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:

1. **Comments on the Draft Guidance from Merck Sharp & Dohme**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. UK Clinical Pharmacy Association
   b. NHS England

3. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Tuesday 17 December 2024**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Merck Sharp & Dohme (UK) Limited**
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** In general, MSD agree that the summary of clinical evidence provided in the Draft Guidance is a reasonable interpretation of the evidence. Specifically, MSD agree that the randomised clinical trial (RCT) evidence is not generalisable to the current endemic situation in the UK, where a significant proportion of people are vaccinated against COVID-19. MSD also agree that real-world evidence taken in its totality is a more appropriate source of evidence for inputs to the cost-effectiveness model. However, MSD do not agree that PANORAMIC is a reasonable source of evidence for the present appraisal. The inclusion criteria for PANORAMIC were much wider than the current or previous criteria for COVID-19 antiviral eligibility due to being at high risk of severe disease. Whilst the study was large, only a small proportion of patients were in the oldest age groups, whilst OpenSAFELY data show that under the interim commissioning policy, molnupiravir is disproportionately used in older patients (aged 70 and above), those who reside in care homes or are housebound and those suffering with dementia and serious mental illness (Antivirals and nMABs for non-hospitalised COVID-19 patients: coverage report | OpenSAFELY: Reports). MSD believe that the Committee has thoroughly considered the cost-effectiveness of molnupiravir compared with no treatment in the overall high-risk population. However, MSD and the Committee agree that the most appropriate positioning for molnupiravir is for the highest unmet need population, which are also those at the highest risk of developing severe disease (for clarity from now on referred to as; "***highest unmet need and at-risk population***"), approximately in line with where it has been used under the interim commissioning policy, as discussed in point 3.5 in the Draft Guidance. Subgroup analyses were therefore conducted on four subgroups: those aged 70 and above, those contraindicated to nirmatrelvir plus ritonavir, those with severe chronic kidney disease (CKD) and the immunocompromised. COVID-19 mortality data in the UK demonstrate that patients with such comorbidities are disproportionately affected (Changes in COVID-19-related mortality across key demographic and clinical subgroups in England from 2020 to 2022: a retrospective cohort study using the OpenSAFELY platform). While overall mortality has decreased across all patient groups, including those at high risk of severe disease, the risk of mortality during the 2021 and 2022 SARS-CoV-2 Omicron waves remained significantly higher for patients with CKD, those on renal replacement therapy, kidney transplant recipients, and patients with haematological malignancies. The elevated risk is also notable for individuals aged over 80 years and those with dementia. MSD therefore consider these subgroups to be reflective of the target population for the optimised positioning based on discussions with clinical experts to date, which are also in line with how the technology has been used under the current NHS Interim Commissioning policy. MSD do not believe that the Committee has adequately considered these subgroup analyses at this point, largely due to time constraints in the Committee meeting of November 2024. MSD willingly accept some of the corrections to the model as suggested by the Evidence Assessment Group (EAG), and are also willing to use the proportion of female patients from PANORAMIC (59%) and a hazard ratio (HR) of 1 for time to discharge for both inpatient treatments (remdesivir and tocilizumab; see Table 2 below for more information and impact of these changes). The EAG-adjusted MSD base-case incremental cost-effectiveness ratio (ICER) for molnupiravir compared with no treatment is therefore [redacted] per quality-adjusted life year (QALY) gained (in the overall high-risk group patients). It should be stressed that this ICER is

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	only reported for replicability purposes in this response as the updated positioning proposed now aligns well with the explored subgroup cost-effectiveness analyses. The ICERs per QALY for the subgroups of interest that MSD believe reflect the ***highest unmet need and at-risk*** population are: [redacted] for those aged 70 and above, [redacted] for those contraindicated to nirmatrelvir plus ritonavir and [redacted] for those with severe CKD (ICERs with partial update of EAG inputs by MSD; refer to comment 7 for more information). Molnupiravir dominates no treatment for the immunocompromised, that is, it is less costly overall and more effective to administer molnupiravir instead of to watch and wait for the patient to require treatment escalation due to deterioration from COVID-19. The results of these analyses are driven by the higher background hospitalisation rates used to inform the economic modelling and/or increased mortality where applicable for those who currently remain untreated, as acknowledged by the Committee in its approval of sotrovimab (TA878) and remdesivir (TA971). **MSD request that the Committee consider the cost-effectiveness of molnupiravir in distinct subgroups that may represent patients within the *highest unmet need and at-risk populations*: those aged 70 and above, those contraindicated for nirmatrelvir plus ritonavir, those with CKD and those who are immunocompromised.**
2	**Has all the relevant evidence been considered?** MSD acknowledge the Committee's concerns detailed in the Draft Guidance around the relevance of the evidence base for molnupiravir to the population they consider eligible for treatment, that is, those of the highest unmet need: • Committee ***"…would need to see evidence that showed the network meta-analyses (NMAs) of real-world evidence (RWE) reflected the highest unmet need population, or an updated NMA of RWE or new RWE evidence to inform the modelling of the highest unmet need population"*** (section 3.9, p.15). • Committee ***"…would like to see various sources of evidence [for relative effectiveness of molnupiravir vs no treatment] explored, including the RWE NMAs, PANORAMIC and single studies including Tazare et al and the OpenSAFELY database. This would be to see which provides the most appropriate estimate of relative effectiveness for the highest unmet need population"*** (section 3.13, p.20). **Defining the highest unmet need and at-risk patient group** To alleviate the Committee's concerns around the patient population likely to be eligible for treatment with molnupiravir, MSD have taken steps, including consulting with clinical experts, to try to clearly define the characteristics of those patients with COVID-19 who are at highest unmet need and at-risk of progressing to severe disease, and, in the absence of a recommendation for molnupiravir, are likely to continue to remain untreated for mild/moderate COVID-19 in the community setting.

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	Patients in the highest unmet need and at-risk group include those: • With ≥1 risk factors for progression to severe COVID-19 (as per the Edmunds or McInnes definition), and • Who are contraindicated to nirmatrelvir plus ritonavir, and • For whom sotrovimab is contraindicated, unfeasible or undesirable (e.g., in cases of complex comorbidities, haematological disease, severe kidney or liver disease, or difficulties accessing sotrovimab due to geographical location). The size of the group with highest unmet need and at-risk is expected to be small. As acknowledged by the Committee, data are sparse for this group of patients in England. According to Hospital Pharmacy Audit data from IQVIA, [redacted] courses of molnupiravir were prescribed in 2023. As discussed in section 3.5 of the Draft Guidance, this highest unmet need and at-risk group is approximately in line with those eligible for molnupiravir according to the interim commissioning policy, therefore our best working estimate is approximately in line with this figure. Figure 1 illustrates the 2023 molnupiravir usage compared with the estimates of patients remaining untreated in the absence of a recommendation for molnupiravir, as estimated in the budget impact analysis submitted by MSD at the time of the NICE submission. The data presented in Figure 1 validate the assumption that molnupiravir usage is likely to be similar to its historical usage under the interim commissioning policy. It should be noted that MSD do not consider that all those aged over 70 would require treatment with molnupiravir, unless they require a treatment option that is less complex to monitor and/or have additional clinical considerations that place them in the highest unmet need and at-risk group (i.e., cannot access currently approved treatment options). An example would be older patients residing in care-homes, which is in line with the funding variation in place for nirmatrelvir plus ritonavir until June 2025, which states that patients falling outside of the McInnes criteria but within the Edmunds criteria (which includes patients aged ≥ 70 without relevant comorbidities) are only eligible for treatment if they are also resident in a care home or currently hospitalised (1 Recommendations | Nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19 | Guidance | NICE). Nonetheless, MSD offer this scenario as a reassurance for planning purposes and consider it indicative of the small patient population that is unlikely to exceed current usage.

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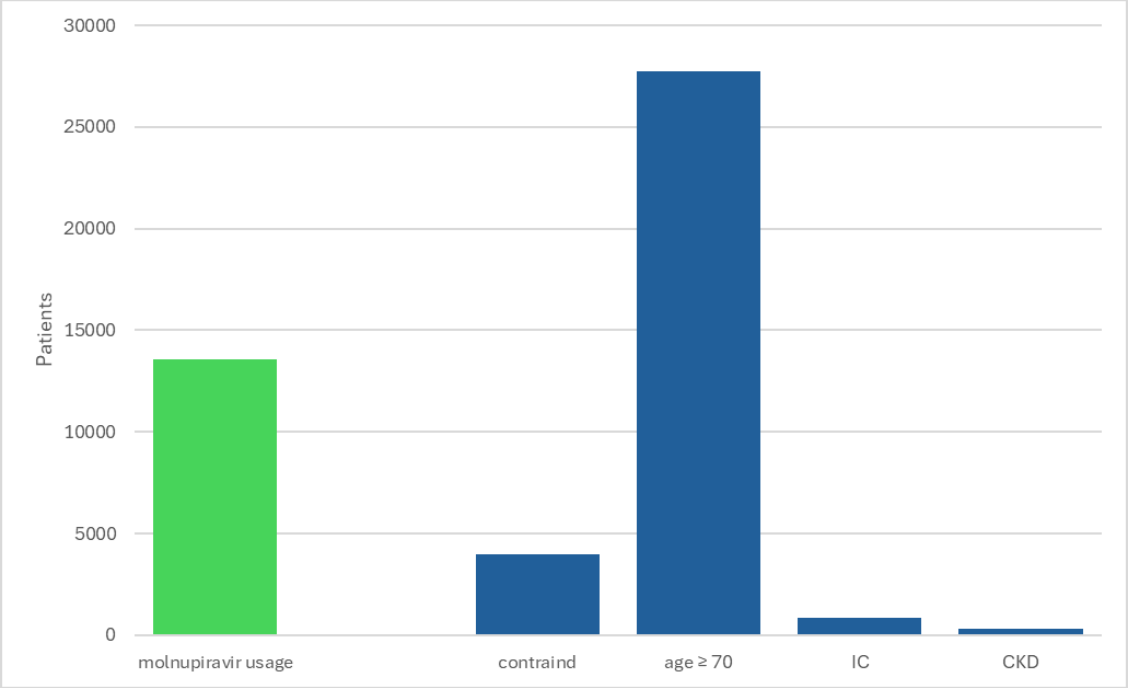
Figure 1. Usage of molnupiravir in 2023, and estimated untreated patient subgroup sizes in the absence of a recommendation for molnupiravir, from MSD budget impact model.



