risk " category.
11. Are there any groups of patients who might benefit more from molnupiravir or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Those who would struggle to get to the hospital. Or who have poor veins etc. those who are already at risk of harm, housebound, as someone else could go and get the medication, reduces risk of contracting further illness from being in hospital environment, especially those immunocompromised etc.
12. Are there any potential equality issues that should be taken into account when considering COVID-19	Those with disability may struggle to access treatment, through lack of knowledge and awareness of its existence. Difficulty accessing health care, testing etc. would

and molnupiravir? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	also apply to those from disadvantaged communities, with a lack of knowledge in the community about treatment available. Difficult of those with poor hearing/deafness/cognitive processing issues accessing the correct place to request antivirals and to have a telephone consultation.
13. Are there any other issues that you would like the committee to consider?	To consider that Long covid/post covid-19 syndrome (although there is no evidence it is post covid syndrome because it could well be due to viral persistence, like in other viruses i.e. chicken pox that live in the body). It **should be considered that those with long covid are at increased risk of harm from covid-19 infections because they are proven to have been harmed already by it. And many get worse after subsequent infections.** From research by long covid support and long covid kids: **"Reinfection worsens the symptoms of Long Covid in the majority those who are still symptomatic. Of those who still had Long Covid at the time of reinfection:** **- 80% had a worsening of symptom severity** **- 85% had either a return of old symptoms or new additional symptoms**

	Of those who were in recovery or remission, reinfection causes a recurrence of Long Covid in 60%."

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Having a tablet which can be delivered/collected by those other than the patient would improve accessibility.
- Not needing to go into hospital makes it more accessible and gives less chance of picking up other infections to immunocompromised/vulnerable individuals.
- There is likely to be a postcode lottery on access and there is a health inequality issue around accessing covid testing and knowing there is anti-viral treatment available
- Long Covid/post covid syndrome, could well mean that the virus is still present so a trial of antiviral should be considered
- Those with Long covid/post covid syndrome are proven to be harmed by the virus they should be clearly in the at-risk group, research shows the majority get worse with a further covid infection so it could be recommended they are covered under one of the existing headings of "at risk" .
- Click or tap here to enter text.

Thank you for your time.

Patient expert statement

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Molnupiravir for COVID-19 (ID6340)

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Date completed	5th September 2024 (version with updated prices)
Source of Funding	This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number NIHR167175.

Acknowledgements

We thank the following for providing expert clinical advice to the project team and for reading and commenting on a draft of the report:

Dr Emanuela Pelosi, Consultant Medical Virologist and Director of Southampton Specialist Virology Centre, University Hospital Southampton NHS Foundation Trust.

Dr Eleri Wilson-Davies, Consultant Medical Virologist, University Hospital Southampton NHS Foundation Trust.

Dr Adhyana Mahanama, Consultant Medical Virologist, University Hospital Southampton NHS Foundation Trust.

Ms Harriet Launders, Anti-Infectives Pharmacist, University Hospital Southampton NHS Foundation Trust.

We also thank Jo Lord Keith Cooper, and Emma Maund, Southampton Health Technology Assessments Centre (SHTAC), for reading and commenting on a draft of this report for quality assurance.

Declared competing interests of the authors and advisors

The authors and clinical experts declare that they have no conflicts

Rider on responsibility for the report

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.

This report should be referenced as follows:

Ribeiro, I., Woods, L.E., Kalita, N., Scott, D.A., Frampton, G. Molnupiravir for COVID-19 (ID6340). A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2024.

