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Cost-effectiveness evaluation of molnupiravir for coronavirus disease 2019

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SARS-CoV-2 による感染症に対するモルヌピラビルの費用対効果評価

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保健医療経済評価研究センター（C2H）

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Abstract

The academic technology assessment group (ATAG) reviewed a report on molnupiravir' s additional benefits and cost-effectiveness compared to standard of care (SoC) in adults with coronavirus disease 2019 (COVID-19) who are at an increased risk of progression to severe COVID-19 (except adults with severe COVID-19). The report was submitted by the manufacturer of molnupiravir (MSD). This report summarizes the results of a review and reanalysis conducted by the ATAG. When evaluating the additional benefits of molnupiravir over the SoC, the manufacturer provided data from the MOVe-OUT trial. The manufacturer insisted on the additional benefits of molnupiravir over SoC based on the MOVe-OUT trial' s findings, which indicated that molnupiravir had a statistically significant effect on the incidence of hospitalization or death at day 29 compared with placebo. The ATAG observed that the MOVe-OUT trial was conducted in unvaccinated adults infected with the delta, gamma, and mu variants of SARS-CoV-2. Given that the main variant of SARS-CoV-2 is Omicron and COVID-19 vaccination has become widespread in Japan, the generalizability of the study results is limited. Therefore, the ATAG proposed that the evaluation should follow the PANORAMIC trial (conducted in the U.K., University of Oxford) for vaccinated adults infected with omicron variants. However, owing to differences in the definition of risk factors for progression to severe COVID-19 and the SoC in Japan versus the U.K., the PANORAMIC trial included participants who were not defined as having risk factors in Japan and those who were treated with other medications indicated for the treatment of COVID-19. Therefore, the ATAG evaluated the treatment effect of molnupiravir after extracting adults who met the Japanese definition of risk factors for progression to severe COVID-19 and the SoC in Japan from the PANORAMIC study. The post-hoc analysis of the PANORAMIC trial demonstrated that the odds ratio for hospitalization or death was 1.053 (95% confidence interval: 0.775–1.396), and the difference in event rate was not significant between the molnupiravir plus usual care group and the usual care group. Based on these results, the ATAG could not determine that molnupiravir had additional benefits for hospitalization or death. Clinical experts have suggested that molnupiravir may have additional benefits for older adults based on the results of the subgroup analysis by age; however, the available evidence is limited, and further data are required to establish these benefits. The manufacturer conducted a cost-effectiveness analysis using a decision-tree model representing the acute phase of COVID-19 and a Markov model representing the post-acute phase of COVID-19. As molnupiravir did not exhibit additional benefits over the SoC, the ATAG conducted a cost-minimization analysis, revealing that molnupiravir increased costs by JPY 94,312. In conclusion, for adults with COVID-19 at an increased risk of progression to severe COVID-19, the results of the ATAG analysis suggest that the ICER for molnupiravir compared with SoC is likely to indicate equivalent effectiveness and cost increase from the perspective of public healthcare payers in Japan.

keywords: molnupiravir, COVID-19, cost-effectiveness analysis, health technology assessment

抄録

公的分析は、モルヌピラビルの製造販売業者（MSD 株式会社）より提出された、SARS-CoV-2 による感染症（COVID-19）患者における、標準療法に対するモルヌピラビルの追加的有用性及び経済評価に関する報告についてレビューを行った。本報告書ではその結果と、公的分析が実施した再分析の内容を要約している。まず追加的有用性の評価に際して、製造販売業者は、COVID-19 患者を対象とした抗ウイルス薬、中和抗体薬、免疫抑制・調節薬のランダム化比較試験に関するシステマティックレビューを実施し、このうち、重症化リスク因子を有する COVID-19 患者を対象とした MOVe-OUT 試験が追加的有用性評価の主たるエビデンスとして用いられた。製造販売業者は、この MOVe-OUT 試験における主要評価項目である無作為化 29 日目までの理由を問わないすべての入院又は死亡した患者の割合で、優越性が検証されたことからモルヌピラビルが追加的有用性を有すると主張した。公的分析では、製造販売業者が追加的有用性評価の主な根拠とした MOVe-OUT 試験はデルタ株、ミュー株、及びガンマ株等の環境下における新型コロナワクチン未接種者を対象とした臨床試験であり、主な流行株はオミクロン株であったことに加えて、新型コロナワクチン接種が普及している本邦の臨床実態と状況が異なると考えられた。そのため、英国でオミクロン株環境下において、ワクチン接種者を対象として実施された PANORAMIC 試験を中心にモルヌピラビルの追加的有用性評価を行った。ただし PANORAMIC 試験には、本邦においては必ずしも重症化リスク因子を有すると定義されない症例や、モルヌピラビル使用時に他の抗ウイルス薬等を併用した症例が含まれていた。そこで、本邦における重症化リスク因子の定義や標準治療の内容に合致した症例のみを抽出した上で、モルヌピラビルの評価を行った。その結果、標準治療に対するモルヌピラビルの入院又は死亡におけるオッズ比は 1.053（95% 信頼区間：0.775 to 1.396）であったことから、公的分析ではモルヌピラビルは比較対照技術に対して追加的有用性を有すると判断できないと評価した。製造販売業者は COVID-19 の発症から急性期治療終了までの分析期間は決定樹モデル、その後の分析期間（生涯）はマルコフモデルにより表現し、費用効果分析を実施した。モルヌピラビルの有効性パラメータ（入院、入院患者の重症化及び死亡に対する効果）には、MOVe-OUT 試験のデータが用いられていた。公的分析ではモルヌピラビルは比較対照技術に対して追加的有用性を有すると判断できないと評価したことから、治療効果に群間差を設定せず、治療費用を比較する費用最小化分析を実施した。その結果、モルヌピラビルは比較対照技術に対して 94,312 円の費用増加であった。以上より、公的分析の結果は、本邦における公的医療の立場において、標準治療に対してモルヌピラビルは「効果が同等（あるいは劣り）、かつ費用が高い」の区間に所属する可能性が高いことを示唆した。

キーワード：モルヌピラビル、COVID-19、費用効果分析、医療技術評価

略語表

略語	正式表記
AE	Adverse Event
ASMR	Amelioration du Service Médical Rendu
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence Interval
EMA	The European Medicines Agency
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
ICER	Incremental Cost-Effectiveness Ratio
IQWiG	Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IQR	Interquartile Range
MSAC	Medical Services Advisory Committee
MTA	Multiple Technology Appraisal
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SR	Systematic Review
SMC	Scottish Medicines Agency
SMR	Service Médical Rendu
STA	Single Technology Appraisal
OR	Odds Ratio
RR	Risk Ratio
RRR	Relative Risk Reduction

0. 分析枠組み

対象品目名は「モルヌピラビル(ラゲブリオカプセル200 mg)」で、製造販売業者はMSD株式会社である。モルヌピラビルは、SARS-CoV-2による感染症(COVID-19)を対象とした抗ウイルス薬であり、2022年8月10日の中央社会保険医療協議会総会において、費用対効果評価の対象品目に指定された。モルヌピラビルの市場規模予測は138億円で、費用対効果評価の区分はH1(市場規模が100億円以上)に該当する。モルヌピラビルに係る分析枠組みは、2022年11月25日の費用対効果評価専門組織を経て、表0-1の通り設定された。

表0-1 評価対象技術に関する分析枠組みの概要

分析対象集団(複数可)	重症化リスク因子を有するSARS-CoV-2による感染症(COVID-19)患者(18歳以上) 但し、有効性が確立していないため、重症度*の高いCOVID-19患者を除く *重症度の定義は新型コロナウイルス感染症(COVID-19)診療の手引き・第8.1版に準ずる。
分析対象集団を設定した理由(適宜記載)	
比較対照技術名	標準治療*(評価対象技術：モルヌピラビル＋標準治療) *COVID-19に対して治療の適応がある薬剤を除く、対症療法
比較対照技術を選定した理由	2022年8月の本剤評価品目選定時点では、臨床において抗ウイルス薬としてモルヌピラビルの他に、レムデシビルやニルマトレルビル/リトナビルが政府確保品目もしくは薬価収載後の一般流通品目として使用されている。レムデシビルは臨床専門家の意見聴取等から、入院外診療において幅広くは使用されておらず、主に入院外で用いる経口薬のモルヌピラビルによっては代替されない。一方で、ニルマトレルビル/リトナビルはモルヌピラビルと同様の経口薬であり、治療上の位置づけが類似している。したがって、本来のところニルマトレルビル/リトナビルが比較対照技術として適当と考えられるものの、ニルマトレルビル/リトナビルは薬価未収載で薬剤価格が不明なため、分析の実施が困難である。よって、その他に公的医療保険で使用が認められ代替されると想定されるものが存在しないことから、比較対照技術は標準治療(評価対象技術：モルヌピラビル＋標準治療)とすることが適当である。
「公的医療の立場」以外の分析の有無	有(その詳細:　　)　　無
効果指標としてQALY以外を使用する場合、その指標と理由	(該当せず)
その他	(該当せず)

1. 諸外国の医療技術評価機関における評価結果

1.1　評価結果の概要

諸外国の医療技術評価機関におけるモルヌピラビルの評価結果を調査し、製造販売業者による報告と比較した。諸外国における評価の概要は表1-1-1~1-1-3に要約した。

表1-1-1 主要国における評価の一覧表

国名	機関名	評価結果	
		製造販売業者	公的分析
イギリス	NICE	推奨/非推奨/条件つき推奨(具体的に:　　)/[その他](MTA実施中) 評価ステータス: 最終ガイダンス/[ドラフト]/[その他](　　)	モルヌピラビルに関するMTAが実施されていたものの、製造販売業者からのアピールに応じて新たなSTAを実施し、その結論が出るまで最終ガイダンスは公表しないことで合意した。
	SMC	該当なし	左記に同じ
フランス	HAS	該当なし	左記に同じ
ドイツ	IQWiG	該当なし	左記に同じ
カナダ	CADTH	該当なし	左記に同じ
オーストラリア	PBAC	推奨/非推奨/条件つき推奨(具体的に:　　)/[その他](評価中)	条件つき推奨(償還される対象に条件が付されている)

表1-1-2 各国における費用対効果評価実施の有無

国名	機関名	評価結果の有無	
		製造販売業者	公的分析
イギリス	NICE	あり/ なし/[評価中]([ドラフトあり]/なし)/不明	MTAについてFinal draft guidanceが存在するが、最終ガイダンスとしては公表しないこととされている。
	SMC	あり/ なし/ 評価中/不明	あり/[なし]/ 評価中/不明
フランス	HAS	あり/ なし/ 評価中/不明	あり/[なし]/ 評価中/不明
カナダ	CADTH	あり/ なし/ 評価中/不明	あり/[なし]/ 評価中/不明
オーストラリア	PBAC	あり/ なし/[評価中]/不明	あり(結果は非公表)