Abbreviations: CKD, severe chronic kidney disease; contraind, contraindicated; IC, immunocompromised.

Patient experts involved in the appraisal for molnupiravir drew attention to the lack of available treatment options for COVID-19, particularly in individuals potentially at highest risk of progression to severe disease and associated serious outcomes. Molnupiravir offers an option for community/outpatients with protected characteristics whose health status may limit the benefit of currently available treatments for mild-to-moderate COVID-19, leaving them vulnerable to progression to severe disease. Molnupiravir can combat inequity in access to COVID-19 treatments for patients who urgently require a treatment option.

Of the available COVID-19 treatments, the requirement that sotrovimab be administered via intravenous infusion by a qualified healthcare professional (HCP) in a dedicated healthcare setting can make accessing treatment challenging for some patients, particularly those who do not live near appropriate healthcare centres and/or do not have access to transport. Thus, with current treatment recommendations, patients with protected characteristics could encounter additional burden from travelling to hospitals or clinics to receive intravenous treatment. Additionally, an analysis of OpenSAFELY data demonstrated the considerable disparity across England and Wales, based on geographic location, in the level of access to NHS healthcare centres (Trends, variation, and clinical characteristics of recipients of antiviral drugs and neutralising monoclonal antibodies for covid-19 in community settings: retrospective, descriptive cohort study of 23.4 million people in OpenSAFELY | BMJ Medicine), potentially exacerbating inequitable access to services and resources for patients, with the most vulnerable patients often the most affected, a view supported by clinical experts consulted by MSD when developing the response to the Draft Guidance.

Patients who are at the highest risk of developing severe COVID-19 may also prefer a self-administered treatment at home. Attending a healthcare setting for treatment increases their exposure to other infectious pathogens and may spread SARS-CoV-2 to other patients who may

	themselves be at high risk for severe disease. As mentioned in the Draft Guidance, clinical experts consider that molnupiravir could address an unmet need for an alternative oral treatment option for COVID-19 that can be administered at home, thus requiring minimal resource. Molnupiravir could help to combat inequity in access to COVID-19 treatments for patients who urgently require a treatment option. Additionally, treatment at home with molnupiravir removes potentially infectious patients from the hospital setting where they could cause infection in healthcare professionals or in other patients who may themselves have conditions putting them at risk of severe COVID-19. Patients contraindicated to nirmatrelvir plus ritonavir include those with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^3 and/or those with current or expected use of any medications with CYP3A4 clearance or inductions, such as antiarrhythmics, anticoagulants, anticonvulsants, antiretrovirals, anxiolytics, cancer drugs or immunosuppressants. Additionally, treatment with nirmatrelvir plus ritonavir can be complex for patients with multiple comorbidities who are receiving multiple medications (such as those with severe hepatic or renal impairment) because of the increased risk of drug–drug interactions or the need to adjust doses. By contrast, molnupiravir offers a simple, alternative treatment with no known drug–drug interactions. It is noted that the current recommendations from NICE for the management of COVID-19 at high risk of progressing to severe disease (TA878) mean that patients with characteristics that fall within the Edmunds, but not the McInnes, criteria for high-risk of progression are not eligible for sotrovimab, leaving these patients without a treatment option should they be contraindicated to nirmatrelvir plus ritonavir. As noted earlier, patients with comorbidities remain at a considerably higher risk of death from COVID-19 compared with other patient groups, including those with CKD, those on renal replacement therapy, kidney transplant recipients, and patients with haematological malignancies. The elevated risk of death is also notable for individuals aged over 80 years and those with dementia. In summary, patients who are contraindicated to both nirmatrelvir plus ritonavir and sotrovimab, and/or who cannot access a hospital or clinic for sotrovimab have no alternative treatment options. HCPs who provide COVID-19 antiviral services have confirmed that there have been cases of patients with mild to moderate COVID-19 at high risk of developing severe disease not being offered therapy due to the 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. 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. **Effectiveness of molnupiravir to treat patients at the highest risk of progression to severe COVID-19 in the UK** The NICE Committee, the EAG and clinical experts considered the NMA of the real-world clinical effectiveness of molnupiravir to be the most relevant source of evidence to support the submission. While RCTs are the preferred source of evidence, RCT evidence does not reflect the most recent endemic situation in the UK (including COVID-19 epidemiology, patient characteristics [such as vaccination status] and SARS-CoV-2 variants). By contrast, the RWE literature captures the real-world use and outcomes of each treatment, something that is fundamentally not possible in an RCT setting. However, the Committee also noted that the NMAs of RWE might not appropriately reflect those with highest unmet need. The Committee also noted that few UK studies were included in the NMA of RWE. Specifically, the EAG noted that the Tazare et al. 2023 (Effectiveness of Sotrovimab and Molnupiravir in

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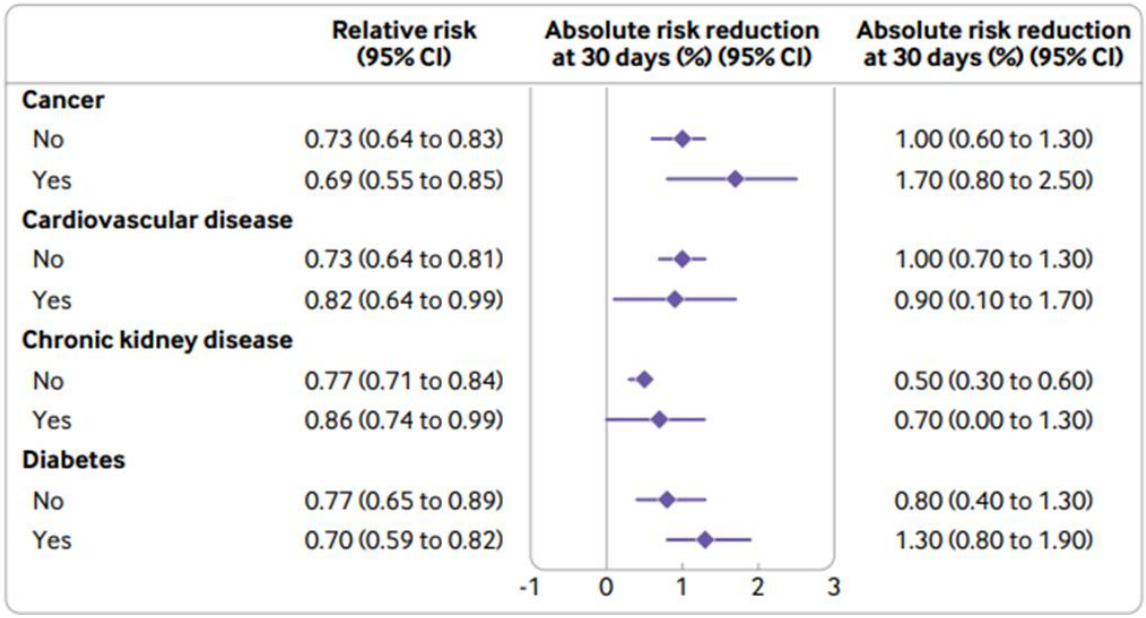
	community settings in England across the Omicron BA.1 and BA.2 sublineages: emulated target trials using the OpenSAFELY platform) study was omitted from the systematic literature review (SLR) due to it being incorrectly indexed as a case report (which is outside of the SLR PICOS criteria). Tazare et al. 2023 concluded that there is no statistically significant difference between molnupiravir and no treatment for the outcome of COVID-19-related hospitalisation or death. Although the Tazare et al. 2023 study used data from the UK derived from the OpenSAFELY database, the study represents a single publication. By contrast, the NMA incorporates OpenSAFELY data from multiple studies and is therefore likely to include data for a proportion of the same patients, meaning that the NMA results are already implicitly adjusted and reflective of the highest unmet need and at-risk population of interest to this submission. Furthermore, results from the Tazare et al. 2023 study are aligned with findings of the RWE NMA (i.e., molnupiravir is similar to no treatment for the outcome of COVID-19-related hospitalisation or death: RR 0.74 [95% CrI: 0.33, 1.20]). A key finding of the RWE NMA was a statistically significant difference between molnupiravir and no treatment for the outcomes of all-cause hospitalisation (RR 0.79 [95% CrI: 0.66, 0.92]) or death (RR 0.31 [95% CrI: 0.21, 0.46]), an outcome not reported by the Tazare et al. 2023 study. All-cause hospitalisation or death was an important outcome to assess in the RWE NMA, in addition to COVID-19-related hospitalisation or death, as all-cause rates reflect the primary treatment effect assessed across studies. Using all-cause hospitalisation as a primary metric allows for better comparison across different diseases and conditions, enabling a more holistic assessment of healthcare needs and resource allocation (Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21). Data on all-cause hospitalisation and death are often more readily available and consistently recorded across healthcare systems, whereas COVID-19-related hospitalisation data may be subject to variations in testing and reporting. Compared to all-cause hospitalisation and death, COVID-19-related hospitalisation and death is less clearly defined across the published literature. Therefore, COVID-19-related hospitalisation or death may not reflect the full treatment benefit of molnupiravir. The COVID-19-related hospitalisation rate from the RWE NMA was similar to values reported in OpenSAFELY and DISCOVER-NOW, confirming the validity of the RWE NMA results. To ensure all potentially relevant RWE was included, MSD carried out two additional investigations as part of its response to the Draft Guidance: • Studies identified from the SLR but carried out in the pre-Omicron time period were re-reviewed, as were the studies included in the RWE NMA; • A targeted review was conducted to identify studies published subsequent to the last search date for the SLR. Re-review of studies retrieved from the original SLR identified one study, Xie et al. 2023, which was included in the original NMA. Xie et al. 2023 (Molnupiravir and risk of hospital admission or death in adults with covid-19: emulation of a randomized target trial using electronic health records) provide results in the subgroups of patients at highest risk of progression to severe disease and support a beneficial treatment effect of molnupiravir among the highest risk group, who also have a greater unmet need, in hospitalisation and death compared to matched untreated controls. The Xie et al. 2023 study included 85,998 patients with SARS-CoV-2 infection in the USA between 5 January and 30 September 2022. Overall, 7,818 patients were eligible for and were treated with molnupiravir and 78,180 did not receive any treatment. All patients included in the study had ≥1 risk factor for progression to severe COVID-19 (which included age >60 years, body mass index [BMI] >30, chronic lung disease, cancer, cardiovascular disease