Contributions of authors

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

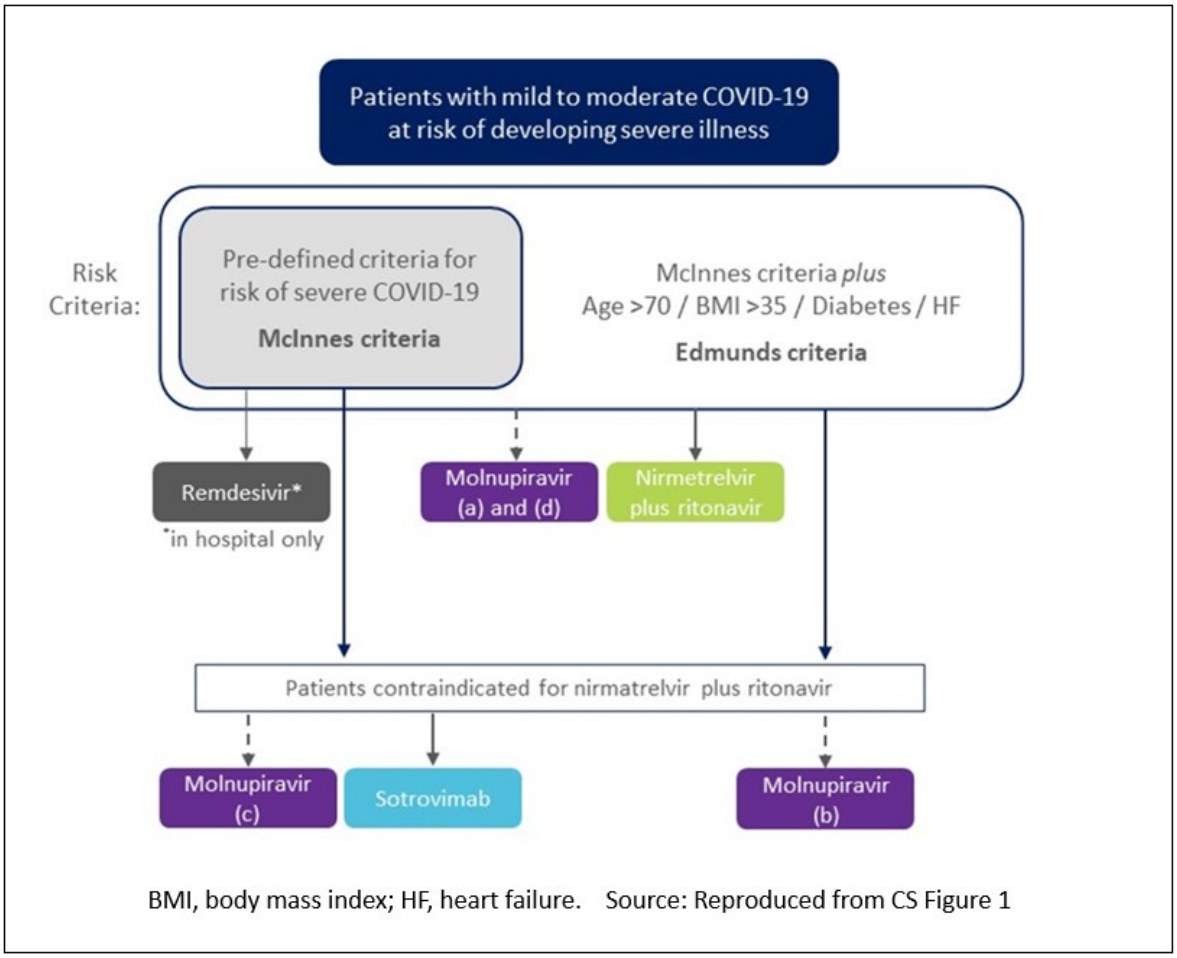
(high risk of severe disease is defined according to the updated Independent Advisory Group Report, i.e. the Edmunds Report, discussed above in section 2.2.1):[11]

- 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.



BMI, body mass index; HF, heart failure. Source: Reproduced from CS 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 4. 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 0 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.