表1-1-3-1 イギリス(NICE)におけるMTAによる費用対効果評価結果の詳細

	製造販売業者	公的分析
国名	イギリス	
機関名	NICE	
評価結果のURLなど	https://www.nice.org.uk/guidance/indevelopment/GID-TA11297(1)	
評価対象技術	モルヌピラビル	左記に同じ
評価結果	N/A(MTA評価中)	MTAの結果に対しては製造販売業者によるアピールが認められ、最終ガイダンスを出さずに改めてSTAを実施することとなった。
条件付き推奨の場合は、その条件の詳細	N/A(MTA評価中)	N/A
評価対象疾患	SARS-CoV-2による感染症	重症化リスク因子を有する軽症のCOVID-19患者
使用方法(※)	通常、18歳以上の患者には、モルヌピラビルとして1回800mgを1日2回、5日間経口投与する。	左記に同じ
比較対照	標準治療	左記に同じ
主要な増分費用効果比の値	N/A(MTA評価中)	•Assessment report 標準治療に対する相対的な治療効果に対し、ネットワークメタアナリシスから得られた点推定値、95%信頼区間の上限、95%の下限をそれぞれ当てはめて推計されたICERは以下の通りであった。 - 点推定値: £13,684/QALY - 95%信頼区間の上限: £9,825/QALY - 95%信頼区間の下限: £69,786/QALY •Draft guidance Committee’s preferred assumptionsを置いた状況で、モルヌピラビルのICERは治療効果の設定に対して鋭敏に変動したが、£30,000/QALYを超える可能性が高いことが示された。

表1-1-3-2 オーストラリア(PBAC)における費用対効果評価結果の詳細

	製造販売業者	公的分析
国名	オーストラリア	
機関名	PBAC	
評価結果のURLなど	https://www.pbs.gov.au/publication/factsheets/covid-19-treatments/Factsheet-lagevrio-molnupiravir-July-2023.pdf(2)	
評価対象技術	モルヌピラビル	左記に同じ
評価結果	推奨	条件付き推奨
条件付き推奨の場合は、その条件の詳細	以下に該当する場合推奨 - 70歳以上(無症状陽性者を含む) - 50歳以上で複数の重症化リスク因子を有する軽症者 - 30歳以上の先住民で複数の重症化リスク因子を有する軽症者 - 18歳以上で中等症～重症の免疫抑制状態の軽症者	以下に該当する軽症から中等症のCOVID-19患者に対して推奨 - 70歳以上(無症状陽性者を含む。また他の重症化リスク因子は必要としない)のもの - 50歳以上で2つ以上の重症化リスク因子を有するもの - 30歳以上の先住民で1つ以上の重症化リスク因子を有するもの - 18歳以上で中等症から重症の免疫抑制状態のもの - 18歳以上で過去にCOVID-19で入院しており、その後再感染したもの またPBACは、PANORAMIC試験の結果をふまえ、ニルマトレルビル/リトナビルが禁忌または適切でない場合にモルヌピラビルを考慮すべきとしている。
評価対象疾患	SARS-CoV-2による感染症	左記に同じ
使用方法(※)	通常、 18歳以上の患者には、モルヌピラビルとして1回800mgを1日2回、5日間経口投与する。	左記に同じ
比較対照	標準治療	左記に同じ
主要な増分費用効果比の値	N/A(評価中)	具体的な値は確認できないが、PBACの推奨は、製造販売業者が提案した価格でのモルヌピラビルの費用対効果に基づくとされている。

1.2 製造販売業者による諸外国の医療技術評価機関における評価報告のレビュー

諸外国の医療技術評価機関の評価報告について、公的分析におけるレビューの結果、製造販売業者の報告内容といくつかの相違が認められたが、最新の情報の反映によること等が理由として考えられた。

1.3 公的分析における参考事項

諸外国の医療技術評価機関や公的機関の報告において、公的分析の参考となりうる項目を下記に列挙した。

<NICE>(1)

MTAの概要

- NICEでは、重症化リスク因子を有する軽症のCOVID-19患者を分析対象集団として、カシリビマブ/イムデビマブ、モルヌピラビル、ニルマトレルビル/リトナビル、レムデシビル、ソトロビマブ、チキサゲビマブ/シルガビマブのMTAが実施された。

- Assessment groupの報告によると、標準治療と比較したときのICERはニルマトレルビル/リトナビルが最も小さく、モルヌピラビルを含むその他の薬剤はニルマトレルビル/リトナビルに対してdominatedであった。
- Final draft guidanceでは、重症化リスク因子を有する軽症のCOVID-19患者の治療薬として、ニルマトレルビル/リトナビルを推奨している。モルヌピラビル、カシリビマブ/イムデビマブ、レムデシビル、ソトロビマブ、チキサゲビマブ/シルガビマブは非推奨と記述されている。

モルヌピラビルの治療効果

- Assessment groupは、ネットワークメタアナリシスの手法を用いて各薬剤の治療効果を評価した。モルヌピラビルに関しては、対象集団の大部分がワクチン等で免疫を獲得しており、かつオミクロン株流行下で行われたPANORAMIC試験を含めて解析が実施されており、入院または死亡に関するリスク比は0.80(95% CI: 0.56 to 1.15)、全死亡に関するリスク比は0.27(95% CI: 0.09 to 0.82)と推計された。
- PANORAMIC試験においてモルヌピラビルが標準治療に対する優越性を示していないことをCommitteeは指摘しているが、重症化リスク因子の定義として最も確実性の高いエビデンスであると考えられるDepartment of Health and Social CareのMcInnes報告(3)に基づくハイリスク集団に比較すると、PANORAMIC試験の対象集団は重症化リスクがより低いことも認識している。
- そこでCommitteeは、英国の実臨床の状況を反映し、McInnes報告に基づくハイリスク集団を含むOpenSAFELYのデータを参照した。このデータは入院率や死亡率に対するモルヌピラビルの限定的な有用性を示しており、ネットワークメタアナリシスやPANORAMIC試験の結果を支持していた。
- モルヌピラビルによる入院または死亡リスクの減少効果は不確かであり、これを正当化するためには強固なエビデンスが必要であるとCommitteeは結論付けた。

現在のendemic期における過去に行われた臨床試験の一般化可能性

- NICEにおける評価時点で懸念される主要な変異型はオミクロン株であったものの、薬剤の効果を評価した臨床試験のほとんどが、それよりも前の株を対象としていることをCommitteeは指摘しており、臨床専門家も、過去に行われた臨床試験のデータを外挿することは誤解を招くものであると述べている。
- Committee並びに臨床専門家は、臨床的なエビデンスをどのように現在のendemic期に外挿するかを検討すべきであると指摘しており、一般化可能性に関する主要な懸念事項として、以下のものを挙げていた。
  - 自然免疫とワクチンによる集団免疫の変化
  - ウイルスの病原性の変化

- ウイルスに関する知識が深まることによるサポーティブケアの有効性の増大
- その他pandemic期との状況の差異

●経済評価モデルでは上述の懸念事項を可能な限り考慮したが、これら懸念事項と治療効果には交互作用が存在しうるため、臨床試験が示す薬剤の効果は依然として一般化可能性を欠く可能性があるとCommitteeは考えた。また、臨床試験が入院率や死亡率の高い時期に行われたものであるため、この交互作用は薬剤が有効であることを示す方向に働く可能性がある。したがってCommitteeは、pandemic期に観察された治療効果はベストサポーティブケアの変化やワクチン接種率の向上によってendemic期では減じるものであると結論付けた。

Appeal panelにおける議論

●製造販売業者のアピールが認められた主な事項は以下の通りである。
- モルヌピラビルの治療効果の評価において、PANORAMIC試験が重視され、その解釈の助けとして特定のreal world evidence(OpenSAFELY)が参照されたが、そのプロセスが不透明であること
- scopeで定義された入院率及び死亡率以外のアウトカムについても精査すべきであること

●製造販売業者のアピールが認められなかった事項は以下の通りである。
- PANORAMIC試験が対象とした集団は、McInnes報告におけるハイリスク集団を15%程度しか含んでおらず、一般化可能性に課題があること(PANORAMIC試験では、免疫不全患者のサブグループ解析が実施されており、これによっても有意な差が認められなかったこと等が説明されている)
- 経済評価において、ネットワークメタアナリシスから得られた治療効果の点推定値、 95%信頼区間の上限及び下限をそれぞれ適用することでICERを推計すること(単純な方法ではあるものの、PANORAMIC試験と他の試験の異質性を考慮すると、このような幅での評価は妥当である等の説明がなされている)

●以上の製造販売業者のアピールの結果、新たなSTAを実施し、その結論が出るまで最終ガイダンスは公表しないことで合意した。

<PBAC>(2)

●2022年2月、PBACは、製造販売業者が提案した価格でのモルヌピラビルの費用対効果に基づきつつ、モルヌピラビルを、条件に合致する酸素吸入を必要としない軽症から中等症のCOVID-19患者に対して推奨した。

●2022年11月には、PANORAMIC試験を考慮して、ニルマトレルビル/リトナビルが禁忌または適切ではない場合のみ、モルヌピラビルによる治療を検討すべきであると提言した。

●PBACは、モルヌピラビルに関する新たなエビデンスを考慮し、Pharmaceutical Benefits Schemeの

アクセス条件を引続き検討する予定である。

1.4　その他の海外公的機関の報告における参考事項

2023年6月にEMA(4)による評価が公表されたため、この情報を追加した。

<EMA>(4)