[CVD], CKD and diabetes) and attended a Veterans Affairs medical centre for COVID-19 during the study period. Xie et al. 2023 reported that molnupiravir reduced the risk of hospital admission or death versus no treatment among patients at the highest-risk of progressing to severe COVID-19, including those with comorbidities such as cancer, CKD, CVD, and diabetes (Figure 2).

Figure 2. Xie et al. 2023 relative and absolute risk reduction for hospital admission or death at 30 days after testing positive for SARS-CoV-2 in patients with comorbidities at high-risk of progression to severe COVID-19



Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2.

In addition to reducing the risk of hospitalisation or death among patients in the highest risk group, molnupiravir improved the time to symptom resolution compared with no treatment in the PANORAMIC study, which is a highly relevant outcome in the endemic setting (as noted by the NICE Committee in appraisal TA878). In PANORAMIC, the hazard ratio for median days to symptom resolution was reported as 1.36 (95% CrI: 1.32, 1.40) for molnupiravir compared to patients who were not randomised to molnupiravir (Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial - The Lancet).

The targeted review identified one additional study — Ahmad et al. 2024 (Effectiveness and safety of molnupiravir in the intended-use population: an observational cohort study) — that provides supportive evidence for the validity of the RWE NMA in the highest risk population.

Ahmad et al. 2024, an updated analysis of a study included in the RWE NMA (Arbel et al. 2022 [Molnupiravir Use and Severe Covid-19 Outcomes During the Omicron Surge]), also reported a treatment benefit with molnupiravir versus no treatment, including a 50% reduced risk of COVID-19 related hospitalisation or death and lower all-cause mortality. The retrospective cohort study included 49,515 patients from a healthcare centre in Israel between 16 January 2022 and 16 February 2023. In total, 3,957 patients received molnupiravir and 19,785 patients were untreated. **All patients included in the study had ≥1 risk factor for progression to severe COVID-19 (which included age ≥60 years, BMI >30, chronic lung disease, cancer, CVD, CKD and diabetes) and were contraindicated for nirmatrelvir plus ritonavir**. The rate of COVID-19-

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	related hospitalisation or death was 5.1 per 10,000 person per day among patients who received molnupiravir compared to 10.4 per 10,000 person per day for untreated patients (risk ratio 0.5; 95% CI: 0.99, 0.64). Similarly, all-cause mortality was lower among molnupiravir-treated patients (3.0 per 10,000 person per day) than untreated patients (6.1 per 10,000 person per day), with a risk ratio of 0.50 (95% CI: 0.36, 0.68). The study authors note the higher effectiveness of molnupiravir in their study compared to previous reports and attribute this trend to the definition of the target population for molnupiravir, which, in the study, was in line with its FDA indication. This 'intended use population' differed from the high-risk populations enrolled in other studies, with almost a third of the intended use population in Ahmad 2024 comprising patients with severe clinical conditions, such as immunocompromised patients who had undergone organ transplantations or who had active malignancies. Molnupiravir reduces the risk of hospitalisation or death among patients at the highest risk of progression to severe COVID-19, as well as improving the time to COVID-19 symptom resolution. If molnupiravir is not recommended by NICE, vulnerable patients in England at the highest risk of severe COVID-19 will be left without a treatment option, potentially leading to preventable hospitalisations and deaths. There is sufficient evidence to demonstrate the value of molnupiravir versus no treatment among patients with the highest unmet need, as described above. MSD urge NICE to reconsider their decision, given the revised positioning of molnupiravir to treat only the highest risk group of patients who would not be eligible for other available treatments. Physicians in the UK strongly advocate for effective COVID-19 treatments that can prevent progression to severe outcomes in patients with the highest unmet need. COVID-19 has placed immense pressure on the NHS, particularly during the winter months, which are already challenging for the NHS and vulnerable patients; thus, a wide arsenal of treatments is essential to alleviate this burden. **The current real-world use of molnupiravir is in the patients at highest unmet need and at-risk of developing severe disease, and the conclusions from the RWE NMA demonstrate that molnupiravir is a clinically effective treatment option for patients who would otherwise remain untreated. As such relative effectiveness estimates can be extrapolated to inform the decision problem.**
3	The Committee expressed a wish for the investigation of hospitalisation rates for those with highest unmet need: • ***"…different hospitalisation rates should be explored if up-to-date hospitalisation rates for the highest unmet need population are available"*** (section 3.12, p.18). MSD acknowledge that there is debate around the most appropriate rate of hospitalisation to use in the economic model, and that there is uncertainty around the efficacy of molnupiravir in those with highest unmet need. Data are provided in the submission for subgroups of patients that may be considered at the highest risk of progression to severe COVID-19, including patients who are contraindicated to nirmatrelvir plus ritonavir, patients >70 years old, immunocompromised patients and those with severe CKD (please see submission Appendices E.1 through to E.4). Subgroup analyses presented in the submission confirm that hospitalisation rates from RWE are highest among patients in the subgroups identified by MSD as those within the highest unmet need and at-risk population (Table 1).

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Table 1. Hospitalisation rate cost-effectiveness model inputs for highest risk subgroups from RWE

Highest-risk subgroup	All cause hospitalisation rate, % (source)	COVID-19 related hospitalisation rate, % (source)
Patients >70 years old	13.0 (Andersen et al. 2023) EPH169 Persons Diagnosed with COVID-19 in Linked Clinical Practice Research Datalink (CPRD) – Hospital Episode Statistics (HES) Data: A Cohort Description	12.84 (Kabore et al. 2023) Real-World Effectiveness of Nirmatrelvir/Ritonavir on Coronavirus Disease 2019-Associated Hospitalization Prevention: A Population-based Cohort Study in the Province of Quebec, Canada
Patients who are contraindicated to nirmatrelvir plus ritonavir	NR	NR
Patients who are immunocompromised	NR	15.90 (Shields et al. 2022) Impact of vaccination on hospitalization and mortality from COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience 22.47 (Kabore et al. 2023) Real-World Effectiveness of Nirmatrelvir/Ritonavir on Coronavirus Disease 2019-Associated Hospitalization Prevention: A Population-based Cohort Study in the Province of Quebec, Canada
Patients with severe CKD	NR	4.15 (OpenSAFELY) Nirmatrelvir plus ritonavir for treating COVID19 (partial review of TA878) 4.4 (DISCOVER-NOW) Characteristics and outcomes of patients with COVID-19 at high risk of disease progression receiving sotrovimab, oral antivirals or no treatment in England: a retrospective cohort study

CKD = chronic kidney disease; COVID-19 = coronavirus disease 2019; NR = not reported; RWE = real-world evidence.