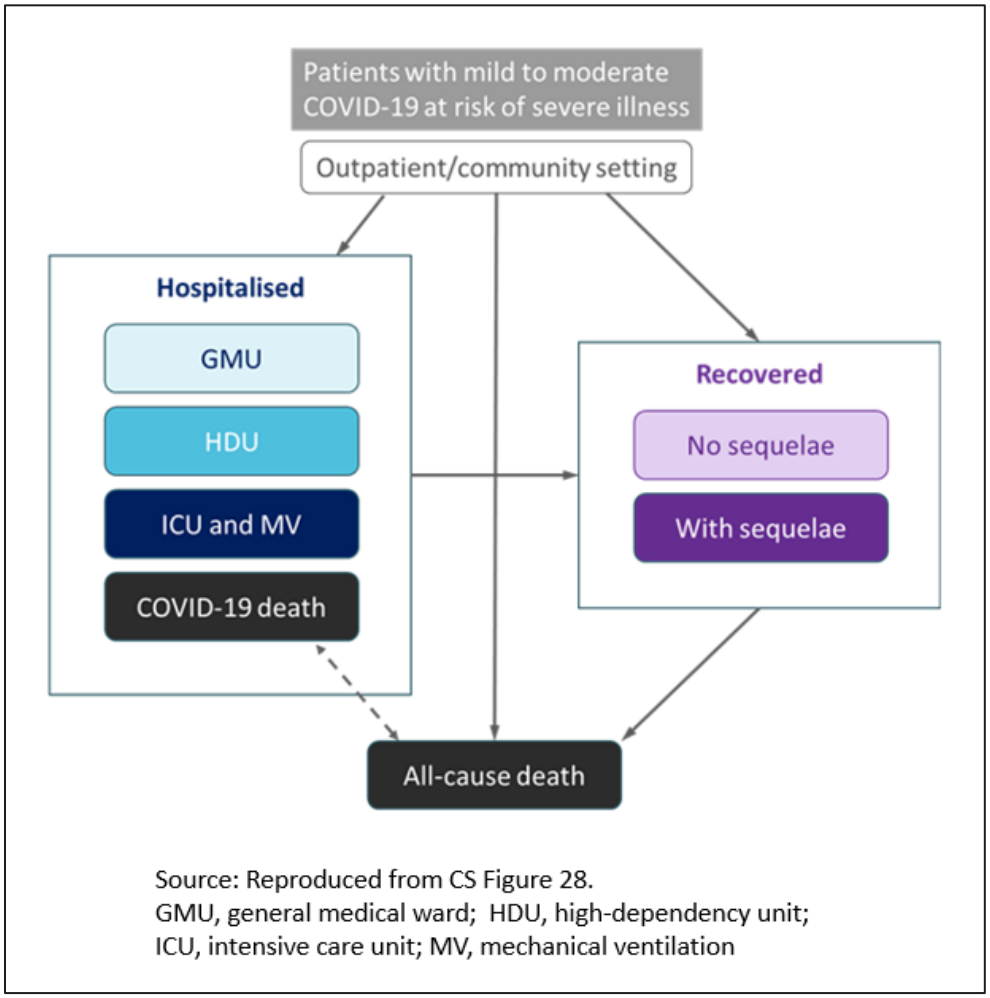


Figure 2 Schematic of the model structure

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 Clarification 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

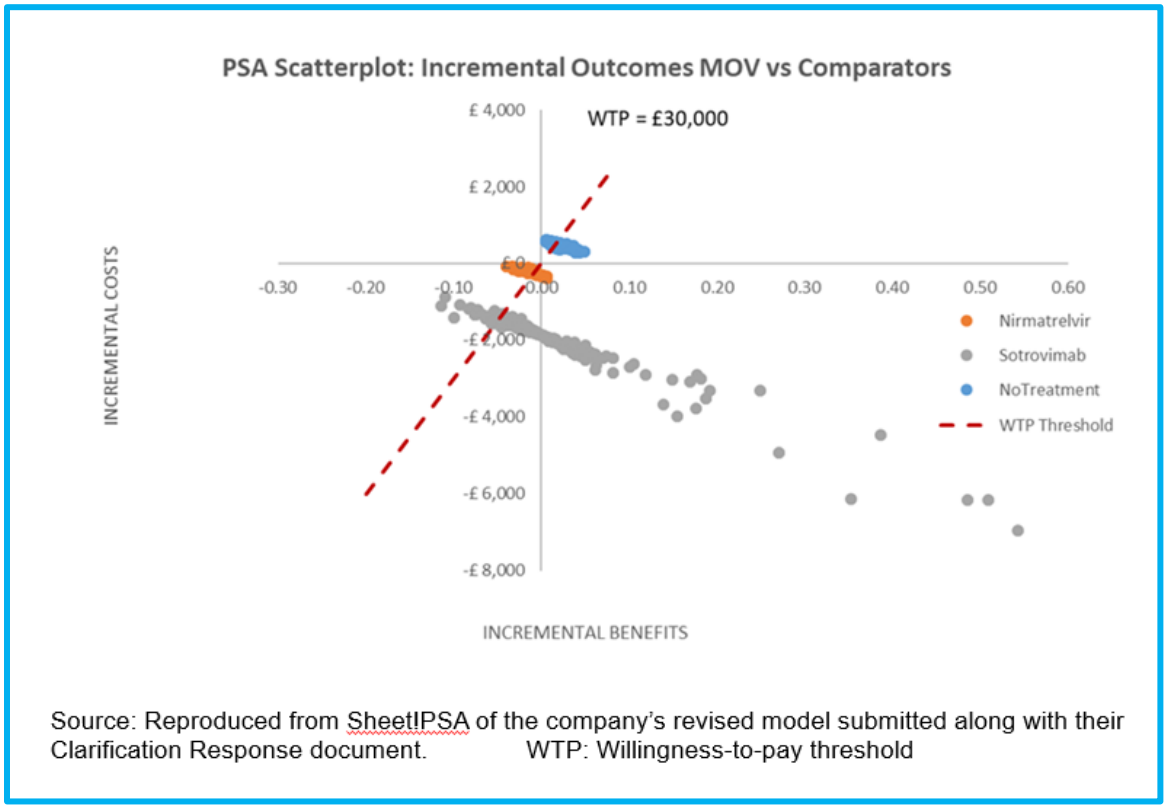


Figure 3 Scatter plot, revised company's model base case

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

Single Technology Appraisal

Molnupiravir for treating COVID-19 [ID6340]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 23 August 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Please note that page numbers cited in the EAG response refer to the EAG Report version with track changes displayed