- EMAは、酸素投与を受けていない、重症化リスク因子を有する成人のCOVID-19患者におけるモルヌピラビルの臨床的有用性が証明されていないとして、モルヌピラビルの販売承認の取下げを勧告した。製造販売業者は再審査請求の後、再審査終了前に販売承認を取下げた。
- EMAの評価において、下記が勧告の根拠となった。
  - MOVe-OUT試験では、IA3/4(事前に計画された中間解析)までの時点のper protocol populationにおいて、 29日目までの入院または死亡の発生におけるモルヌピラビルの優越性が示された(群間差, -5.6%; 95% CI, -9.8　to -1.5)。一方、IA3/4後のper protocol populationでは、入院または死亡の発生に群間差が認められなかった(群間差, 0.0%; 95% CI, -3.3 to 3.3)。すなわち、モルヌピラビルの治療効果に関する一貫した結果が示されておらず、MOVe-OUT試験はモルヌピラビルの有効性を証明していない。またMOVe-OUT試験において、モルヌピラビル群における29日目までの入院または死亡の発生は、IA3/4までの時点で5.7%、IA3/4後で4.2%であった。一方、プラセボ群はIA3/4までの時点で11.3%、IA3/4後で4.2%に低下していた。したがってIA3/4までの時点を対象として示されたモルヌピラビルの有効性は、リスクが高いより早期のpandemic期におけるワクチン未接種者を対象として観察されており、現在のヨーロッパの集団に対して外挿することはできないという懸念がある。
  - さらに、ヨーロッパの状況に結果を外挿することができると考えられるPANORAMIC試験は、入院または死亡の発生におけるモルヌピラビルの優越性を示していない。
  - その他、 3件のインドで行われた非盲検ランダム化比較試験のデータも参考情報として提出されたが、ヨーロッパにおける一般化可能性や評価項目の性質からモルヌピラビルの有効性を裏付けるためには不十分である。
  - リアルワールドデータに基づく研究はモルヌピラビルの有効性を支持するものの、ランダム化の欠如によるコントロールできないバイアスが懸念される。したがって、これらの研究はMOVe-OUT試験で認められた結果の一貫性の欠如に対する懸念を覆す根拠とするには十分でない。

2. 追加的有用性の評価

2.1　公的分析におけるシステマティックレビュー

COVID-19患者におけるモルヌピラビルの追加的有用性を検討するために、ランダム化比較試験(RCT)を対象としたシステマティックレビュー(SR)を実施した。

2.1.1　公的分析が設定したリサーチクエスチョン

公的分析が設定したリサーチクエスチョンを表2-1-1に示す。

表2-1-1 公的分析によるシステマティックレビューのリサーチクエスチョン

項目	内容
対象集団	COVID-19患者
介入	モルヌピラビル
比較対照	標準治療
アウトカム	有効性、安全性
研究デザイン	RCT
文献検索期間	指定なし(検索実施時点である2023年6月まで)

2.1.2　実施の流れ

文献検索では、医学情報サービス・文献検索の専門家が、疾患名、薬剤名、研究デザイン、検索対象期間等の条件を組合わせて検索式を構築した。論文のアブストラクトに基づくスクリーニング、追加的有用性評価に用いる論文を特定する作業は、 2名の独立したレビューアーが盲検下にて実施した。論文の採否は事前に設定した組み入れ基準、除外基準に従い判定した。レビューアー間の不一致等は、両者の協議により解消した。最終的に特定されたランダム化比較試験の概要を要約し整理し、最後に特定された文献の批判的吟味をおこなった。

2.1.3　臨床研究の組み入れ基準や除外基準

SR の主な組み入れ基準と除外基準を以下に示す。

表2-1-3 適格基準

	組み入れ基準	除外基準
対象集団	COVID-19患者	左記以外
介入	ラゲブリオ/モルヌピラビル	左記以外
比較対照	標準治療	ラゲブリオ/モルヌピラビル以外の抗ウイルス薬
アウトカム	有効性、安全性	左記以外
研究デザイン	第II相または第III相RCT	左記以外
文献の種類	原著論文	レビュー、レター、会議録、臨床試験登録
言語	英語、日本語	左記以外

2.1.4　使用したデータベース

SRには、PubMed、Embase/Embase Preprints、Cochrane Central Register of Controlled Trials (CENTRAL)、医中誌webを用いた。

2.1.5　使用した検索式

SR の検索式を表2-1-5-1~表2-1-5-4に示す。

表2-1-5-1 PubMedに対して用いた検索式

通番	検索式	結果数
#1	"LitCGeneral"[Filter]	365,030
#2	"molnupiravir"[Supplementary Concept] OR "molnupiravir"[Title/Abstract] OR "EIDD 2801"[Title/Abstract] OR "lagevrio"[Title/Abstract] OR "MK 4482"[Title/Abstract]	567
#3	#1 AND #2	534
#4	"Randomized Controlled trial"[Publication Type] OR "random*"[Text Word] OR "placebo"[Text Word]	1,726,934
#5	#3 AND #4	57
#6	#5 NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	56
最終検索日		2023/6/6
件数		56

表2-1-5-2 Embaseに対して用いた検索式

通番	検索式	結果数
s1	((EMB.EXACT.EXPLODE("Severe acute respiratory syndrome coronavirus 2")) OR (EMB.EXACT.EXPLODE("coronavirus disease 2019")) OR ab("covid19" OR "covid 19" OR "covid-19" OR "sars-cov-2" OR "sars cov 2" OR "sarscov2" OR "severe acute respiratory syndrome coronavirus" OR "2019-ncov") OR ti("covid19" OR "covid 19" OR "covid-19" OR "sars-cov-2" OR "sars cov 2" OR "sarscov2" OR "severe acute respiratory syndrome coronavirus" OR "2019-ncov"))	410,055
s2	EMB.EXACT("molnupiravir") OR ab("molnupiravir" OR "EIDD 2801" OR "EIDD-2801" OR "lagevrio" OR "MK 4482") OR ti("molnupiravir" OR "EIDD 2801" OR "EIDD-2801" OR "lagevrio" OR "MK 4482")	
s3	S2 AND S1	988
s4	(EMB.EXACT.EXPLODE("randomized controlled trial") OR ab(random*) OR ab(placebo) OR ti(random*) OR ti(placebo))	2,170,016
s5	(S4 AND S3) not (rtype.exact("Conference Abstract" OR "Note" OR "Erratum"))	55
最終検索日		2023/6/6
件数		55

表2-1-5-3 CENTRALに対して用いた検索式

通番	検索式	結果数
#1	MeSH descriptor: [COVID-19] explode all trees	4,374
#2	MeSH descriptor: [SARS-CoV-2] explode all trees	2,282
#3	("severe acute respiratory syndrome coronavirus" OR "sars-cov" OR "sars cov" OR "sarscov"):ti,ab,kw OR ("covid19" OR "covid 19" OR "covid-19" OR "2019-ncov"):ti,ab,kw	16,181
#4	#1 OR #2 OR #3	16,615
#5	(molnupiravir):ti,ab,kw OR ("lagevrio"):ti,ab,kw OR ("EIDD 2801" OR "EEIDD-2801"):ti,ab,kw OR ("MK 4482" OR "MK-4482"):ti,ab,kw	80
#6	#4 AND #5	74
	in CENTRAL	73
	最終検索日	2023/6/6
	件数	73

表2-1-5-4 医中誌Webに対して用いた検索式

通番	検索式	結果数
#1	SARSコロナウイルス-2/TH or COVID-19/TH or COVID-19/AL or (コロナ/TA and DT=2020:2023)	50,527
#2	"Molnupiravir"/TH or "molnupiravir"/TA or "EIDD 2801"/TA or "EIDD-2801"/TA or "EIDD2801"/TA or "lagevrio"/TA or "MK 4482"/AL or "MK-4482"/TA or "MK4482"/TA or "モルヌピラビル"/TA or "ラゲブリオ"/TA	99
#3	#1 and #2	97
#4	#3 and (ランダム化比較試験/TH or ランダム/TA or 無作為/TA or RCT/TA or radom*/TA or プラセボ/TA or RD=ランダム化比較試験,準ランダム化比較試験)	3
	最終検索日	2023/6/6
	件数	3

2.1.6　検索結果

SRの結果、COVID-19を対象としたRCTの原著論文を8件特定した。この内、第II相RCTはAGILE (5)、NCT04405570 (6)、第III相RCTはMOVe-OUT 2報 (7, 8)、MOVe-OUTのサブグループ解析 (9)、PANORAMIC (10)、CTRI/2021/07/034588 (11)、ChiCTR2200056817 (12)であった (図2-1-6)。臨床試験の概要を、表2-1-7-1~表2-1-7-8に示す。

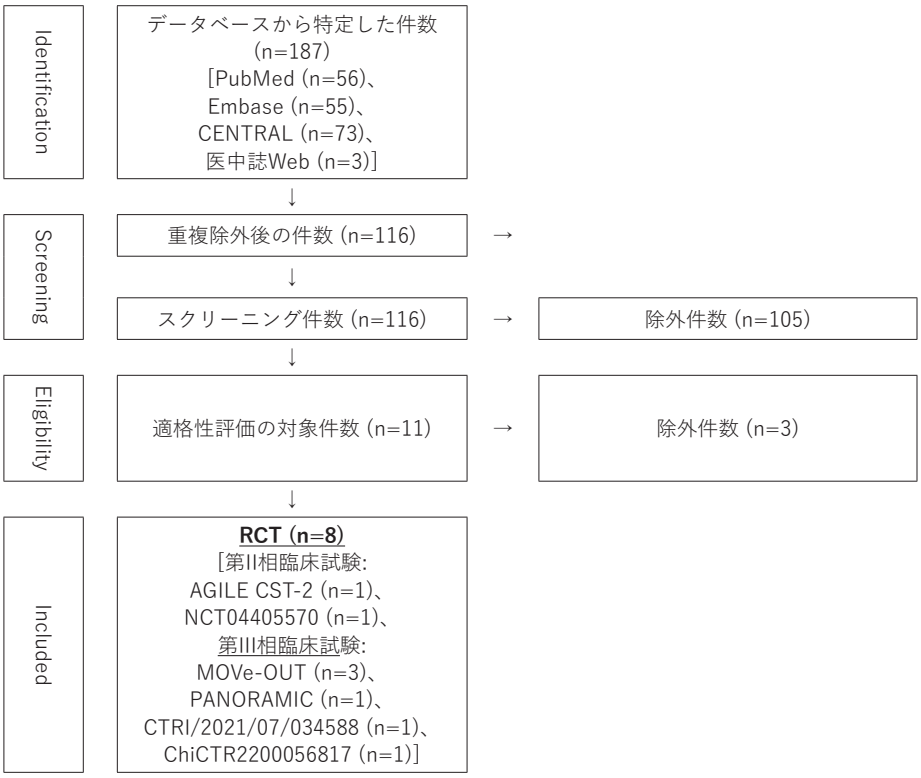

図2-1-6 フローチャート

2.1.7　臨床試験の概要

表2-1-7-1 臨床試験の概要

試験名	AGILE CST-2
書誌情報	Khoo SH, FitzGerald R, Saunders G, Middleton C, Ahmad S, Edwards CJ, et al. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Infect Dis. 2023;23(2):183-95.(5)
臨床試験登録情報	NCT04746183
試験を実施した場所	イギリス
試験の登録期間	2020年11月～2022年3月
対象集団	軽症～中等症のCOVID-19外来患者
適格基準	•18歳以上 •症状発現から5日以内 •コントロール不良の慢性疾患がない
主な除外基準	•妊婦または授乳中 •重度の慢性腎臓病または透析患者 •肝機能不全または腎機能障害 •入院、酸素投与、人工呼吸器等の介入を必要とする呼吸器疾患
介入方法の詳細	モルヌピラビル(800mg1日2回5日間経口投与)＋標準治療(n=90)
比較対照の詳細	プラセボ＋標準治療 (n=90)
試験デザイン	第II相、多施設共同、無作為化比較試験
盲検化法	二重盲検
主要評価項目	ランダム化からPCR陰性までの時間
主な副次的評価項目	•29日目まで死亡率 •29日目まで入院率 •安全性、等
有効性	モルヌピラビル群 (n=90)、プラセボ群 (n=90) ランダム化からPCR陰性までの時間の中央値 (95% CI): モルヌピラビル群：8日 (8 to 9) VS プラセボ群：11日 (10 to 11) HR 1.30 (95% CI： 0.92 to 1.71) 29日目までの入院: モルヌピラビル群：0% VS プラセボ群：4% 29日目までの死亡: モルヌピラビル群：0% VS プラセボ群：0%
安全性	グレード3以上AE： モルヌピラビル群：1% VS プラセボ群：3% グレード3以上SAE： モルヌピラビル群：0% VS プラセボ群：1%
日本人集団における有効性	NA
日本人集団における安全性	NA