The values presented in Table 1 align with real-world hospitalisation rates used in previous NICE submissions for nirmatrelvir plus ritonavir, sotrovimab and tocilizumab (TA878), and remdesivir and tixagevimab plus cilgavimab (TA971). MSD recently engaged clinical experts to validate the sources and range of background hospitalisation rates. Feedback from clinicians was that the range of values reported in the table above are plausible in the current context for patients at highest risk and who are currently untreated across all subgroups explored explicitly in the present appraisal. Clinicians noted that baseline risk for hospitalisation for immunosuppressed

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	individuals varies by level of hospitalisation and concomitant treatment, with use of brentuximab in Hodgkin lymphoma highlighted as an example of a treatment impacting hospitalisation rate, with a concluding remark that "if left untreated, this patient group would ultimately progress in the end". For those contraindicated to nirmatrelvir plus ritonavir clinicians noted that baseline hospitalisation rates from TA878 seemed reasonable, although they acknowledged that there may be slight variation depending on the subpopulation and/or the presence or absence of other factors mediating disease severity. For those with severe CKD and patients older than 70 years of age, clinicians noted that current estimates used appeared reasonable. Subgroup analyses from the PINETREE RCT of remdesivir versus placebo (Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients) support findings from RWE studies, demonstrating a high baseline hospitalisation rate among patients in the highest risk group. In patients with ≥3 risk factors for severe COVID-19, 9.2% in the placebo group had a COVID-19-related hospitalisation, compared to 1.7% in the remdesivir group. For those with ≥4 risk factors, COVID-19-related hospitalisation rates were 13% for placebo and 1.9% for remdesivir. Data from PINETREE were included in the NMA of RCTs submitted to NICE (using the intention-to-treat population owing to lack of data from comparators to conduct subgroup analyses). **MSD have validated the baseline hospitalisation rates as used in the economic model for the original submission for this technology appraisal. Clinical expert testimonies support the appropriateness of the subgroup analyses for the decision problem. Patients in the highest unmet need and at-risk group are highly likely to experience higher baseline hospitalisation rates than the overall population at risk of severe COVID-19 if not treated with a suitable alternative option early on.**
4	The Committee expressed a wish for the exploration of utility values applied in the economic model • ***"…additional evidence should be explored to ensure that the utility values used in the model reflect the highest unmet need population"*** (section 3.14, p.21). In the HTA submission for this appraisal, MSD referenced a vignette study that had been designed and carried out to understand the health-related quality of life (HRQoL) associated with different COVID-19 health states (Health-Related Quality of Life in COVID-19: A Vignette Study). However, this study was associated with several limitations due to the EuroQol-5 Dimension utility instrument (EQ-5D) ratings being elicited from members of the general public rather than patients currently in each health state, and it was rejected by the EAG. The EAG suggested use of a different study, Soare et al 2024 (Health-related quality of life in mild-to-moderate COVID-19 in the UK: a cross-sectional study from pre- to post-infection | Health and Quality of Life Outcomes | Full Text), which was administered retrospectively and therefore suffers from recall bias as well as sample selection bias. MSD therefore does not consider this an appropriate source of utilities, especially when considering the highest unmet need and at-risk population. MSD sought to identify more appropriate utility values as inputs for the economic model. In line with our approach to other evidence in this appraisal, we looked to the available RWE in an attempt to inform the model utility inputs. **Hospitalised health states** Due to the short-term nature of the hospitalised health states, and small proportion of patients hospitalised, the model is largely insensitive to the utility values for the general ward (GW) and intensive care unit (ICU). The EAG preferred a value calculated from Soare et al for the GW

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	utility (0.28) and a value of 0 for the ICU, as used in previous appraisals TA878 and TA971. MSD accept that the values suggested by the EAG may be better suited to maintain consistency between the appraisals and in the absence of higher quality evidence, although we do still have reservations about their sources.
	
	Symptomatic outpatient health state
	
	The model is somewhat sensitive to the utility used for the symptomatic outpatient state. As discussed in our response to the EAG's clarification questions, MSD suggest the use of the UK Health Security Agency (HSA) study by Sandmann et al (2021), which reports a utility of 0.57 for the "worst day of COVID". This is not dissimilar to the value derived from Soare et al which was suggested by the EAG (0.59), but MSD prefer the use of a value derived from a prospective study that recruited randomly selected patients from the routine laboratory reporting system, over that from a smaller retrospective study that recruited through online panels and social media campaigns.
	
	Long COVID health state
	
	The ICER given by MSD's model is sensitive to the long COVID utility value given the longer-term nature of this health state, so adequate consideration should be given to selecting the most appropriate value. The impact of long COVID based on the patient representative testimony heard during the Committee meeting demonstrates that the value suggested by the EAG (0.67) is too optimistic and frankly lacks validity. Only 186 patients in the Soare et al study reported long COVID, and the study relied on patient self-report and may suffer from selection bias as those most severely impacted by long COVID may have been less likely to engage. After all, the Soares study suffers from similar limitations to those noted for the utilities vignette study.
	
	MSD conducted a SLR of studies reporting long COVID utility elicited using the EQ-5D, which identified eight publications carried out in UK populations:
	• Two conference abstracts reporting on the Welsh Adferiad (Recovery) service, providing limited data with a risk of double-counting:
	  • Collins et al 2023: P107 Health-related quality of life in long covid (post-COVID-19 syndrome) service users in Wales is much worse than the general population;
	  • Frizzati et al 2022: A35 National evaluation of the 'Adferiad' (Recovery) Programme supporting the Welsh Long COVID Service.
	  • A summary report combining the data from the two conference abstracts was also identified: Woolley et al 2023 – Analysis of NHS Wales Long COVID Service User Data.
	• Three of the publications recruited patients in 2020 and 2021 exclusively, before Omicron was the dominant variant, and were therefore deemed unrepresentative of the current endemic period. This is in line with the selection criteria employed during the SLR of RWE efficacy data, and with the views of clinical experts as reported in section 3.6 of the Draft Guidance:
	  • Evans et al 2022: Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study;

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	• Lloyd-Evans et al 2022: Early experiences of the Your COVID Recovery® digital programme for individuals with long COVID; • Dennis et al 2023: Multi-organ impairment and long COVID: a 1-year prospective, longitudinal cohort study. • One small study did not report study dates and was therefore also excluded: • Parker et al 2023: Effect of using a structured pacing protocol on post-exertional symptom exacerbation and health status in a longitudinal cohort with the post-COVID-19 syndrome. • The remaining two publications were relatively large studies, evaluating between 500 and 2,000 patients, and likely reported on mutually exclusive populations: • Carlile et al 2023 – OpenPROMPT, A HRQoL study using the OpenSAFELY platform (Impact of long COVID on health-related quality-of-life: an OpenSAFELY population cohort study using patient-reported outcome measures (OpenPROMPT)); • Smith et al 2023 – Nuffield Health COVID-19 Rehabilitation Programme (Improved clinical outcomes in response to a 12-week blended digital and community-based long-COVID-19 rehabilitation programme); As highlighted in the response to the EAG's clarification questions, MSD believe that the OpenPROMPT study remains the most relevant study to inform utility values. It is a recent, large cohort study using the OpenSAFELY database, data from which have been preferentially used in previous COVID-19 technology appraisals TA878 and TA971, as well as by the EAG in the present appraisal. The study reported a long COVID utility of 0.49. As a sensitivity analysis, MSD calculated a pooled mean of data from Carlile et al 2023, Smith et al 2023 and Woolley et al 2023, in line with our approach taken for other model inputs in the submission, which generated a long COVID utility of 0.538, but such an approach is associated with caveats due to differences in patients and methodologies employed in the three studies. Nonetheless, it does show that when considering appropriate sources of evidence and cross-validating these against the patient testimonies, long COVID has a substantial impact on the HRQoL of patients. It also clearly shows that the EAG value is an outlier and as such should not be considered further for decision-making purposes. Due to the small number of appropriate published studies, utility values specific to the highest unmet need and at-risk population do not exist. However, 51% of long COVID patients in the OpenPROMPT study reported a disability and 48.1% had at least one comorbidity (the two may not be mutually exclusive). The study found that participants with comorbidities and disability were more likely to report a disutility associated with long COVID, and that comorbidities and disability were associated with a greater long COVID disutility. Therefore, the average reported utility of 0.49 may be an optimistic assumption, nonetheless, MSD consider it to be the best available evidence to inform this model input. It is important to note that the utility value for long COVID is only applied for 2 years in the model, which may represent a conservative assumption given the testimony of the patient representative in the committee meeting.

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	In the MSD scenario, with utility values for the symptomatic outpatient COVID-19 of 0.57 and for long COVID of 0.49, the ICER for molnupiravir compared with no treatment in the overall population is [redacted](only reported here for the purposes of replicability as this no longer reflects the updated positioning of the technology). Subgroup analyses as described in point 1 found that, in this scenario, molnupiravir dominates no treatment in those who are immunocompromised, and the ICERs per QALY for molnupiravir compared with no treatment are [redacted] in those aged 70 and above, [redacted] in those contraindicated to nirmatrelvir plus ritonavir and [redacted] in those with severe CKD. In the sensitivity analysis, using the pooled mean utility value for long COVID (0.538), the ICERs for molnupiravir compared with no treatment were [redacted] in the overall high risk population, [redacted] in those aged 70 and above, [redacted] in those contraindicated to nirmatrelvir plus ritonavir and [redacted] in those with severe CKD. In those who are immunocompromised, molnupiravir continued to dominate no treatment. **<u>MSD urge the Committee to endorse the use of OpenPROMPT as the most relevant utility estimate for long COVID to ensure that patients at highest unmet need and at-risk of progressing to severe disease are not disadvantaged as a result of inappropriate modelling inputs being used for decision making purposes.</u>**
5	**Are the recommendations sound and a suitable basis for guidance to the NHS?** MSD are disappointed in the negative Draft Guidance and do not believe that the recommendations are sound and a suitable basis for guidance to the NHS. SARS-CoV-2 is now endemic in the UK and disease caused by the virus (COVID-19) is likely to burden the NHS seasonally at the same time as other seasonal respiratory infections, such as influenza and pneumonia. MSD believe that any clinically effective and cost-effective intervention that may help to lessen this burden should be utilised, especially for those with the ***<u>highest unmet medical need and at risk of progressing to severe disease for which no suitable alternatives exist</u>***. Molnupiravir has been available under interim commissioning policy for several years and is still being prescribed to a number of patients: according to Hospital Pharmacy Audit data from IQVIA, [redacted] courses were prescribed in 2023, demonstrating that clinicians believe it has a place in therapy. This has been confirmed by MSD through conversations with clinical experts. Withdrawing a recommendation for molnupiravir in the UK would remove a potential treatment option for patients and clinicians, both of whom have indicated that they value having different treatment options available. For some patients at high risk of severe COVID-19 molnupiravir may represent their only treatment option, if they are contraindicated to nirmatrelvir plus ritonavir and are either unable to receive treatment with sotrovimab in a timely manner, or fall outside the sotrovimab recommendation. **<u>MSD urge the Committee to reconsider its negative Draft Guidance for molnupiravir, to allow its continued use in patients at highest unmet need and at-risk of severe COVID-19 but for whom both nirmatrelvir plus ritonavir and sotrovimab are contraindicated or unsuitable.</u>**
6	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