Introduction and background

Issue 1 Recruitment into PANORAMIC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that patients who are ineligible for any of the first- to fourth-line treatments in the clinical care pathway on page 19 could have been recruited to the PANORAMIC trial (page 19).	For clarity, amend wording to reflect that patients at highest risk of progression to severe COVID-19 would not be recommended for the PANORAMIC trial, despite being ineligible for treatment with first- to fourth- line treatments. As noted by the authors of the PANORAMIC study: "*Patients with COVID-19 who were extremely clinically vulnerable, although eligible for participation in PANORAMIC, were referred and encouraged to access and be considered for monoclonal antibody or antiviral treatment directly from the NHS. Our findings might therefore be less applicable to patients in this highest risk category.*"	Although MSD recognise the importance and robustness of PANORAMIC RCT, we consider that the study does not include those patients who are at highest risk of progressing to severe COVID-19 and so is not fully representative of the population most likely to be treated with molnupiravir.	Not a factual inaccuracy. Section 2.2.3 (page 19) is describing the treatment pathway for English patients at high risk of progressing to severe disease according to the description in the Interim Clinical Commissioning Policy. No change made. PANORAMIC, as a potentially relevant trial for comparative evidence, is discussed in section 3.4.2.1.

Issue 2 Sotrovimab in treatment care pathway position (b)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect assertion that sotrovimab should be considered an alternative to molnupiravir in the treatment care pathway position (b): Page 20: "*This differs from the interim guidance as it eliminates the requirement to consider sotrovimab as the next treatment in line after consideration of nirmatrelvir plus ritonavir, positioning molnupiravir as an alternative to sotrovimab (see also group (c) below)*". Page 21: *"It shows molnupiravir as an alternative to sotrovimab whereas the current guidance requires sotrovimab to be considered before*	Discussion of sotrovimab should be removed from "Position (b)" in the treatment care pathway.	According to NICE guidance (TA878), ***sotrovimab is recommended for patients with mild to moderate COVID-19 at high risk of severe disease according to the McInnes criteria.*** Position (b) refers to the group of patients who meet the Edmunds criteria (used for the expanded recommendations in TA878) and, thus, who, if contraindicated to nirmatrelvir plus ritonavir, would not be eligible for treatment with sotrovimab.	The EAG find CS Figure 1 ambiguous and not intuitive to understand. We assume that the intended meaning in this FAC response is that (i) patients meeting the additional Edmunds criteria, but not the McInnes criteria would not be eligible for sotrovimab, and therefore (ii) molnupiravir is positioned as a relevant alternative to sotrovimab only for those who meet the McInnes criteria but not any of the additional Edmunds criteria. To improve clarity in the EAG Report we have deleted a sentence on each of pages 20 and 21 to remove the statements about the company's positioning of molnupiravir relative to the interim guidance.

treatment with molnupiravir".			

Issue 3 Decision Problem population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the EAG report, the EAG states that the population addressed by the company in its submission is narrower than the NICE scope, with the population limited to non-hospitalised patients with 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 (page numbers provided below). • Section 1.3, page 3; • Page 21; • Page 22; • Table 4, page 23; • Page 32;	Amend wording that the population addressed in the company submission (CS) as being limited to non-hospitalised patients to reflect that the company has highlighted throughout its submission that there are patients who acquire COVID-19 while in hospital but the lack of data for this population, as acknowledged by the EAG, has precluded MSD from formally modelling the clinical effectiveness and cost-effectiveness of treatments for incidental COVID-19 cases. The same simplifications were applied in TA878 MTA due to data limitations. As such, we propose that the EAG change the wording within the report to read as *"in-hospital incidental COVID-19 was not formally explored due to data limitations but the company has provided justification for this decision and takes the view that*	The Decision Problem issued by NICE does not specify a setting. While the focus of the CS was on non-hospitalised patients with mild to moderate COVID-19, patients with mild to moderate COVID-19 acquired in hospital (i.e., 'incidental COVID-19') were not formally excluded and discussion on this patient population is provided in the CS. Moreover, the EAG agrees that there are limited data available for patients with incidental COVID-19 and the EAG's clinical experts do not believe that these patients would differ from non-hospitalised patients.	As stated in the EAG Report the company's rationale for the focus of the Decision Population on non-hospitalised patients is not explicitly described. However, we have added a sentence in the table for Issue 1 (page 3) to clarify that the EAG and our clinical experts agree there is a lack of data for hospitalised patients. We are unclear why the company are referring to Table 4 and pages 21-23, 32, and 60 here which, as far as we are aware, do not contain any inaccurate or misleading statements. The company's response suggestion, provided left in italics, is still ambivalent about whether/how hospitalised patients should be

• Section 3.7.2, page 60.	*RWE NMA evidence may be used to guide treatment decisions alongside other clinical considerations and patient preferences".*		considered within this technology appraisal. We also note that the company's SLR eligibility criteria and economic analysis do not include hospitalised patients.