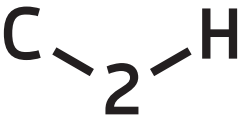

表2-1-7-2 臨床試験の概要

試験名	Fischer 2022
書誌情報	Fischer WA, 2nd, Eron JJ, Jr., Holman W, Cohen MS, Fang L, Szewczyk LJ, et al. A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med. 2022;14(628):eabl7430.(6)
臨床試験登録情報	NCT04405570
試験を実施した場所	米国
試験の登録期間	2020年6月～2021年1月
対象集団	軽症～中等症のCOVID-19外来患者
適格基準	•SARS-CoV-2のワクチン接種 •18歳以上 •症状発現から7日以内
主な除外基準	記載なし
介入方法の詳細	•モルヌピラビル200mg 1日2回5日間 (n=23) •モルヌピラビル400mg 1日2回5日間 (n=62) •モルヌピラビル800mg 1日2回5日間 (n=55)
比較対照の詳細	プラセボ (n=62)
試験デザイン	第IIa相、多施設共同、無作為化比較試験
盲検化法	二重盲検
主要評価項目	•ウイルスRNAクリアランスまでの時間 •グレード3以上のAE
主な副次的評価項目	患者報告のCOVID-19の重症度 患者報告の症状持続時間
有効性	モルヌピラビル800mg群 (n=55)、プラセボ群 (n=62) ウイルスRNAクリアランスまでの時間 (中央値、95% CI): モルヌピラビル800mg群:14.0日 (13.0-14.0) VS プラセボ群:15.0日 (15.0-27.0) p= 0.013
安全性	グレード3以上のAE: モルヌピラビル800mg 群: 7.3% VSプラセボ群: 8.1%
日本人集団における有効性	NA
日本人集団における安全性	NA

表2-1-7-3 臨床試験の概要

試験名	MOVe-OUT
書誌情報	Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2022;386(6):509-20.(7)
臨床試験登録情報	NCT04575597
試験を実施した場所	日本を含まない20か国
試験の登録期間	2021年5月～2021年11月
対象集団	軽症～中等症のCOVID-19外来患者
適格基準	•18歳以上 •症状発現から5日以内 •1つ以上のCOVID-19症状を有する •重症化リスク因子を有する（60歳以上、活動性のがん、慢性腎臓病、慢性閉塞性肺疾患、BMI≧30、重篤な心疾患、糖尿病）
主な除外基準	•48時間以内にCOVID-19による入院の可能性がある •透析患者またはeGFR<30 mL/min/1.73㎡ •妊婦 •重度の好中球減少症(好中球絶対数<500/ mL) •血小板数<100,000/μL •SARS-CoV-2のワクチン接種
介入方法の詳細	モルヌピラビル800㎎1日2回5日間（n=716）
比較対照の詳細	プラセボ（n=717）
試験デザイン	第III相、多施設共同、無作為化比較試験
盲検化法	二重盲検
主要評価項目	•mITT集団(無作為化後、モルヌピラビルまたはプラセボを1回以上投与され、初回投与前に入院していない集団)における29日目までの入院または死亡 •AE
主な副次的評価項目	•29日目までのWHO 11-point Clinical Progression Scale •患者報告のCOVID-19の兆候及び症状
有効性	29日目までの入院または死亡: 中間解析: モルヌピラビル群: 7.3% (28/385) VSプラセボ群: 14.1% (53 /377) 群間差 -6.8 (95% CI: -11.3 to -2.4)、p=0.001 Post-hoc: モルヌピラビル群: 6.8% (48/709) VSプラセボ群: 9.7% (68 /699) 群間差 -3.0 (95% CI: -5.9 to -0.1)、p=0.001
安全性	Post-hoc AE発生割合: モルヌピラビル群: 30.4% (216/710) VSプラセボ群: 33.0% (231/701)
日本人集団における有効性	NA
日本人集団における安全性	NA

表2-1-7-4 臨床試験の概要

試験名	MOVe-OUT
書誌情報	Johnson MG, Puenpatom A, Moncada PA, Burgess L, Duke ER, Ohmagari N, et al. Effect of Molnupiravir on Biomarkers, Respiratory Interventions, and Medical Services in COVID-19 : A Randomized, Placebo-Controlled Trial. Ann Intern Med. 2022;175(8):1126-34.(8)
臨床試験登録情報	MOVe-OUTと同じ(表2-1-7-3と同じ)
試験を実施した場所	
試験の登録期間	
対象集団	
適格基準	
主な除外基準	
介入方法の詳細	
比較対照の詳細	
試験デザイン	
盲検化法	
主要評価項目	•安全性評価の対象集団におけるベースラインから29日目までのCRP濃度、及びSpO2の平均変化量 •mITT集団における呼吸介入の使用、及び急性期治療の受診
主な副次的評価項目	記載なし
有効性	安全性評価の対象集団(モルヌピラビル群 n=710、プラセボ群 n=701)におけるベースラインから29日目までのCRP濃度の平均変化量: モルヌピラビル群: –14.69 VSプラセボ群: –12.32 安全性評価の対象集団におけるベースラインから29日目までのSpO2の平均変化量: モルヌピラビル群: 0.76 VSプラセボ群: 0.69 mITT集団(モルヌピラビル群 n=709、プラセボ群 n=699)における呼吸介入の使用: プラセボ群に対するモルヌピラビル群のRRR: 34.3% (95% CI:4.3 to 54.9) mITT集団における急性期治療の受診: プラセボ群に対するモルヌピラビル群のRRR (95% CI): 32.1% (4.4 to 51.7)
安全性	NA
日本人集団における有効性	NA
日本人集団における安全性	NA

表2-1-7-5 臨床試験の概要

試験名	MOVe-OUT
書誌情報	Johnson MG, Strizki JM, Brown ML, Wan H, Shamsuddin HH, Ramgopal M, et al. Molnupiravir for the treatment of COVID-19 in immunocompromised participants: efficacy, safety, and virology results from the phase 3 randomized, placebo-controlled MOVe-OUT trial. Infection. 2023:1-12.(9)
臨床試験登録情報	NCT04575597
試験を実施した場所	MOVe-OUTと同じ(表2-1-7-3と同じ)
試験の登録期間	同上
対象集団	免疫不全者で、軽症～中等症のCOVID-19外来患者
適格基準	MOVe-OUTと同じ
主な除外基準	同上
介入方法の詳細	モルヌピラビル800mgを1日2回5日間 (N=24)
比較対照の詳細	プラセボを1日2回5日間 (N=31)
試験デザイン	MOVe-OUTと同じ
盲検化法	同上
主要評価項目	同上
主な副次的評価項目	•29日目までのWHO 11-point Clinical Progression Scale •患者報告のCOVID19の兆候及び症状
有効性	モルヌピラビル群 (n=31)、プラセボ群 (n=24) 29日目までの入院または死亡: モルヌピラビル群: 22.6%VSプラセボ群: 8.3% 群間差 -14.2 (95% CI: -33.5 to 6.6)
安全性	AE発生割合: モルヌピラビル群: 45.2% VSプラセボ群: 25.0%
日本人集団における有効性	NA
日本人集団における安全性	NA

表2-1-7-6 臨床試験の概要

試験名	PANORAMIC
書誌情報	Butler CC, Hobbs FDR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, et al. 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. Lancet. 2023;401(10373):281-93.(10)
臨床試験登録情報	ISRCTN30448031
試験を実施した場所	イギリス
試験の登録期間	2022年3月～2022年4月
対象集団	軽症～中等症のCOVID-19外来患者
適格基準	•18歳以上 •症状発現から5日以内 •1つ以上のCOVID-19症状を有する •50歳以上、あるいは18歳以上で合併症を有する(免疫抑制、慢性腎臓病、慢性閉塞性肺疾患、BMI≧35、慢性心疾患、慢性血管疾患、慢性肝疾患、糖尿病、慢性神経疾患、重度の学習障害、重度の精神疾患、ダウン症、固形臓器、骨髄、幹細胞移植患者、ケアホーム入居者、その他臨床的に脆弱と判断された患者)
主な除外基準	•妊婦または授乳中
介入方法の詳細	モルヌピラビル800mg1日2回5日間＋標準治療 (n=12,529)
比較対照の詳細	標準治療 (n=12,525)
試験デザイン	多施設共同、無作為化比較試験
盲検化法	非盲検
主要評価項目	•28日目までの入院または死亡
主な副次的評価項目	•患者報告の症状回復までの時間 •医療、または福祉サービスの利用 •安全性
有効性	モルヌピラビル群 (n=12,529)、標準治療群 (n=12,525) 28日目までの入院または死亡: モルヌピラビル群 1%　VS 標準治療 1% OR: 1.06 (95% CI:0.81 to 1.41) 患者報告の初回回復までの時間 (中央値、IQR): モルヌピラビル群 9日(5-23) VS 標準治療群15日(7-未到達) OR: 1.36 (95% CI:1.32 to 1.40) NHS111サービスの利用: モルヌピラビル群5% VS標準治療群6% OR: 0·72 (95% CI:0·64 to 0·80)
安全性	SAE発生割合: モルヌピラビル群 0.4%　VS 標準治療群0.3%
日本人集団における有効性	NA
日本人集団における安全性	NA