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	MSD believe that there are several points that should be borne in mind: • The cost-utility analysis of the PANORAMIC study published by Png et al presented evidence demonstrating that molnupiravir is likely to be cost-effective in patients aged ≥ 75, in agreement with MSD's conclusions. Data from the OpenSAFELY platform confirm that, under the interim commissioning policy, molnupiravir is disproportionately used in older patients (Antivirals and nMABs for non-hospitalised COVID-19 patients: coverage report | OpenSAFELY: Reports). Should molnupiravir not be recommended going forward, these patients at increased risk of severe COVID due to age may lose the most appropriate, perhaps their only, antiviral option. • CKD is more prevalent in ethnic minorities, especially those of black African or Afro-Caribbean origin (CKD due to Genetic Factors in people of African ancestry | UK Kidney). Severe CKD is a contraindication for nirmatrelvir plus ritonavir, so in the absence of a recommendation for molnupiravir, the only treatment option for these patients would be sotrovimab, which is administered as an infusion, usually in a secondary care setting. Any patients unable or unwilling to travel to access sotrovimab would no longer have an alternative oral antiviral option to reduce the risk of progression to severe COVID-19. • Nirmatrelvir plus ritonavir is likely to be an effective COVID-19 antiviral. However due to contraindications and drug–drug interactions it is unsuitable for many people at risk of severe COVID-19: in a small study of 298 clinically extremely vulnerable patients in the North Central London CMDU, 37% had a contraindication/drug–drug interaction that prevented them receiving nirmatrelvir plus ritonavir (Experiences of using Paxlovid to treat clinically extremely vulnerable non-hospitalised patients with COVID-19). Those with a physical disability limiting their ability to travel to a secondary care setting for receipt of sotrovimab may lose their only antiviral option should molnupiravir not be recommended. **To ensure adequate COVID-19 antiviral options for all patients regardless of age, race or disabilities, MSD urge the Committee to recommend molnupiravir for use in those for whom both nirmatrelvir plus ritonavir and sotrovimab are contraindicated or unsuitable. These groups reflect the highest unmet need and at-risk patients that would benefit the most from having a suitable treatment option.**
7	**MSD revised cost-effectiveness estimates** In the original submission, MSD presented an estimated ICER of [redacted] for molnupiravir compared with no treatment in the overall high-risk population. **However, given the updated positioning of molnupiravir in the subgroup of patients at highest unmet need and at-risk, this is no longer of relevance for decision making.** MSD presented cost-effectiveness estimates for the subgroups of interest, which may represent these patients at highest unmet need. ICERs per QALY in the original submission (prior to any changes by the EAG) were [redacted] for patients aged ≥ 70, [redacted] for patients contraindicated for nirmatrelvir plus ritonavir and [redacted] for patients with severe CKD, with molnupiravir dominant for the subgroup of patients who are immunocompromised. These ICERs are presented in row 1 of Table 2 in the confidential appendix to this consultation response.

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	The EAG made some minor corrections to the MSD economic model, adjusted the proportion of female patients in line with PANORAMIC, and applied a HR of 1 for time to discharge for inpatient COVID treatments. MSD accept these amendments and note that they have little impact on the estimated cost-effectiveness of molnupiravir in the overall high-risk population or any of the subgroups of interest (row 2, Table 2). In point 4 above, MSD present a revised utility scenario, utilising the most appropriate available utility values for outpatient COVID-19 and long COVID. This represents the MSD revised base case. Molnupiravir remains cost-effective compared with no treatment in all subgroups of interest (row 3, Table 2). MSD also carried out three sensitivity analyses: • with a pooled mean long COVID utility value (row 4, Table 2); • with a baseline hospitalisation rate of 8% for those aged ≥ 70 from OpenSAFELY as suggested by the EAG (row 5, Table 2); and • with lower baseline hospitalisation and mortality rates for those who are immunocompromised as suggested by the EAG (row 6, Table 2). In all cases, molnupiravir dominated no treatment in those who are immunocompromised, and ICERs remained below the NICE willingness-to-pay threshold of £30,000 per QALY gained in all other subgroups of interest. **In summary, MSD present a revised base case and results from a number of sensitivity analyses, and in all cases molnupiravir remained cost-effective compared with no treatment in the subgroups of interest, which represent the patients at highest unmet need and at risk. MSD therefore urge the Committee to recommend this cost-effective treatment option for mild-to-moderate COVID-19 for patients at highest unmet need, to reduce the risk of severe COVID-19 in those at high risk of disease progression and hospitalisation.**

Insert extra rows as needed

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comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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Appendix

Table 2. ICERs (£ per QALY gained) for the overall high-risk population and subgroups that may represent the subgroup of patients at highest unmet need, in the MSD submission base case, MSD revised base case and scenarios of interest

		Overall high-risk population ** included for completeness, no longer relevant for decision making **	**Age ≥ 70**	**Contraindicated to nirmatrelvir plus ritonavir**	**Immuno-compromised**	**Severe chronic kidney disease**
1	MSD submission base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	EAG corrections plus adjustments for % female and HR=1 for inpatient treatments – accepted by MSD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	**MSD revised base case – revised utility values***	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	MSD utility scenario with pooled mean long COVID value**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	MSD revised base case with baseline 8% hospitalisation rate for ≥ 70 from OpenSAFELY suggested by EAG^	N/A	[redacted]	N/A	N/A	N/A

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6	MSD revised base case with lower baseline hospitalisation and mortality rates for immunocompromised suggested by EAG^^	N/A	N/A	N/A	[redacted]	N/A

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
*Utilities used: Symptomatic outpatient: 0.57 from Sandmann et al (UK HSA); General ward (GW): 0.28 derived from Soare et al (as suggested by the EAG); Intensive care unit (ICU): 0 as per TA878 and TA971 (as suggested by the EAG); Long COVID: 0.49 from Carlile et al (OpenSAFELY).
**Utilities used: Symptomatic outpatient: 0.57 from Sandmann et al (UK HSA); GW: 0.28 derived from Soare et al (as suggested by the EAG); ICU: 0 as per TA878 and TA971 (as suggested by the EAG); Long COVID: 0.538 from MSD pooled analysis of relevant UK studies.
^Baseline hospitalisation rate of 8% for those aged ≥ 70 (from OpenSAFELY) instead of 12.84% (from Kaboré et al).
^^For immunocompromised patients, baseline hospitalisation rate of 15.9% (from Shields et al) instead of 22.47% (from Kaboré et al) and baseline mortality rate of 10.39% (from TA971) instead of 24.98% (from Evans et al).

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pharmacy Infection Network (subgroup of UK Clinical Pharmacy Association)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	[Insert disclosure here]
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Has all of the relevant evidence been taken into account?** Yes
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The language around sotrovimab needs reviewing due to the evidence of its lack of effect. Otherwise yes

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4	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** None that we can identify
5	**Sections 1.1 (Recommendations) and 3.18 (Equality)** We are concerned that the current availability of sotrovimab is patchy across the UK, and reference to this drug as the only alternative to Paxlovid might drive demand that adversely impacts on community IV drug administration. During the uncertainty of the pandemic, Sotrovimab having a NNT of 17 to prevent an admission or death was considered to be an appropriate strategy. The NICE committee reviewing TA878 in 2023 (https://www.nice.org.uk/guidance/ta878/chapter/3-Committee-discussion) indicated concern about the rapid mutation of the covid-19 virus and the latest research (Sotrovimab: A Review of Its Efficacy against SARS-CoV-2 Variants Viruses 2024, 16(2), 217; https://doi.org/10.3390/v16020217) indicates no immunological response to recent covid-19 variants. There are limited services commissioned or resources available to deliver this without compromising other IV antimicrobial services (e.g. OPAT) and consequently the NHS needs to decide whether resources should devoted to sotrovimab infusions going forward. The language in this TA needs to be clear about whether the NHS will be resourcing this so as to set the expectations of clinicians and patients. We also note that the FDA https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization-archived-information?#covid19 in December 2024 has revoked the licences for covid-19 monoclonal antibodies, at the manufacturer's request; with the consequence that sotrovimab may not be available to use.
6	**Section 3.2: The rapidly evolving SARS-CoV-2 virus** We agree that the evidence for the benefit of molnupiravir is based upon the pre-vaccine stage of the pandemic, and so it is not generalisable to the current endemic situation where there is herd immunity from mass vaccination and primary infections. We suggest that there needs to be reference to ensuring patients are vaccinated in the absence of alternatives to Paxlovid.
7	**Section 3.5: Proposed positioning of molnupiravir** We are concerned that MOVe-OUT is not generaliable to current practice and PANORAMIC sub-group data needs to be further investigated before it is accepted. We agree that the evidence at present cannot support the recommendation to offer molnupiravir.
8	**Section 3.10: Risk of novel mutations and risk of resistance with molnupiravir** The risk of novel mutations, and further resistance developing, is something that should be noted as a risk in a population that has the risk of reduced clearance of the virus. It is important that immunosuppressed people receive therapy to reduce the risk of