Clinical effectiveness

Issue 4 Number of RCTs informing the economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Error in reporting of the number of RCTs informing the NMA. Page 31: "*One of the 15 RCTs of high relevance was the company-sponsored MOVe-OUT trial[23] which informs scenario analyses in the economic model and is discussed below in section 3.2. The remaining 14 RCTs and the RCT NMAs do not inform the economic analysis*".	The last sentence should be correct to read: "The remaining 13 RCTs…".	A total of 15 RCTs were identified in the company's SLR of clinical effectiveness and safety evidence of treatments for mild to moderate COVID-19 in patients at risk of developing severe illness. In the CS, the pivotal MOVe-OUT trial was used as direct evidence for supporting molnupiravir in the treatment of mild to moderate COVID-19. However, supportive evidence from the PANORAMIC RCT was also	Thank you for highlighting this inaccuracy. We have amended the text on page 31 to clarify that both MOVe-OUT and PANORAMIC informed the economic analysis.

		used in the economic analysis presented in the CS and the rationale for this was given (applied in the high efficacy scenario). Thus, two RCTs identified in the SLR were used for supportive evidence in the CS and the remaining 13 RCTs did not inform the economic analysis. The company agree that the company-sponsored MOVe-OUT trial was the most relevant RCT identified in the SLR but would ask that it be made clear that data derived from the PANORAMIC study also informed parts of the economic analysis (some model inputs).	

Issue 5 Number of UK sites in the MOVe-OUT trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG incorrectly amended the number of UK sites in MOVe-OUT to one (the Royal Free London NHS Foundation Trust), as per the Jayk Bernal et al. 2022 supplementary appendix. Page 33: *"…but according to the trial publication supplement only one UK site, the Royal Free London NHS Foundation Trust, recruited at least one participant although the total number of UK participants is not reported".*	Amend the text for clarity. As per the clinicaltrials.gov register for the MOVe-OUT trial (NCT04575597; last updated June 2023), the total number of UK sites opened in the MOVe-OUT trial was six: • Layton Medical Centre; • Newcastle upon Tyne Hospitals NHS Foundation Trust; • The Adam Practice; • Accellacare South London Quality Research Centre; • Royal Free London NHS Foundation Trust; • King's College Hospital. However, four sites recruited patients:	It is important for the number of UK sites in the MOVe-OUT trial to be correctly reported.	Not a factual inaccuracy. The EAG correctly quoted the sites listed in the trial publication. The company's list provided here includes the Adam Practice which is not included in the specified June 2023 update of the trial information at clinicaltrials.gov. We have amended the text on page 33 to clarify that four UK sites recruited patients.

	• Layton Medical Centre; • Newcastle upon Tyne Hospitals NHS Foundation Trust; • Royal Free London NHS Foundation Trust; • King's College Hospital. Therefore, the number of UK sites in the EAG report should be amended to either six or four, making it clear whether the sites referred to did or did not recruit patients.		

Issue 6 Mutagenicity

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report quotes concerns in the scientific literature on the mutagenic potential of molnupiravir in humans and states that it could be too early to say whether molnupiravir is safe in this respect and	Amend wording to make clear that this is EAG opinion and not fact.	The topic of mutagenicity is beyond the scope of this appraisal and is not relevant to the Decision Problem issued by NICE. Thus, we request that references to mutagenicity are removed from the EAG report. The UK Medicines & Healthcare product Regulatory Agency	Not a factual inaccuracy. However, we appreciate that mutagenicity is not an outcome of direct interest in the NICE scope but a wider concern given the therapy's mechanism of action. We have edited the text on pages 40-41 to emphasise that the interpretation is EAG opinion.

that some reviews advise caution. Page 40: *"We also note concerns in the scientific literature on the mutagenic potential of molnupiravir in humans.[29] It could be too early to say whether molnupiravir is safe in this respect and some reviews advise caution*".		(MHRA), which has issued a conditional marketing authorisation, has considered molnupiravir's safety profile in totality. The Summary of Product Characteristics for molnupiravir issued by the MHRA does not mention concerns around mutagenicity. The MHRA's position is that they believe molnupiravir demonstrates a positive benefit-risk profile, with no major safety concerns. The label for molnupiravir has the following conclusion in the Mutagenesis section: "*Based on the totality of the genotoxicity data, molnupiravir is of low risk for genotoxicity or mutagenicity in clinical use*".	We have also added a reference to the MHRA report alongside the existing statement that the SmPC considered data from animal studies to show molnupiravir would have low risk for genotoxicity or mutagenicity in clinical use.