表2-1-7-7 臨床試験の概要

試験名	Sinha 2022
書誌情報	Sinha S, N K, Suram VK, Chary SS, Naik S, Singh VB, et al. Efficacy and Safety of Molnupiravir in Mild COVID-19 Patients in India. Cureus. 2022;14(11):e31508.(11)
臨床試験登録情報	CTRI/2021/07/034588
試験を実施した場所	インド
試験の登録期間	2021年5月～2021年8月
対象集団	軽症のCOVID-19外来患者
適格基準	•18歳以上60歳以下 •症状発現から5日以内
主な除外基準	•中等度から重度のCOVID-19 (SpO2 ≦ 93%、または呼吸数 ≧ 24回/分) •重度の肝疾患 •活動性のC型肝炎、B型肝炎 •HIV •急性膵炎、慢性膵炎の既往 •重度の腎障害、または腎代替療法を継続的に受けている
介入方法の詳細	モルヌピラビル (800mg1日2回5日間)＋標準治療 (n=608)
比較対照の詳細	標準治療 (n=610)
試験デザイン	第III相、多施設、無作為化比較試験
盲検化法	非盲検
主要評価項目	•14日目までの入院 •AE
主な副次的評価項目	記載無し
有効性	モルヌピラビル群(n=608)、標準治療群(n=610) 14日目までの入院: モルヌピラビル群 1.48% VS 標準治療群4.26% 群間差 -2.78(95% CI: -4.65 to -0.90)、p=0.0053
安全性	AE発生割合: モルヌピラビル群 4.8% VS 標準治療群　2.6%
日本人集団における有効性	NA
日本人集団における安全性	NA

表2-1-7-8 臨床試験の概要

試験名	Zou 2022
書誌情報	Zou R, Peng L, Shu D, Zhao L, Lan J, Tan G, et al. Antiviral Efficacy and Safety of Molnupiravir Against Omicron Variant Infection: A Randomized Controlled Clinical Trial. Front Pharmacol. 2022;13:939573.(12)
臨床試験登録情報	ChiCTR2200056817
試験を実施した場所	中国
試験の登録期間	2022年3月～2022年3月
対象集団	軽症～中等症のCOVID-19外来患者
適格基準	•18歳以上80歳以下 •症状発現から5日以内
主な除外基準	•重度の嘔吐やそれ以外の理由によって経口治療が困難 •妊婦または授乳中 •抗体療法、血漿療法、SARS-CoV-2に対するその他の治験薬の治療歴
介入方法の詳細	モルヌピラビル (800mg1日2回5日間)＋標準治療 (n=76)
比較対照の詳細	標準治療 (n=31)
試験デザイン	第III相、無作為化比較試験
盲検化法	非盲検
主要評価項目	ウイルスRNA消失までの時間
主な副次的評価項目	5日、7日、10日目におけるSARS-CoV-2ウイルス陰性化
有効性	モルヌピラビル群 (n=76)、標準治療群 (n=31) ウイルスRNA消失までの時間の中央値 (95% CI): モルヌピラビル群9日(7 to 9) VS 標準治療群10日 (9 to 11) p=0.0092
安全性	グレード3以上のAE発生割合: モルヌピラビル群0% VS 標準治療群0%
日本人集団における有効性	NA
日本人集団における安全性	NA

2.2　製造販売業者によるシステマティックレビューと公的分析におけるレビュー結果の概要

2.2.1　製造販売業者によるシステマティックレビューについて

製造販売業者は、COVID-19外来患者を対象とし、比較対照技術はモルヌピラビル含む抗ウイルス薬、中和抗体薬、免疫抑制・調節薬の薬物療法を対象とした幅広い条件でSRを実施した。費用対効果評価専門組織で決定された分析枠組みにおける分析対象集団は「重症化リスク因子を有するSARS-CoV-2 による感染症(COVID-19)患者」であったが、製造販売業者のSRでは外来患者に限定したリサーチクエスチョンの設定が行われていた。一方で、介入については分析枠組みよりも広くエビデンスの検索が行われていた。製造販売業者のSRは必ずしも分析枠組みと合致するものではなかったが、追加的有用性の評価に重要な論文はすべて含まれていた。

2.2.2　製造販売業者の実施したシステマティックレビューとの結果の差異について

●製造販売業者によるSRの結果、COVID-19患者を対象とした抗ウイルス薬、中和抗体薬、免疫抑制・調節薬の薬物療法のRCTの原著論文等を86件(60試験)特定した。このうち、モルヌピラビル

と標準治療を比較した第II相RCTとして、AGILE CST-2試験、NCT04405570を特定した。第III相RCTは、MOVe-OUT試験、CTRI/2021/07/034588、ChiCTR2200056817を特定した。SR終了後にPANORAMIC試験を特定した。

- 公的分析のSRにおいても第II相RCTとして、AGILE CST-2試験とNCT04405570が特定され、第III相RCTとして、MOVe-OUT試験、PANORAMIC試験、ChiCTR2200056817が特定された。
- また、製造販売業者は2020年1月から2022年12月までの期間を対象として、SRを実施した。一方、公的分析では、2023年6月までの期間を分析対象としたために、製造販売業者が実施したSR以降に出版された原著論文として、新たに、MOVe-OUTのサブグループ解析(9)、CTRI/2021/07/034588の原著論文(11)を特定した。
- なお、CTRI/2021/07/034588は製造販売業者によるSRにおいて、学会抄録として特定されていた。
- また、モルヌピラビル(ラゲブリオカプセル200mg)の添付文書における用法及び用量に関連する注意として、「SARS-CoV-2による感染症の症状が発現してから速やかに投与を開始すること。臨床試験において、症状発現から6日目以降に投与を開始した患者における有効性を裏付けるデータは得られていない」とされている。公的分析が特定したNCT04575584、jRCT2031200404、及びEUCTR2020-003367-26-GBは下記原著論文の臨床試験登録情報であり、症状発現から6日目以降に投与を開始した患者が研究参加者に含まれている臨床試験であった。そのため、当該3件はモルヌピラビルの追加的有用性評価に適していないと考えられた。

Arribas, José R, Bhagani S, Lobo SM, Khaertynova I, Mateu L, et al. Randomized trial of molnupiravir or placebo in patients hospitalized with Covid-19. NEJM Evidence. 2022;1(2).

【製造販売業者の提出資料（システマティックレビュー）に対するレビュー結果】

システマティックレビューの結果は、製造販売業者の提出したものと

□ 完全に一致している。
■ おおむね一致し、追加的有用性の評価に重要な論文はすべて含まれている。
□ 結果に解離があり、追加的有用性評価に重要な文献が欠けている。
□ その他(　　)

2.3　製造販売業者による追加的有用性評価と公的分析におけるレビュー結果の概要

2.3.1　製造販売業者による追加的有用性評価

製造販売業者は、下記を根拠として、モルヌピラビルは標準治療に対して追加的有用性を有すると主張した。

- COVID-19外来患者におけるモルヌピラビルの有効性を、入院又は死亡を主要アウトカムとして評価したRCTは、MOVe-OUT試験とPANORAMIC試験に限られる。しかし、2試験の異質性、例数の偏りを考慮すると2試験の統合は不適切である。
- PANORAMIC試験の対象集団において重症化リスク因子(合併症)の保有割合が69%であったこと、標準治療群に中和抗体やレムデシビルの使用が許容されていたことから、当該試験において、入院又は死亡リスクに関してモルヌピラビルの優越性を証明することは、困難であった。
- MOVe-OUT第III相試験の中間解析の結果、主要評価項目である無作為化29日目までの入院又は死亡の患者割合は、モルヌピラビル群7.3%、プラセボ群14.1%、群間差は-6.8%(95% CI：-11.3 to -2.4)であり、プラセボ群に対するモルヌピラビル群の優越性が示された。
- MOVe-OUT第III相試験において、モルヌピラビルの安全性は、標準治療と同程度であった。AE発生割合は、モルヌピラビル群30.4%、プラセボ群33.0%と両群で同程度であった。有害事象による投与中止は、モルヌピラビル群1.4%、プラセボ群2.9%であった。
- MOVe-OUT試験の有効性評価の結果は、重症化リスクを有するCOVID-19外来患者を対象に、無治療に対するモルヌピラビルの有効性を評価した観察研究によって支持された。米国退役軍人保険のデータベースを用いたTarget Trial Emulation法による有効性評価(13)の結果、 30日目までの入院又は死亡割合は、モルヌピラビル群2.7%、無治療群3.8%、RRは0.72(95% CI：0.64 to 0.79)と、MOVe-OUT試験で示されたHR 0.69(95% CI：0.48 to 1.01)とMOVe-OUT試験の結果に近かった。

2.3.2　公的分析におけるレビュー結果

公的分析のSRで特定された臨床試験において、入院又は死亡を主要評価項目とした第III相臨床試験は、MOVe-OUT試験、PANORAMIC試験、及びCTRI/2021/07/034588の3試験であった。しかし、製造販売業者が追加的有用性の主な根拠としたMOVe-OUT試験はデルタ株、ミュー株、及びガンマ株等の環境下における新型コロナワクチン未接種者を対象とした臨床試験であった。また、CTRI/2021/07/034588も同様に、研究実施期間からデルタ株、ミュー株、及びガンマ株等の環境下において実施された臨床試験であった。しかし、公的分析期間中における主な流行株はオミクロン株であったことに加えて、新型コロナワクチン接種率(1回以上接種)が8割を超えていたことから(14)、当該2試験は本邦の臨床実態とは状況が異なることが考えられた。そのため、公的分析では、オミク

ロン株環境下において、ワクチン接種者を対象として実施されたPANORAMIC試験を中心にモルヌピラビルの追加的有用性評価を行うこととした。

ただし本邦と英国において、主に用いられる重症化リスク因子の定義や標準治療の内容等が異なることに起因して、PANORAMIC試験には、本邦においては必ずしも重症化リスク因子を有すると定義されない症例や、モルヌピラビル使用時に他の抗ウイルス薬や中和抗体薬等を併用した症例が含まれていた。本品目の評価において、この重症化リスク因子の定義や標準治療の内容の違いが考慮されないまま評価を進めることには課題があると考えられた。そのため、PANORAMIC試験の著者(PANORAMIC Trial Collaborative Group)へ問い合わせを行い、本邦における重症化リスク因子の定義や標準治療の内容に合致した症例のみを抽出した上で、モルヌピラビルの評価を行うこととした。具体的に実施した解析手順及び結果を下記に示す(別添1参照)。なお、症例抽出後の統計学的解析等は全てPANORAMIC試験原著論文において実施された方法に準じた。