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	development and transfer of viral mutations reinforcing the need for effective options to be available.
9	**Section 3.20: Recommendation** We concur that there is a huge unmet need for patients and that this needs to be called out and promoted as an area of research

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Consultation on the draft guidance document – deadline for comments: 5pm on **Tuesday 17 December 2024**. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	n/a
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The treatment administration costs used for molnupiravir cost effectiveness calculations are too low. TA878 utilised a range of administration cost for nirmatrelvir plus ritonavir from £117 to £410. Given that molnupiravir is dominated by nirmatrelvir plus ritonavir in both the company and EAG base cases and the proposed place in treatment would be for patients contraindicated for

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	nirmatrelvir plus ritonavir, the same administration prices as for both treatments should apply. Whilst it is noted that the EAG has carried out a scenario analysis at £117, a further analysis at £410 is required to show the range of possible ICERs. [redacted]
2	
3	
4	
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6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. 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 submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 during our consultations 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.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Molnupiravir for treating COVID-19 [ID6340]

External Assessment Group's critique of the company's response to the Draft Guidance following the November 2024 Advisory Committee Meeting

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Date completed	31st January 2025

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LIST OF ABBREVIATIONS

CKD	Chronic kidney disease
CS	Company submission
DDI	Drug-drug interactions
DGD	Draft guidance document
EAG	External Assessment Group
eGFR	Estimated glomerular filtration rate
HR	Hazard ratio
HRQoL	Health-related quality of life
ICB	Integrated Care Board
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IV	Intravenous
MV	Mechanical ventilation
NHS	National Health Service
N+R	Nirmetravir plus ritonavir (Paxlovid)
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
QALY	Quality-adjusted life year
RWE	Real-world evidence
SLR	Systematic literature review
UK	United Kingdom
USA	United States

1 Introduction

This document is the External Assessment Group (EAG)'s critique of the response by the company, Merck Sharp & Dohme (UK) Limited, to NICE's draft guidance consultation document (DGD), issued in November 2024 following the first Advisory Committee Meeting for the technology appraisal of molnupiravir for treating COVID-19 [ID6340]. The EAG received the company's response to the DGD on 18th December 2024 and a new economic model on 19th December 2024. Additionally, the EAG was provided by NICE with consultee responses to the DGD from NHS England and the Pharmacy Infection Network (subgroup of UK Clinical Pharmacy Association).

The company's response to the DGD contains the following documents:

- The Company Response document
- An updated economic model

In this report we present the following:

- A critique of the company's response to NICE's DGD and the company's new evidence (section 2). This addresses seven key suggestions and preferences noted by the NICE Committee in the DGD, which are summarised in Table 1 below.
- A brief commentary on the NHS England response to the DGD, as this influences an EAG scenario analysis (section 3).
- A validation of the results of the company's updated cost-effectiveness analysis (section 4).
- Results of the EAG's economic base case and scenario analyses (section 5).

Table 1 Summary of the NICE Committee's preferred assumptions and recommendations in the Draft Guidance Consultation Document (DGD) and the company's responses to these

NICE Committee's preferred assumptions and recommendations in the DGD		Company's response	EAG comments
1 Definition of the highest unmet need population	The NICE Committee needs to see additional evidence that better defines the highest unmet need population, including why these treatments would be contraindicated and why sotrovimab might not be feasible or desired (DGD section 3.5).	The company have defined the highest unmet need population which they refer to as the "highest unmet need and at-risk population" (see section 2.1 below): • With ≥1 risk factors for progression to severe COVID-19 (as per the Edmunds or McInnes definition), and • Who are contraindicated to nirmatrelvir plus ritonavir, and • For whom sotrovimab is contraindicated, unfeasible or undesirable (e.g., in cases of complex comorbidities, haematological disease, severe kidney or liver disease, or difficulties accessing sotrovimab due to geographical location). No additional evidence for why these criteria define the highest unmet need population has been provided beyond that already presented in the CS (CS section B.1.3.2).	The "highest unmet need and at-risk population" does not fully align with the clinical effectiveness evidence provided by the company, which is from four patient subgroups that were already reported in CS Appendices E.1 to E.4 (see section 2.2 below): • Patients aged ≥70 years • Patients contraindicated to N+R • Patients with severe chronic kidney disease (CKD) • Immunocompromised patients These four subgroups do not explicitly capture patients for whom sotrovimab is contraindicated, unfeasible, or undesirable; and do not capture all risk factors listed in the McInnes and Edmunds criteria. The EAG assume that the company intend these subgroups to be generally reflective of the wider set of McInnes and Edmunds risk factors but this is not stated in the company's response.

NICE Committee's preferred assumptions and recommendations in the DGD		Company's response	EAG comments
2 Clinical effectiveness of molnupiravir in the highest unmet need population	The NICE Committee needs to see updated evidence on the clinical effectiveness of molnupiravir in this highest unmet need population (DGD section 3.5) (see also DGD sections 3.7 to 3.9).	The company have not provided any new evidence for the clinical effectiveness of molnupiravir beyond that reported in the original CS and CS Appendices.	The evidence for clinical effectiveness of molnupiravir for the "highest unmet need and at-risk population" is taken from the four subgroups reported in CS Appendices E.1 to E.4. These were analysed as subgroups in the original economic analysis reported in the CS but have now been incorporated in the company's economic analysis base case (see section 2.2 below).
3 Exploration of PANORAMIC subgroups to clarify clinical effectiveness of molnupiravir in the highest unmet need population	The NICE Committee would like to see PANORAMIC subgroups explored to inform the clinical effectiveness of molnupiravir compared with no treatment in the highest unmet need population (DGD section 3.7).	The company do not agree that the PANORAMIC trial provides relevant evidence due to its overall broader risk population (Company Response document page 2). The company's response does not explore the potential relevance of subgroups within the PANORAMIC trial (see section 2.3 below).	The company have not addressed this aspect of the NICE Committee's request in the DGD. The EAG is uncertain how much publicly accessible data on subgroups within PANORAMIC is available. A systematic exploration of this has not been provided.
4 Relevance of evidence from RWE studies and RWE NMAs to the highest unmet need population	The NICE Committee would need to see either evidence that the network meta-analyses (NMAs) of real-world evidence (RWE) studies reflect the highest unmet need population, or an updated NMA of RWE studies or new RWE evidence to inform modelling of the highest unmet need population (DGD section 3.9).	The company discuss the RWE NMAs and OpenSAFELY studies, as well as studies by Xie and Ahmad identified by re-review/ targeted review, on pages 6-7 of their response to the DGD. However, the company's response does not provide any new evidence that the RWE NMAs or individual studies reflect the "highest unmet need and at-risk population" as defined in their response to the DGD (summarised in issue 1 above).	The company's re-review / targeted review process is unclear and we are uncertain whether other relevant studies with high-risk subgroups exist. The Xie and Ahmad studies have uncertain relevance to the UK NHS. The company do not discuss whether the RWE NMAs could or should be amended to focus on one or more high-risk subgroups (see section 2.4 below).

NICE Committee's preferred assumptions and recommendations in the DGD		Company's response	EAG comments
5 Most appropriate estimate of the relative effectiveness of molnupiravir compared to no treatment	The Committee would like to see various sources of clinical evidence explored, including the RWE NMAs, PANORAMIC, and single studies including Tazare et al. and the OpenSAFELY database to see which provides the most appropriate estimate of relative effectiveness for the highest unmet need population (DGD section 3.13).	The company have updated their cost-effectiveness analysis reflect the "highest unmet need and at-risk population" instead of the "overall high risk population", using existing data for subgroups of patients in the original CS. However, they have not explored the potential role of these different sources of clinical evidence for informing the subgroups.	The company have not systematically weighed up the strengths and limitations of these different sources of evidence and have not provided any new evidence on the clinical effectiveness of molnupiravir compared to no treatment (section 2.5 below).
6 Economic analysis: baseline hospitalisation rates for those with highest unmet need	The NICE Committee noted that company and EAG base case values for hospitalisation rates were specific to the initial marketing authorisation. The Committee thought that considering different hospitalisation rates should be explored if up-to-date hospitalisation rates for the highest unmet need population are available (DGD section 3.12).	The company have not submitted any new evidence on the hospitalisation rates for the highest unmet need population. They assumed that the patients of the four subgroups (viz, contraindicated to nirmatrelvir plus ritonavir, patients aged over 70 years, immunocompromised patients and those with severe CKD) are a reasonable proxy for the highest unmet need population.	The company have not addressed this aspect of the NICE Committee's request in the DGD. We are uncertain whether the hospitalisation rates for the subgroups are representative of the highest unmet need population defined by the company. For completeness, we conducted two exploratory scenario analyses using lower hospitalisation rates for patients aged over 70 years (8%) and for the immunocompromised patients (15.90%). For further details, see sections **Error! Reference source not found.** and 5.2 below.
7 Economic analysis: source of utility values for those with highest unmet need	The NICE Committee suggested that additional evidence should be explored to ensure that the utility values used in the model reflect the highest unmet need population (DGD section 3.14).	The company noted that utility values specific to the highest unmet need patients are limited in the literature. They attempted to address the NICE Committee's suggestion by applying revised utility values for the health states in their revised base case model submitted as part of their response to the	We acknowledge that applying the utility for long COVID from Soare et al.[1] might be an underestimation, particularly for the highest unmet need patients. Therefore, we accept the company's revised estimate of 0.49 for this health state. The EAG updated our revised base case applying this change in utility value, with no

NICE Committee's preferred assumptions and recommendations in the DGD		Company's response	EAG comments
		DGD. They applied the EAG values for the hospitalisation health states (for the general ward and the intensive care unit) and updated the values for the two health states- 'symptomatic outpatient' and 'long COVID'.	other change for the remaining health states. For further details, see sections 2.7 and 5 below.