Issue 7 Van Heer et al. 2023

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
MSD disagree with the EAG's assessment on the Van Heer et al. 2023 study. The EAG describes the Van Heer et al. 2023 study and comments that patients treated with antivirals were added to the 'no treatment' group for the analysis. The EAG argue that the study should have been linked to the network via the 'uncertain no treatment node'. Page 50: "*A further study which appears to have had antiviral treatment included in the no-treatment group at the analysis stage (and was not included in the 'uncertain no treatment node'), Van Heer et al. 2023,61 is discussed in*	The two statements should be removed: *"A further study which appears to have had antiviral treatment included in the no-treatment group at the analysis stage (and was not included in the 'uncertain no treatment node'), Van Heer et al. 2023,61 is discussed in terms of risk of bias impact on the NMAs in section 3.4.4.2 below".* *"Figures 1 and 2 in the trial publication show that patients treated with antivirals were added to the 'no treatment' group for the analysis".*	Van Heer et al. 2023 recoded patients treated on the day prior to, or on the day of, hospitalisation or death as untreated. This was done to minimise selection bias and to limit the treatment group to patients where there was sufficient time for the drug to have an effect (>24 hour). More than 97% of patients in the control group did not receive any treatment. The exact proportion of patients included in the 'untreated' cohort who had received nirmatrelvir plus ritonavir or molnupiravir within two days of hospitalisation, or within one day prior to death, is unclear. The mortality analysis includes ≥10,286 patients who received no treatment. Hence, it would be inappropriate to exclude this	Thank you for highlighting our interpretation of the Van Heer et al. 2023 study publication. Our concern was to understand whether 'no oral antivirals' actually meant no treatment received. However, we agree that Van Heer et al. conducted extensive sensitivity analyses to explore the impact of recoding treated patients to untreated. We have deleted the statement about the 'uncertain treatment node' on page 50 and have amended text on page 54 to reflect this. However, our overall assessment of Van Heer et al. 2023 retains a serious risk of bias judgement due to the risk of confounding caused by using hospitalization as a proxy for comorbidities. Nevertheless, as stated on

terms of risk of bias impact on the NMAs in section 3.4.4.2 below". Page 54: "*Figures 1 and 2 in the trial publication show that patients treated with antivirals were added to the 'no treatment' group for the analysis*".		data from the 'no treatment' analyses just because 351 or fewer out of 10,637 patients (≤3%) received treatment.	page 54, exclusion of Van Heer et al. 2023 has little impact on the NMA results and would have no substantive impact on the economic analysis.

Issue 8 Informative prior

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Potentially misleading discussion on the use of an informative prior. Page 55: "*The CS and NMA reports do not discuss whether heterogeneity could have been modelled in these networks using an informative prior*".	Amend wording to explain why an informative prior cannot be appropriately used or delete the text	There are insufficient data to identify the 'right' informative prior for such an analysis. In addition, due to the number of studies, the estimate of variance should not be unduly affected by the choice of prior.	Not a factual inaccuracy. The CS does not explain why an informative prior could not be used, nor does it report any feasibility assessment to investigate this. Informative priors were developed to enable heterogeneity to be modelled in data-sparse situations, so stating that there is 'insufficient data' without providing any further explanation or feasibility

			assessment is not a logical reason for discarding this approach. No changes made.

Issue 9 Tazare et al. 2023 and Zheng et al. 2023

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 9, page 58. For comparative purposes, the EAG presents results from Zheng et al. 2023, Tazare et al. 2023, and OpenSAFELY alongside the NMA results. The company consider that presentation of results from separate studies, together with the results from the NMA, could be taken to mean that all individual studies were omitted from the NMA.	For clarity, add a footnote to the table to indicate that Zheng et al. 2023 informed the NMA.	Zheng et al. 2023 was included in the NMA.	Thank you for highlighting this possibility for misinterpretation. We have added footnotes to Table 9 to clarify which of the Zheng and Tazare studies were included in the NMAs.

Issue 10 Tazare et al. 2023

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
MSD disagree with the EAG's description of the reason for exclusion of the study by Tazare et al. 2023. The EAG report states that UK study Tazare et al. 2023 was not included in the RWE SLR because of the review's cut-off dates. Page 62: "*We note that the company's cut-off date for selecting studies (2021-2022; CS Appendix Figure 14) excludes a UK study that demonstrates lack of clinical effectiveness of molnupiravir (Tazare et al. 2023 2). The EAG are uncertain whether this study should have been excluded due to lack of generalisability to current clinical practice"*.	The statement in the EAG report is factually inaccurate. Amend wording to clarify why the study was not picked up in the searches. Amend text to read: *"…that demonstrates lack of clinical effectiveness of molnupiravir (Tazare et al. 2023 2). However, the company informed the EAG that the study by Tazare et al. 2023 is incorrectly indexed in Embase as a case report and was thus not retrieved by the literature search*".	The study by Tazare et al. 2023 is incorrectly indexed in Embase as a case report. As is standard practice, the literature search strategy for the RWE SLR used study filters which remove case reports from the search results, therefore, this article was not retrieved by the literature searches. Tazare et al. 2023 was not excluded from the analysis because of the study dates; given that this study was conducted in the UK, it would have been prioritised and considered relevant for inclusion in the analyses, if the article been retrieved by the search. However, as the EAG notes in page 62, there is uncertainty as to whether	The original source of the Tazare et al. 2023 paper, as a preprint, is medRxiv which the company stated in CS Appendix D.1.1.1 was a source that they had included for supplementary searching. So, the EAG could only assume that this paper should have been found and had not been included. We have amended the text on page 62 to clarify that the company's searches did not identify this paper and that the company confirmed at the FAC stage that they would have included it, had they identified it, given its UK relevance.

		this study is generalisable to current clinical practice, so perhaps this study may have been suitable for inclusion in a sensitivity analysis rather than the base case NMA. There is an element of sample size overlap with the multiple OpenSAFELY publications that one needs to be cognisant of when it comes to evidence synthesis, which could complicate interpretation of the results.	