重症化リスク因子の定義に関する扱い(基本分析)

PANORAMIC試験の適格基準は、 50歳以上あるいは特定の合併症を有するCOVID-19患者であり、本邦において主に用いられる定義に照らし合わせると、必ずしも重症化リスク因子を有すると定義されない症例が含まれていた。そのため、公的分析期間での最新版であった新型コロナウイルス感染症(COVID-19)診療の手引き・第10.0版における重症化リスク因子の定義に基づき、それらのリスク因子を有する症例のみを抽出した(表2-3-2-1)。新型コロナウイルス感染症(COVID-19)診療の手引き・第10.0版における重症化リスク因子の定義は、アメリカ疾病予防管理センターにおける定義に基づいて、重症化リスク因子をエビデンスレベルが高(Higher Risk[conclusive])から低(Mixed Evidence[inconclusive: no conclusions can be drawn from the evidence])に分類していた。本解析では、エビデンスレベルが高(Higher Risk[conclusive])に該当する重症化リスク因子を有する症例のみを抽出した。なお、各重症化リスク因子の定義方法はPANORAMIC試験において用いられた方法に準じた。

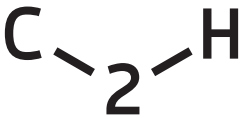

表2-3-2-1 重症化リスク因子の定義(基本分析)

Risk factor	Diagnostic criteria or definition
Older adults aged ≥ 65 years	Aged ≥ 65 years
Asthma	From free text and collected under lung disease.
Cancer (Hematologic malignancies)	From free text only. Mentions “blood cancer”.
Cerebrovascular disease	From free text, mentions “stroke” or “cerebral aneurysm”
Chronic kidney disease (People receiving dialysis)	Collected as “long term kidney disease”, not clear if receiving dialysis. Have counted anyone who has this checked.
Bronchiectasis	Collect “long term lung disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis or asthma requiring at least daily use of inhalers)” .
COPD (Chronic obstructive pulmonary disease)	Collected as lung disease
Interstitial lung disease	Collected as lung disease
Pulmonary embolism	Collected as lung disease
Pulmonary hypertension	Collected as lung disease
Cirrhosis	Collected as liver disease
Non-alcoholic fatty liver disease	Collected as liver disease
Alcoholic liver disease	Collected as liver disease
Autoimmune hepatitis	Collected as liver disease
Cystic fibrosis	Collected as lung disease
Diabetes mellitus, type 1	Collected as diabetes, not separated by type.
Diabetes mellitus, type 2	Collected as diabetes, not separated by type.
Down syndrome	Down syndrome
Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)	Defined as long term heart or vascular disease
HIV (Human immunodeficiency virus)	Comes under weakened immune system or free text mentions HIV
Mood disorders, including depression	Collected under severe mental health disorder
Schizophrenia spectrum disorders	Free text mentions “Schizoaffective disorder” or collected under
Neurologic conditions limited to dementia	Collected as long term neurological disease (including dementia, stroke, epilepsy).
Obesity	Defined as BMI ≥ 35 kg/㎡
Primary immunodeficiencies	Collected as weakened immune system due to a condition you were born with or due to disease or treatment (e.g. sickle cell, HIV, cancer, chemotherapy)
Smoking, current and former	Current only
Solid organ or blood stem cell transplantation	Collected as transplant
Use of corticosteroids or other immunosuppressive medications	Free text mentions “steroids” or “immunosuppressant”

標準治療に関する扱い(基本分析)

PANORAMIC試験では、モルヌピラビル使用時に他の抗ウイルス薬や中和抗体薬等を併用した症例が含まれていた。そのため、モルヌピラビル使用時に下記薬剤を併用していた症例を除外した(表2-3-2-2)。

表2-3-2-2 モルヌピラビル以外のCOVID-19治療薬(基本分析)

Remdesivir	Tixagevimab/cilgavimab	Any other neutralizing antibody for COVID-19
Nirmatrelvir/ritonavir	Tocilizumab	Any other immunosuppressive medications for COVID-19
Ensitrelvir	Baricitinib	Favipiravir
Casirivimab/imdevimab	Dexamethasone	Ivermectin
Sotrovimab	Any other antiviral medications for COVID-19	

解析結果(基本分析)

重症化リスク因子を有する症例の抽出とモルヌピラビル以外のCOVID-19治療薬を併用した症例を除外した結果、 18,274例(モルヌピラビル群:9,120例及び標準治療群:9,154例)が解析対象となった(図2-3-2-1)。本解析対象における平均年齢は56.8歳、男性7,683例(42.0%)であった(図2-3-2-2)。

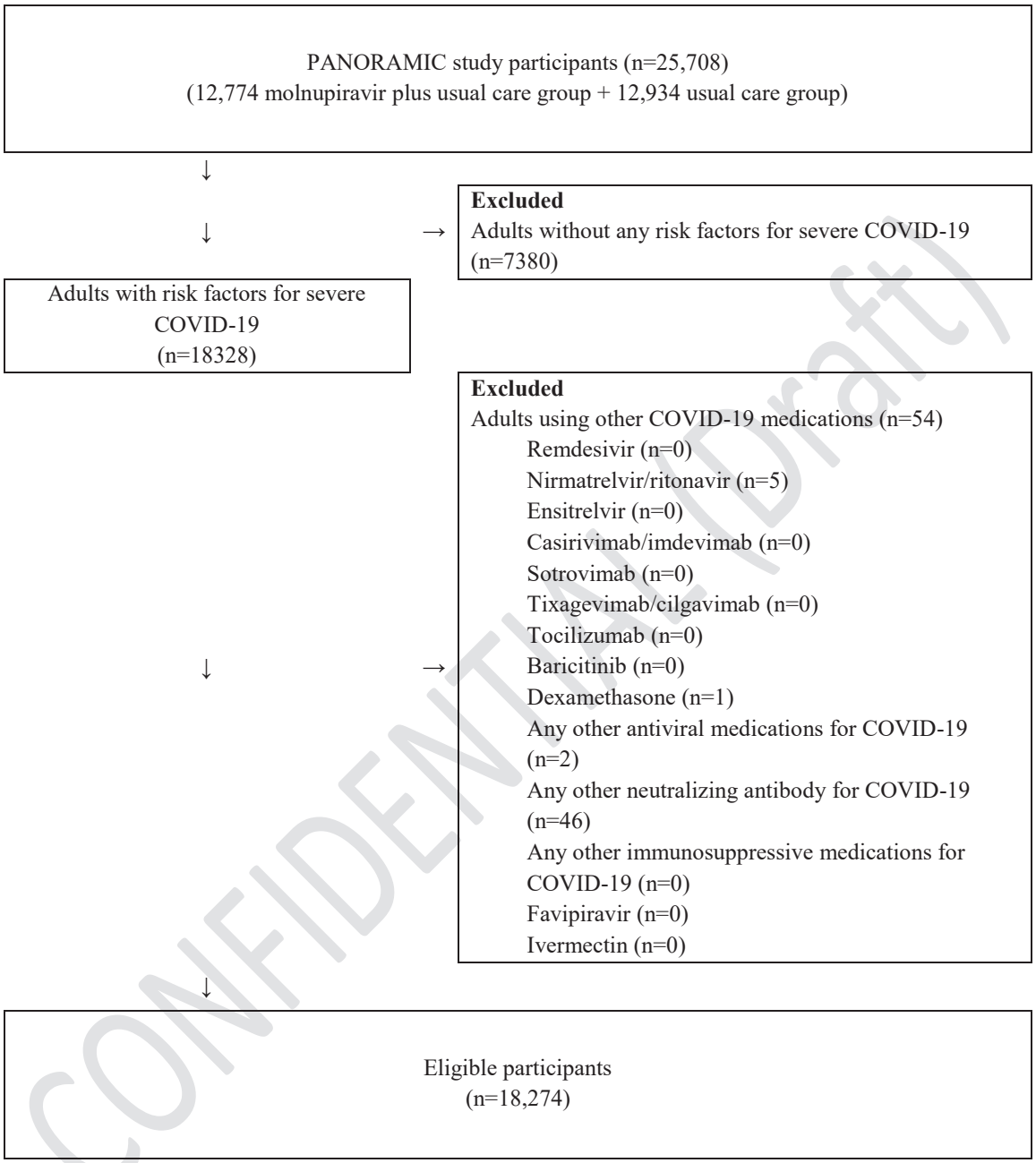

図2-3-2-1 解析対象者選定のフローチャート(基本分析)

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
Age, mean(SD) [min,max]	56.9 (14.4) [18.0 to 99.0]	56.7 (14.7) [18.0 to 98.0]	56.8 (14.5) [18.0 to 99.0]
Sex, n(%)			
Female	5267 (57.8%)	5319 (58.1%)	10586 (57.9%)
Male	3851 (42.2%)	3832 (41.9%)	7683 (42.0%)
Other	2 (0.0%)	3 (0.0%)	5 (0.0%)
Days from randomisation to reporting receipt of medication*, median(IQR)	2.0 (2.0 to 2.0) [0.0 to 7.0]	N/A	2.0 (2.0 to 2.0) [0.0 to 7.0]
Days from start of symptoms to taking medication*, median(IQR)	4.0 (3.0 to 5.0) [1.0 to 29.0]	N/A	4.0 (3.0 to 5.0) [1.0 to 29.0]
Data unavailable, n(%)	7163 (78.5%)	0 (0.0%)	7163 (39.2%)
Ethnicity category, n(%)			
White	8589 (94.2%)	8596 (93.9%)	17185 (94.0%)
Asian	257 (2.8%)	318 (3.5%)	575 (3.1%)
Mixed Race	150 (1.6%)	138 (1.5%)	288 (1.6%)
Black	54 (0.6%)	52 (0.6%)	106 (0.6%)
Other	70 (0.8%)	50 (0.5%)	120 (0.7%)
NHS priority category, n(%)			
Aged ≥80	256 (2.8%)	271 (3.0%)	527 (2.9%)
Aged ≥75 and <80	537 (5.9%)	573 (6.3%)	1110 (6.1%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1115 (12.2%)	1108 (12.1%)	2223 (12.2%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1488 (16.3%)	1463 (16.0%)	2951 (16.1%)
Aged ≥18 and <65 in an at risk group	5577 (61.2%)	5582 (61.0%)	11159 (61.1%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at risk group	37 (0.4%)	35 (0.4%)	72 (0.4%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at risk group	43 (0.5%)	56 (0.6%)	99 (0.5%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at risk group	67 (0.7%)	66 (0.7%)	133 (0.7%)
Predicted risk quintile, n(%)			
1 (lowest risk)	623 (6.8%)	633 (6.9%)	1256 (6.9%)
2	1810 (19.8%)	1780 (19.4%)	3590 (19.6%)
3	2108 (23.1%)	2157 (23.6%)	4265 (23.3%)
4	2442 (26.8%)	2439 (26.6%)	4881 (26.7%)
5 (highest risk)	2137 (23.4%)	2145 (23.4%)	4282 (23.4%)
Confirmed PCR positive, n(%)	4267 (46.8%)	4161 (45.5%)	8428 (46.1%)
IMD quintile, n(%)			
(Most deprived) 1	985 (10.8%)	930 (10.2%)	1915 (10.5%)
2	1427 (15.6%)	1466 (16.0%)	2893 (15.8%)
3	1838 (20.2%)	1833 (20.0%)	3671 (20.1%)