2 EAG CRITIQUE OF THE COMPANY'S RESPONSE TO THE DRAFT GUIDANCE DOCUMENT

The EAG's critique below addresses the seven specific recommendations of the NICE Committee in the DGD, as listed in Table 1 above and summarised, respectively, in sections 2.1 to 2.7 below.

2.1 Definition of the highest unmet need population (DGD section 3.5)

The company refers to this as the "highest unmet need and at-risk population" (Company Response pages 3-4) which they have defined as follows:

- People with ≥1 risk factor(s) for progression to severe COVID-19 (as per the Edmunds or McInnes definitions), and
- Who are contraindicated to nirmatrelvir plus ritonavir, and
- For whom sotrovimab is contraindicated, unfeasible or undesirable (e.g., in cases of complex comorbidities, haematological disease, severe kidney or liver disease, or difficulties accessing sotrovimab due to geographical location).

The EAG agree that the target population appears appropriate as it includes all high-risk groups listed in the McInnes criteria[2] and Edmunds criteria[3] who would be unable to receive both nirmatrelvir plus ritonavir (N+R) and sotrovimab, i.e. patients for whom no other treatment options exist. As noted by the company, this highest unmet need and at-risk group approximates that specified in the NHS England Interim Clinical Commissioning Policy.[4] Whilst the company have defined the highest unmet need and at-risk population broadly in terms of the risk factors, we note that the clinical evidence for this target population is from more specific subgroups (see section 2.2 below).

Patients who are at risk of progression to severe COVID-19 would be a priority group for COVID-19 vaccination. The company do not state whether their target population is vaccinated and/or unvaccinated patients or discuss whether or how vaccination would influence use of molnupiravir. We assume that all at-risk patients in the company's target population would have been vaccinated.[5]

In DGD section 3.5 the NICE Committee expressed uncertainty around how the subpopulation who could not have N+R or sotrovimab is defined, including why N+R would be contraindicated and why sotrovimab might not be feasible or desired. The company's response reiterates information that had previously been provided in the CS as follows:

- Patients contraindicated to N+R include those with inadequate estimated glomerular filtration rate (eGFR), and/or those with current or expected use of any medications with CYP3A4 clearance or inductions due to drug-drug interactions (DDI) (e.g. antiarrhythmics, anticoagulants, anticonvulsants, antiretrovirals, anxiolytics, cancer drugs or immunosuppressants) (Company Response document page 6). The company cite a study conducted by Gahir et al. 2022 [6] in north central London which showed that 37% of patients (109/298) were contraindicated to N+R. Primary reasons were DDI in 75% of those contraindicated (83/109) and CKD in 17% (18/109) (Company Response document page 15).
- Patients that fall within the Edmunds criteria [3] but not the McInnes criteria [2] for high risk of progression to severe COVID-19 are not eligible to receive sotrovimab (Company Response document page 6).
- Access to sotrovimab, which requires IV infusion, can be challenging for some patients, particularly those who live further away from, or lack transport to reach, the relevant healthcare centres (Company Response document page 5).
- Patients who are at highest risk of developing severe COVID-19 may prefer to self-administer treatment at home rather than risk exposure to COVID-19 and other pathogens in healthcare centres (Company Response document page 5).

2.2 Clinical effectiveness of molnupiravir in the highest unmet need population (DGD section 3.5)

The company response implies that there are four relevant subgroups for the "highest unmet need and at risk population": patients aged ≥70 years, those contraindicated to N+R, those with severe chronic kidney disease (CKD), and those immunocompromised (NB the Company Response document refers inconsistently to the age group being ≥70 years and also above 70 years). However, these subgroups are narrower than the company's definition of the highest unmet need and at risk population noted in section 2.1 above, as they do not explicitly capture all potential comorbid conditions listed in the McInnes and Edmunds criteria and do not cover people unable to receive sotrovimab. The EAG assume that data are limited for other relevant subgroups; however, the company have not clarified this. These four subgroups were identified in the original CS, with the data available to support their clinical effectiveness outcomes reported in CS Appendices E.1 to E.4. In the company's response to the DGD these four subgroups have been included in the company's economic analysis base case (for discussion see section **Error! Reference source not found.** below).

The company have not provided any new evidence relating to the clinical effectiveness of molnupiravir in the four highest unmet need and at-risk population subgroups, beyond that already reported in CS Appendices E.1 to E.4.

2.3 Exploration of PANORAMIC subgroups to clarify clinical effectiveness of molnupiravir in the highest unmet need population (DGD section 3.7)

The company disagree that the PANORAMIC trial population is relevant due to the trial's overall broad eligibility criteria. The company have not explored high-risk subgroups within PANORAMIC as suggested by the NICE Committee. We note that on page 8 of their response the company cite the hazard ratio for the time to symptom resolution in PANORAMIC, comparing molnupiravir versus usual care, but this is for the overall trial population.[7]

2.4 Relevance of evidence from RWE studies and RWE NMAs to the highest unmet need population (DGD section 3.9)

The company acknowledge the lack of UK studies included in the RWE NMAs (Company Response document page 6). They argue that although the Tazare et al. 2023 OpenSAFELY study [8] is relevant to the UK it is only a single publication whereas the NMAs included multiple studies. However, this argument does not resolve the problem that the NMAs contain non-UK studies and therefore have questionable relevance to UK clinical practice. The company further state on page 7 of their response that "the NMA incorporates OpenSAFELY data from multiple studies" which is incorrect. For most of the analysed outcomes no UK studies were included in the NMAs whilst for all-cause and COVID-related hospitalisation or death only one OpenSAFELY study, by Zheng et al. 2023,[9] was included (EAG Report Appendix 6).

The company also argue on page 7 of their response that the RWE NMAs of all-cause hospitalisation and all-cause death provide an important finding for outcomes that were not reported by Tazare et al. 2023. However, this argument again does not resolve the problem that the NMAs for all-cause hospitalisation and all-cause death contained no UK studies and therefore have questionable generalisability to the NHS. Moreover, the company's discussion does not alter any of the information which had already been presented in slide 19 at the November 2024 Advisory Committee Meeting.

In their response to the DGD the company say that "to ensure all potentially relevant RWE was included" they carried out "two additional investigations" (Company Response document page 7):

- "Studies identified from the SLR but carried out in the pre-Omicron time period were re-reviewed, as were the studies included in the RWE NMA".
- "A targeted review was conducted to identify studies published subsequent to the last search date for the SLR".

The methods of these additional company investigations are not described. The company identified two studies which refer to cohorts already included in the RWE NMAs but which also report results for high-risk subgroups:

- A study by Xie et al. 2023 [10] conducted in the USA (January to September 2022) which had been included in the RWE NMAs and which the company argue provides results for patients at highest risk of progression to severe disease. The company report results from this study in Figure 2 of the Company Response document which show that molnupiravir reduced the risk of hospitalisation or death at 30 days for subgroups of people with cancer, CKD, diabetes and cardiovascular disease.

- A study in Israel by Ahmad et al 2024 [11] which updates an existing study in the RWE NMA by Arbel et al. 2022.[12] The company claim that Ahmad et al. 2024 has a higher risk population than those enrolled in other studies in the NMAs, with almost a third comprising patients with severe clinical conditions, although this is difficult to verify in an objective sense since the studies in the NMAs were diverse and heterogeneous in their populations (EAG Report Appendix 4).

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

2.5 Most appropriate estimate of the relative effectiveness of molnupiravir compared to no treatment (DGD section 3.13)

The company have not provided any new evidence on the clinical effectiveness of molnupiravir compared to no treatment. Rather, they have updated their cost-effectiveness

analysis using existing data from the four subgroups of patients noted in section 2.2 above and reported in Appendices E.1 to E.4 of the original company submission (and discussed in sections 2.6, 2.7 and 4.1 below), for the ICERs to reflect the "highest unmet need and at-risk population".

2.6 Hospitalisation rate (DGD section 3.12)

The NICE Committee note in the DGD that both the company's and EAG's base case values were specific to the initial marketing authorisation population and that the Committee would like to see updated hospitalisation rates for untreated patients for the highest unmet need population, if available (DGD Section 3.12). The company have not submitted any new evidence on the hospitalisation rates for the highest unmet need population. Instead, they referred to the already used hospitalisation rates for untreated patients in their original model for the subgroups who are: i) contraindicated to N+R, ii) aged over 70 years, iii) immunocompromised and iv) with severe CKD (CS Appendices E.1 to E.4; Company Response document Table 1). As discussed above, the company assumed that the patients of these four subgroups are a reasonable proxy for the highest unmet need population (see section 2.2).