Cost effectiveness

Issue 11 Hospitalisation rate

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Use of the hospitalisation rate of 2.41% from OpenSAFELY in the EAG base case (page 74). The rate is a lower range estimate of hospitalisation reported in TA878 and TA971.	A hospitalisation rate of 2.41% biases against molnupiravir. MSD consider that the all-cause hospitalisation rate from the RWE NMA (3.79%) is the most appropriate input with alternative COVID-19 related hospitalisation from the NMA used as a secondary input (explored by the EAG as a scenario). MSD's base-case uses the all-cause baseline hospitalisation rate derived from the NMA (3.79%) to ensure consistency with the primary endpoint definition in the clincial trials and to account for any incidental COVID-19 cases in the modelling of baseline risks.	In 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%. Use of 2.41% introduces an unfair bias against molnupiravir. MSD consider that all-cause hospitalisation and COVID-19 related hospitalisation rates from the NMA are more robust to inform crucial model parameters as they were derived from synthesis of recent evidence from multiple studies.	Not a factual inaccuracy. The reasons for the EAG base case preference are presented and explained in EAG report section 4.2.6.1.1.1 and Key issue 4. Moreover, the EAG explored alternative hospitalisation rates and acknowledges in Key Issue 4 that there is uncertainty.

Issue 12 Hospitalisation rate for patients aged over 70 years

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
MSD disagree with the EAG's assumption around the level of hospitalisation observed in clinical practice for patients aged over 70 years. Page 75: "*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 …, which might be unlikely to occur in practice given the current endemic setting*".	Remove wording that the hospitalisation rate of 12.84% is unlikely to occur in practice.	The hospitalisation rate of 12.84% for patients aged over 70 years was taken from a Canadian RWE study conducted between March and October 2022. Thus, this rate is both recent and relevant to the endemic setting, being conducted after the initial COVID-19 waves and after widespread vaccination.	The EAG agrees that the wording might be misleading and therefore we have changed it to "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…. It is uncertain whether this occurs in practice given the current endemic setting" (page 76).

Issue 13 Length of stay

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that input values for length of	Clarify that the length of stay values can be reproduced.	Please see below more details on the breakdown of	Not a factual inaccuracy. But thank you for providing more details on the

stay could not be replicated (page 79).		steps for the calcuation of length of stay: • For overall high risk, the mean length of stay was 9.9 days. The proportion of patients with critical care (CC) stay was 14.1%. The average length of stay in CC was 11.4 days. • Multiplying the proportion in CC with duration in CC gives 1.61 days. The mean length of stay (9.9 days) minus the CC days (1.61 days) gives a length of stay in general ward of 8.29 days. • The same calcuation is used for the population aged over 70 years.	calculation of length of stay in general wards (relating to section 4.2.6.1.3 of the EAG report). However, we are still unable to obtain the same results as the company because we cannot find the inputs of 9.9 days, 14.1%, and 11.4 days in the study by Yang et al. 2023. Table 2 of Yang et al. 2023 reports a mean length of hospital stay of 9.2 days, a proportion of patients with critical care stay of 14.8% and a mean length of stay in critical care of 11.5 days. We note that changing this assumption appears to have a minor impact on the model results.

Issue 14 Nirmatrelvir plus ritonavir acquisition cost

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
MSD disagree with the acquisition cost used for nirmatrelvir plus ritonavir. Throughout the EAG report, the acquisition cost of nirmatrelvir plus ritonavir is listed as £2.50 (pages 13, 103, 123, 127, 128, 132, 134), with the BNF cited as the source: page 101: *"A list price of £2.50 for nirmatrelvir plus ritonavir is shown in the BNF website".*	MSD assert that BNF costs in this case cannot be considered list price costs to generate and present cost-effectiveness analyses pertaining to this comparator and doing so is both factually incorrect and misleading. The price of £2.50 is not a true acquisition cost or list price, but is rather the nominal ***reimbursement value*** provided to pharmacy contractors as per Drug Tariff Part VIIIC for products that have been centrally procured such as COVID-19 therapeutics. This is stated in the NHS Drugs Tariff Part VIIIC, where molnupiravir is also reported to be associated with the same nominal reimbursement price.	This cost is not comparable to the true acquisition cost of nirmatrelvir plus ritonavir but is rather a nominal price and cannot be used to generate C/E for decision making. Additionally, conclusions around molnupiravir being dominated are therefore misleading, as they were reached using minimal reimbursement values provided to pharmacy contractors and not the true acquisition costs or list price for nirmatrelvir plus ritonavir.	Thank you for highlighting this issue. We appreciate that the wrong acquisition price for nirmatrelvir plus ritonavir has been used in the EAG report. We are now waiting for a confirmation on whether the list price of £829 used in the CS has changed or not. We will update our EAG base case accordingly once we have this confirmation.