図2-3-2-2 PANORAMIC試験から抽出した症例の背景因子(基本分析)

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
4	2248 (24.6%)	2238 (24.4%)	4486 (24.5%)
(Least deprived) 5	2590 (28.4%)	2640 (28.8%)	5230 (28.6%)
Data unavailable, n(%)	32 (0.4%)	47 (0.5%)	79 (0.4%)
Took at least 4 doses IMP, n(%)	8412 (92.2%)		8412 (46.0%)
Received vaccination, n(%)	9015 (98.8%)	9064 (99.0%)	18079 (98.9%)
Number of COVID-19 vaccine doses, n(%)			
1	67 (0.7%)	72 (0.8%)	139 (0.8%)
2	369 (4.0%)	329 (3.6%)	698 (3.8%)
3	8361 (91.7%)	8440 (92.2%)	16801 (91.9%)
4	218 (2.4%)	223 (2.4%)	441 (2.4%)
Data unavailable, n(%)	105 (1.2%)	90 (1.0%)	195 (1.1%)
Smoker, n(%)	787 (8.6%)	799 (8.7%)	1586 (8.7%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	4011 (44.0%)	3948 (43.1%)	7959 (43.6%)
Minor problem	3289 (36.1%)	3393 (37.1%)	6682 (36.6%)
Moderate problem	1585 (17.4%)	1577 (17.2%)	3162 (17.3%)
Major problem	235 (2.6%)	236 (2.6%)	471 (2.6%)
Fatigue, n(%)			
No problem	853 (9.4%)	836 (9.1%)	1689 (9.2%)
Minor problem	3251 (35.6%)	3254 (35.5%)	6505 (35.6%)
Moderate problem	3672 (40.3%)	3694 (40.4%)	7366 (40.3%)
Major problem	1344 (14.7%)	1370 (15.0%)	2714 (14.9%)
Muscle ache, n(%)			
No problem	2501 (27.4%)	2384 (26.0%)	4885 (26.7%)
Minor problem	3051 (33.5%)	3295 (36.0%)	6346 (34.7%)
Moderate problem	2724 (29.9%)	2649 (28.9%)	5373 (29.4%)
Major problem	844 (9.3%)	826 (9.0%)	1670 (9.1%)
Vomiting, n(%)			
No problem	7361 (80.7%)	7340 (80.2%)	14701 (80.4%)
Minor problem	1339 (14.7%)	1381 (15.1%)	2720 (14.9%)
Moderate problem	380 (4.2%)	371 (4.1%)	751 (4.1%)
Major problem	40 (0.4%)	62 (0.7%)	102 (0.6%)
Diarrhoea, n(%)			
No problem	7414 (81.3%)	7476 (81.7%)	14890 (81.5%)
Minor problem	1237 (13.6%)	1249 (13.6%)	2486 (13.6%)
Moderate problem	380 (4.2%)	358 (3.9%)	738 (4.0%)
Major problem	89 (1.0%)	71 (0.8%)	160 (0.9%)
Loss of smell or taste, n(%)			
No problem	6379 (69.9%)	6567 (71.7%)	12946 (70.8%)
Minor problem	1791 (19.6%)	1686 (18.4%)	3477 (19.0%)
Moderate problem	614 (6.7%)	600 (6.6%)	1214 (6.6%)

図2-3-2-2 PANORAMIC試験から抽出した症例の背景因子(基本分析) 続き

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
Major problem	336 (3.7%)	301 (3.3%)	637 (3.5%)
Headache, n(%)			
No problem	1912 (21.0%)	2015 (22.0%)	3927 (21.5%)
Minor problem	3630 (39.8%)	3570 (39.0%)	7200 (39.4%)
Moderate problem	2718 (29.8%)	2734 (29.9%)	5452 (29.8%)
Major problem	860 (9.4%)	835 (9.1%)	1695 (9.3%)
Dizziness, n(%)			
No problem	5820 (63.8%)	5748 (62.8%)	11568 (63.3%)
Minor problem	2286 (25.1%)	2373 (25.9%)	4659 (25.5%)
Moderate problem	855 (9.4%)	864 (9.4%)	1719 (9.4%)
Major problem	159 (1.7%)	169 (1.8%)	328 (1.8%)
Abdominal pain, n(%)			
No problem	7311 (80.2%)	7280 (79.5%)	14591 (79.8%)
Minor problem	1329 (14.6%)	1410 (15.4%)	2739 (15.0%)
Moderate problem	417 (4.6%)	417 (4.6%)	834 (4.6%)
Major problem	63 (0.7%)	47 (0.5%)	110 (0.6%)
Generally unwell, n(%)			
No problem	383 (4.2%)	381 (4.2%)	764 (4.2%)
Minor problem	3449 (37.8%)	3521 (38.5%)	6970 (38.1%)
Moderate problem	4160 (45.6%)	4138 (45.2%)	8298 (45.4%)
Major problem	1128 (12.4%)	1114 (12.2%)	2242 (12.3%)
Fever, n(%)			
No problem	3990 (43.8%)	4052 (44.3%)	8042 (44.0%)
Minor problem	3428 (37.6%)	3481 (38.0%)	6909 (37.8%)
Moderate problem	1541 (16.9%)	1464 (16.0%)	3005 (16.4%)
Major problem	161 (1.8%)	157 (1.7%)	318 (1.7%)
Cough, n(%)			
No problem	1004 (11.0%)	937 (10.2%)	1941 (10.6%)
Minor problem	4242 (46.5%)	4352 (47.5%)	8594 (47.0%)
Moderate problem	3277 (35.9%)	3291 (36.0%)	6568 (35.9%)
Major problem	597 (6.5%)	574 (6.3%)	1171 (6.4%)
Wellness score, mean(SD) [min,max]	5.1 (1.7) [0.0 to 10.0]	5.1 (1.7) [0.0 to 10.0]	5.1 (1.7) [0.0 to 10.0]
People in household, n(%)			
0	1245 (13.7%)	1236 (13.5%)	2481 (13.6%)
1	4489 (49.2%)	4368 (47.7%)	8857 (48.5%)
2	1376 (15.1%)	1409 (15.4%)	2785 (15.2%)
3	1156 (12.7%)	1309 (14.3%)	2465 (13.5%)
4	580 (6.4%)	547 (6.0%)	1127 (6.2%)
5	274 (3.0%)	285 (3.1%)	559 (3.1%)
Taking inhaled corticosteroids, n(%)	2848 (31.2%)	3010 (32.9%)	5858 (32.1%)

図2-3-2-2 PANORAMIC試験から抽出した症例の背景因子(基本分析) 続き

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
Taking inhaled corticosteroids for COVID, n(%)	159 (1.7%)	143 (1.6%)	302 (1.7%)
Monoclonal antibodies for COVID, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Comorbidities			
Lung disease	2989 (32.8%)	3161 (34.5%)	6150 (33.7%)
Heart disease	993 (10.9%)	952 (10.4%)	1945 (10.6%)
Kidney disease	222 (2.4%)	253 (2.8%)	475 (2.6%)
Liver disease	158 (1.7%)	143 (1.6%)	301 (1.6%)
Neurological disease	423 (4.6%)	432 (4.7%)	855 (4.7%)
Learning disability	33 (0.4%)	27 (0.3%)	60 (0.3%)
Down's syndrome'	24 (0.3%)	29 (0.3%)	53 (0.3%)
Diabetes	1473 (16.2%)	1507 (16.5%)	2980 (16.3%)
Weakened immune system	1110 (12.2%)	1055 (11.5%)	2165 (11.8%)
Transplant recipient	50 (0.5%)	60 (0.7%)	110 (0.6%)
Obesity	1957 (21.5%)	1932 (21.1%)	3889 (21.3%)
Mental illness	196 (2.1%)	220 (2.4%)	416 (2.3%)
Hypertension	2285 (25.1%)	2303 (25.2%)	4588 (25.1%)
Other vulnerability	1886 (20.7%)	1883 (20.6%)	3769 (20.6%)

*Median and interquartile range presented for non-normally distributed variables.