The EAG has critiqued the hospitalisation rates for the subgroups in section 4.2.6.1.1.2 of our original EAG report. To reiterate briefly, we were uncertain whether the company's COVID-19-related hospitalisation rates for patients aged over 70 years (12.84%) and for immunocompromised patients (22.47%) (Company Response document Table 1) were overestimated, as we note that these estimates are similar or higher than the hospitalisation rates reported in the MOVe-OUT trial which was conducted in the pandemic setting. For immunocompromised patients, it is unclear whether the hospitalisation rates of untreated patients have changed significantly in the endemic setting, given the characteristics of these individuals (e.g., lower efficacy of the vaccines). Another issue with the estimates for immunocompromised patients is that the definition of immunocompromised patients is not consistent across the studies. Due to these uncertainties, we tested the use of lower hospitalisation rates for these subgroups in scenario analyses: an exploratory value of 8% for the patients aged over 70 years and 15.90% for the immunocompromised patients, as reported by Shields et al. 2022.[13] We agree with the company's base case inputs for the other subgroups (around 4%). It should be noted, however, that we are unclear whether the hospitalisation rates for these subgroups are representative of the highest unmet need population defined by the company. On page 11 of their response to the DGD, the company state that they obtained clinical validation for the appropriateness of the baseline hospitalisation rates used for the subgroups in their original company model. They argued

that patients in the highest unmet need and at-risk group are likely to experience higher baseline hospitalisation rates than the overall population at risk of severe COVID-19 if left untreated with suitable alternative options. We note that this argument does not change the original interpretation at the November 2024 Advisory Committee Meeting.

2.7 Utility values for those with highest unmet need (DGD section 3.14)

In the Draft Guidance, the NICE Committee noted that the population with the highest unmet need was likely to include those with pre-existing health conditions and comorbidities, who are already on treatments that might affect quality on life. Therefore, the committee sought additional evidence on the utility values to reflect the highest unmet need population (DGD Section 3.14).

As discussed by the EAG in section 4.2.7.2 of our original EAG report and acknowledged by the company in their response to the DGD, the vignette studies used in the company's original base case are associated with several limitations. The EAG used an alternative source for utilities in our original base case, the study by Soare et al.[1] However, the NICE Committee noted that the values for long COVID appeared implausible according to the patient-expert's testimony and that this study might be associated with negative bias which could have underestimated the utilities.

The company stated that they attempted to identify more appropriate utility values for the economic model by looking at the available RWE. They agreed with the EAG values for the hospitalisation health states (0.28 for the general ward and 0 for the intensive care unit), but used alternative utilities for the symptomatic outpatient health state and long COVID health state:

- Symptomatic outpatient health state: the company used a utility value of 0.57 in their revised base case, reported as the utility for the "worst day of COVID" in the UK Health Security Agency study by Sandmann et al.[14]

- Long COVID health state: the company conducted a systematic literature review of studies reporting long COVID utilities elicited using EQ-5D carried out in the UK. From eight studies identified, the company considered the OpenPROMPT study [15] the most relevant to inform utility values. This is a recent HRQoL study using the OpenSAFELY platform. This study reported a utility value of 0.49, which was used in the company's revised base case.

The company also stated that utility values specific to the highest unmet need patients are limited in the literature. Although 51% of long COVID patients in the OpenPROMPT study reported a disability and 48.1% had at least one comorbidity, they consider that the average utility of 0.49 may be an optimistic assumption.

The EAG acknowledge that the utility for long COVID from Soare et al. might be an underestimation, particularly for the highest unmet need patients. Also, changing the utility for the symptomatic outpatient health state from 0.59 (EAG original base case) to 0.57 (company's revised base case following the Draft Guidance) has a minor impact on the model results. And, using the value of 0.59 is aligned with the remaining values taken from Soare et al. Therefore, in the EAG revised base case, we used the utility for long COVID suggested by the company (0.49) and kept the remaining utilities as in the EAG original base case. Table 2 presents the utility values used in the company and EAG revised base case analyses. For further details on the impact of this revision on the overall cost-effectiveness results, see section 5 below.

Table 2 Utility values used in the company's and EAG's revised models

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

MV: Mechanical ventilation

3 EAG COMMENT ON THE NHS ENGLAND RESPONSE TO THE DRAFT GUIDANCE DOCUMENT

The NHS England response to the DGD raises a unique point concerning the administration costs for molnupiravir. NHS England considers the administration costs of molnupiravir are too low and suggests they should be more similar to the administration costs estimated for nirmatrelvir plus ritonavir (between £117 and £410). They note that the EAG has carried out a scenario analysis using the £117 cost but suggest that a further analysis with the £410 cost should be conducted. In addition, they highlight that [redacted].

Based on this advice from NHS England, the EAG has conducted an additional scenario analysis with an alternative administration cost of £410 for molnupiravir and repeated the scenario with the cost of £117 (see section 5.2 below).

4 VALIDATION OF THE COMPANY'S REVISED COST-EFFECTIVENESS RESULTS

4.1 Company's revised cost-effectiveness results

The company applied revised utility values in their revised base case (as shown in Table 2 above), which also included the following accepted changes suggested by the EAG:

- EAG corrections to the company's original model.
- Applying the proportion female as 59%.
- Applying a hazard ratio (HR) of 1 for inpatient treatments.

The EAG re-ran the company's revised analyses and was able to replicate their revised base case results as well as the results reported for the scenarios shown in Table 2 of the company's response to the DGD, except for the following scenario, shown in Table 3.

Table 3 Discrepancy in the ICERs (£ per QALY) obtained by the EAG versus the company for a scenario for molnupiravir versus no treatment

Scenario	Company results	EAG results
Company revised base case with baseline 8% hospitalisation rate for patients aged ≥ 70 from OpenSAFELY suggested by EAG	[redacted]	[redacted]

5 EAG ANALYSES

5.1 EAG's preferred assumptions

Based on the EAG's critique presented throughout sections 2 and 3 above, we have updated the EAG preferred assumptions to include the revised utility for long COVID suggested by the company (0.49), while making no other change to the original EAG assumptions as discussed in section 6.4 of the post Factual Accuracy Check version of the EAG report. For clarity and completeness, we have listed the revised EAG preferred assumptions for the subgroups below:

Overall population

- Proportion of females at baseline: 59% based on the PANORAMIC trial rather than 51.3% based on the MOVe-OUT trial.
- 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.
- Treatment effect of inpatient treatments (time to discharge): Hazard ratio 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.
- Health state utilities: symptomatic outpatient (0.59); hospitalisation in the general ward (0.28); hospitalised in ICU and mechanical ventilation (0) and long-term sequelae (0.49) as shown in Table 2.

Subgroups: Those aged over 70 years; contraindicated to nirmatrelvir plus ritonavir and those with chronic kidney disease

- Proportion of females at baseline: 59% based on the PANORAMIC trial rather than 51.3% based on the MOVe-OUT trial
- 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.
- Health state utilities: symptomatic outpatient (0.59); hospitalisation in the general ward (0.28); hospitalised in ICU and mechanical ventilation (0) and long-term sequelae (0.49) as shown in Table 2 .

Immunocompromised subgroup

- Proportion of females at baseline: 59% based on the PANORAMIC trial rather than 51.3% based on the MOVe-OUT trial.
- Mortality: 10.39% based on TA971 rather than 24.98% based on the INFORM study.
- Health state utilities: Health state utilities: symptomatic outpatient (0.59); hospitalisation in the general ward (0.28); hospitalised in ICU and mechanical ventilation (0) and long-term sequelae (0.49) as shown in Table 2.

The results of the revised EAG base case are presented below in Table 4. Comparing the results with the company's revised base case, applying the EAG assumptions [redacted]. Molnupiravir [redacted] for the immunocompromised subgroup when compared against no treatment.

Table 4 EAG base case results, ICER (£ per QALY) molnupiravir versus no treatment

	Overall high-risk population	Age ≥ 70	Contraindicated to nirmatrelvir plus ritonavir	Immuno-compromised	Severe chronic kidney disease
Company revised base case – revised utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2 Scenario analysis conducted on the EAG's base case

The EAG conducted several scenario analyses on our revised base case, the results of which are presented for molnupiravir versus no treatment in Table 5.

Table 5 Scenarios conducted on the EAG revised base case results, ICER (£ per QALY) molnupiravir versus no treatment

Analysis	Overall high-risk population	Age ≥ 70	Contraindicated to nirmatrelvir plus ritonavir	Immuno-compromised	Severe chronic kidney disease
EAG revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation rate of 8% for age ≥70 years	N/A	[redacted]	N/A	N/A	N/A
Hospitalisation rate of 15.9% for immunocompromised	N/A	N/A	N/A	[redacted]	N/A

Molnupiravir administration cost of £410	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Molnupiravir administration cost of £117	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.3 Additional scenarios conducted on the EAG base case post PMB-2

In response to a request of the NICE Technical team raised in the pre-meeting briefing 2 on 21-January 2015, the EAG conducted the following scenario analyses on our revised base case, the results of which are presented for molnupiravir versus no treatment in Table 6.

Table 6 Additional scenarios conducted on the EAG revised base case results for two subgroups, ICER (£ per QALY) molnupiravir versus no treatment

Immuno-compromised	**ICER (£ per QALY)**
EAG revised base case	[redacted]
Hospitalisation rate of 4%	[redacted]
Hospitalisation rate of 4% plus molnupiravir administration cost of £117	[redacted]
Aged over 70 years	**ICER (£ per QALY)**
EAG revised base case	[redacted]
Hospitalisation rate of 0.77% (based on PANORAMIC)	[redacted]
Hospitalisation rate of 0.77% (based on PANORAMIC) plus molnupiravir administration cost of £117	[redacted]

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