	C/E analyses using the £2.50 are not reflective of the true list or acquisition costs for nirmatrelvir plus ritonavir and are misleading. MSD request that these analyses are either replaced with values reported in Metry et al., as is the case in MSD's submission, or the value of £2.50 is also used for molnupiravir. If this is not actioned, MSD request that appropriate explanation is introduced when analyses are presented that lead to the conclusion that molnupiravir is being dominated by the comparator, as we do not consider those analyses to be valid for decision making.		

Issue 15 Values for scenario results in EAG model versus EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Inability to replicate the results from Scenario analysis 3, page 109. MSD are unable to replicate the results of scenario 3 and believe	Amend the results in table 32 using the correct value and/or relabel the name of scenario 4.	There is inconsistency between the model and results reported in the EAG and incorrect utilities have been used for this scenario. It would aid the reader if the	Thank you for highlighting this inaccuracy. The EAG was unable to clearly identify which utility values were used in the company's scenarios reported in Tables 41 and 42 of the Clarification Response

reported utility values from Table 25 have not been used for this scenario. We believe scenario 4 is using the values from TA878 and TA971.		exact utility values used would be reported as a table footnote for scenarios that may not be easily replicable.	document. As the exact utility values used were not explicitly reported in the tables, we relied on the model sheet "Scenarios" (cells J30 and K30) and assumed that the values from rstUtilTA (Reset Ranges!B452:B457) were the utilities used in the scenario reported in Table 41 and that the values from rstUtilSA (Reset Ranges!B460:B465) were the utilities used in the scenario reported in Table 42. We have now corrected this, by using the same set of utilities for both scenarios (rstUtilSA). To correct the EAG Report we have amended the text of sections 4.2.7.2.2 (pages 98-99) and 5.2.2 (pages 108-109) and updated Tables 25, 32 and 42.

MSD have not been able to validate the following ICERs and ask that the EAG check again extracted values and carry out relevant updates where necessary. As some EAG preferred values have been hardcoded, additional information around the model inputs in question to enable replication of the ICERs below is welcomed: - Table 42 company scenarios 2 ICERs; - Table 42 company scenarios 3 ICERs; - Table 48 ICERs vs molnupiravir.	Request for additional information.	As some EAG preferred values have been hardcoded, additional information around the model inputs in question to enable replication of the ICERs.	Table 42 of the EAG report shows the results of the company's scenarios (listed in section 5.2.2) and some EAG scenarios applied to the EAG corrected company revised model base case. The EAG corrected company revised model base case is described in section 5.3.4 of the EAG report, Table 39. Scenarios 2 and 3 correspond to the company scenarios 2 and 3 in section 5.2.2 of the EAG report. Table 48 shows the EAG base case assumptions applied to the subgroup of immunocompromised patients. The EAG preferred assumptions for this subgroup of patients are listed in section 6.4 of the EAG report, just above Table 48. Also, the EAG analyses model details the changes needed to obtain the ICERs for the subgroup of immunocompromised patients – see EAG analyses sheet, cells C35:J47.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Table 29, row relating to molnupiravir.	Information in the following columns is **not** marked as commercial in confidence • Total costs (£); • Total LYG; • Total QALYs; Incremental ICER (£/QALY).	***Mark as commercial in confidence as the list price of molnupiravir remains confidential and back-calculation can occur.***	Thank you for highlighting this. We have added the CON markup to Table 29.
Table 31, row relating to molnupiravir	Information in the Incremental ICER (£/QALY) column is **not** marked as commercial in confidence.	Mark as commercial in confidence.	Thank you for highlighting this. We have added the CON markup to Table 31.
Table 32, row relating to molnupiravir	Information in the Incremental ICER (£/QALY) column is **not** marked as commercial in confidence.	Mark as commercial in confidence.	Thank you for highlighting this. We have added the CON markup to Table 32.
Table 35, row relating to no treatment	Information in the Incremental ICER (£/QALY) column is marked as commercial in confidence.	Remove commercial in confidence marking.	Thank you for highlighting this. We have removed the CON markup from Table 35.
Table 51, row relating to risk of bias assessment	Information is marked as commercial in confidence.	MSD apologise for the confusion caused in sharing the full reports for the SLRs.	Thank you for highlighting this. We have removed the CON markup from Table 51.

		MSD is happy for the text to be in the public domain – please remove the commercial in confidence marking.	