図2-3-2-2 PANORAMIC試験から抽出した症例の背景因子(基本分析) 続き

本解析対象者において、モルヌピラビルの標準治療に対する主要評価項目(入院又は死亡)のオッズ比は1.053 (95% CI：0.775 to 1.396)であった(図2-3-2-3)。サブグループ解析の結果は図2-3-2-4に示す。

	Molnupiravir plus usual care (N=9120)	Usual care (N=9154)	Estimated treatment effect (95% BCI)	Probability of superiority
Hospitalization or death	92/8932 (1.0%)	87/8822 (1.0%)	1.053 (0.775 to 1.396)	0.3919
Deaths	3/8932	5/8822	Not estimable	
Hospitalizations	90/8932 (1.0%)	85/8822 (1.0%)	1.055 (0.773 to 1.413)	0.3963

*OR < 1 favours molnupiravir

図2-3-2-3 主要評価項目の結果(基本分析)

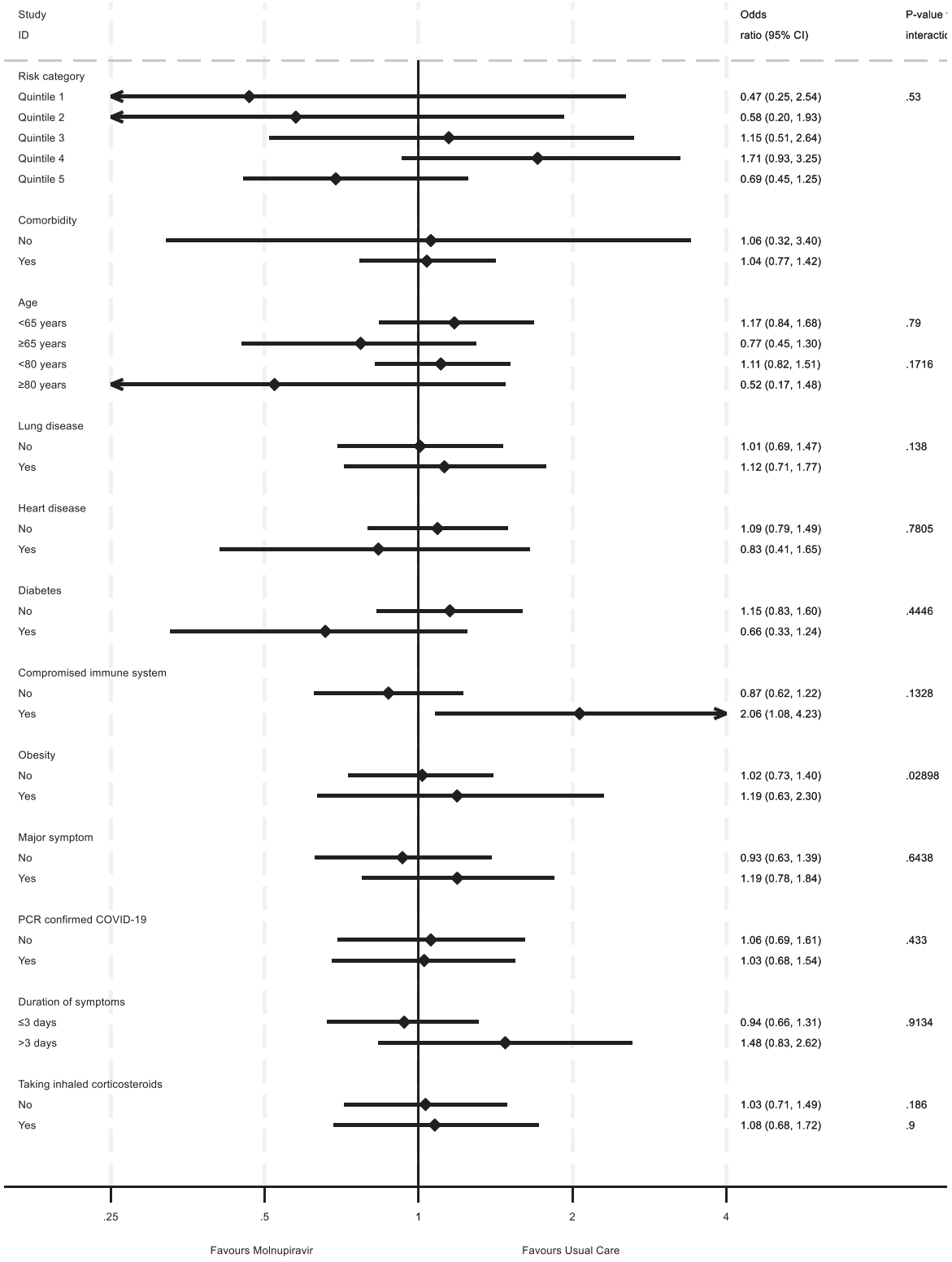

図2-3-2-4 主要評価項目のサブグループ解析結果(基本分析)

感度分析

新型コロナウイルス感染症(COVID-19)診療の手引き・第10.0版は公的分析期間中である2023年8月に公表されたものであるが、前版である第9.0版から第10.0版に更新に際して、当該資料内における重症化リスク因子の定義が大きく変更された。分析枠組み決定時(2022年11月)では、第8.1版における重症化リスク因子の定義が臨床現場で用いられていた可能性があったことを考慮して(第8.1版と第9.0版では重症化リスク因子の定義に差異はない)、第8.1版及び第9.0版における重症化リスク因子の定義を適用させた場合の解析を感度分析として実施した(別添2参照)。

重症化リスク因子の定義と標準治療に関する扱い(感度分析)

感度分析として、新型コロナウイルス感染症(COVID-19)診療の手引き・第8.1版及び第9.0版における重症化リスク因子の定義に基づき、それらのリスク因子を有する症例のみを抽出した(表2-3-2-3)。なお、各重症化リスク因子の定義方法はPANORAMIC試験において用いられた方法に準じた。また、標準治療に関する扱いは基本分析での解析方法に準じた(表2-3-2-2)。

表2-3-2-3 重症化リスク因子の定義(感度分析)

Risk factor	Diagnostic criteria or definition
Older adults aged ≥ 65 years	Aged ≥ 65 years
Cancer or chemotherapy	Free text field mentions “cancer” . Only current cancers included.
Chronic respiratory disease	Self-reported long term lung disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis or asthma requiring at least daily use of inhalers)
Chronic kidney disease	Self-reported long term kidney disease
Diabetes	Self-reported diabetes
Hypertension (high blood pressure)	Self-reported high blood pressure
Chronic heart or vascular disease	Self-reported long term heart or vascular disease
Stroke	Self-reported long term neurological disease (including dementia, stroke, epilepsy) or free text mentions stroke
Obesity	BMI ≥ 35 kg/㎡
Current smoker	Current smoker
Solid organ, bone marrow and stem cell transplant recipients	Self-report have had a transplant (e.g. kidney, liver, heart, lung, bone marrow or stem cells)
Immunosuppression	Self-reported weakened immune system due to a condition you were born with or due to disease or treatment (e.g. sickle cell, HIV, cancer, chemotherapy)
HIV infection	Collected under immunosuppression

解析結果(感度分析)

重症化リスク因子を有する症例の抽出とモルヌピラビル以外のCOVID-19治療薬を併用した症例を除外した結果、 16,134例(モルヌピラビル群:8,088例及び標準治療群:8,046例)が解析対象となった(図2-3-2-5)。本解析対象の背景因子は図2-3-2-6に示す。

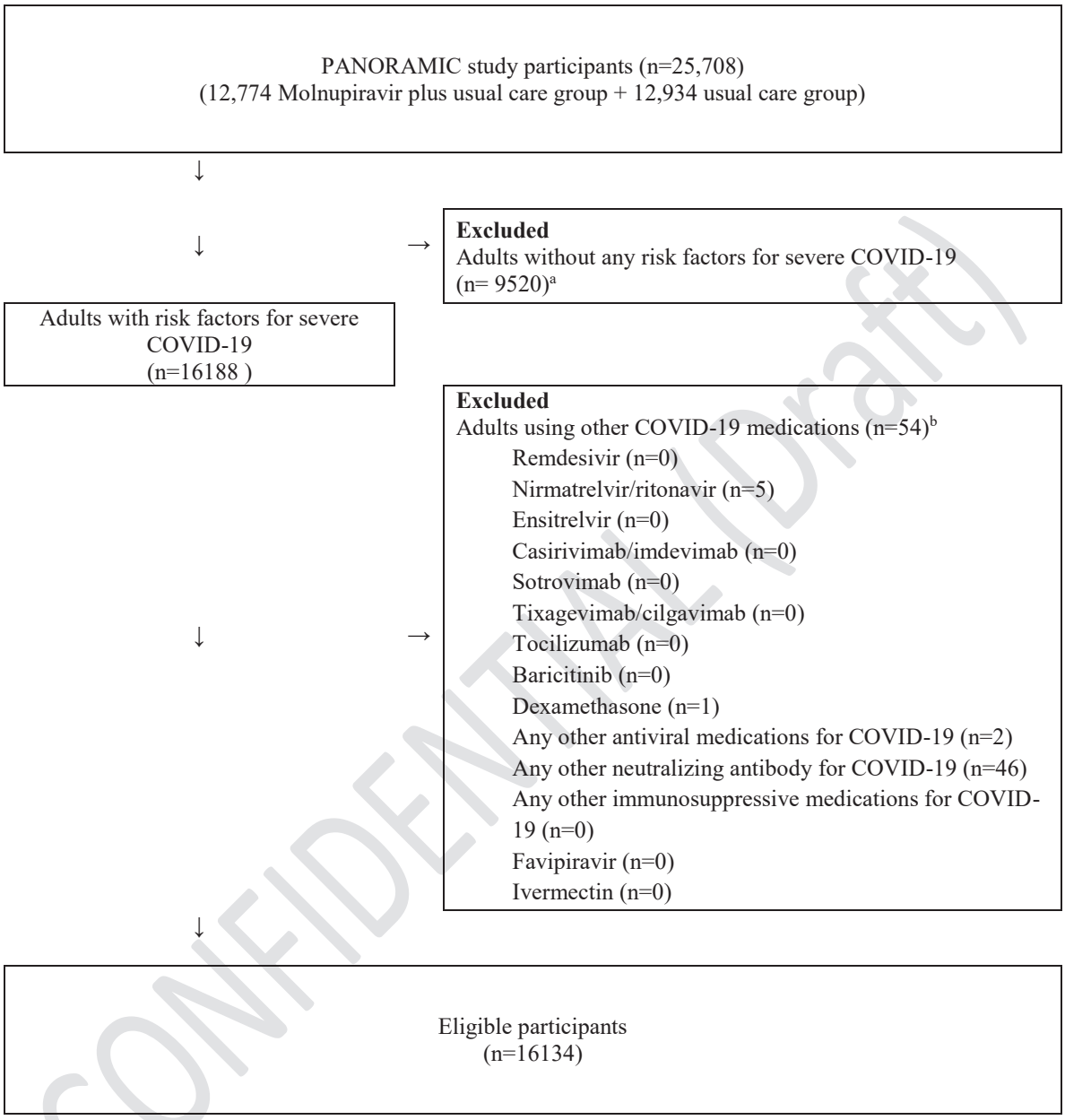

図2-3-2-5 解析対象者選定のフローチャート(感度分析)

	Molnupiravir plus usual care (N=8088)	Usual Care (N=8046)	Overall (N=16134)
Age, mean(SD) [min,max]	59.2 (13.4) [18.0 to 99.0]	59.2 (13.6) [18.0 to 98.0]	59.2 (13.5) [18.0 to 99.0]
Sex, n(%)			
Female	4452 (55.0%)	4450 (55.3%)	8902 (55.2%)
Male	3634 (44.9%)	3595 (44.7%)	7229 (44.8%)
Other	2 (0.0%)	1 (0.0%)	3 (0.0%)
Days from randomisation to reporting receipt of medication*, median(IQR)	2.0 (2.0 to 2.0)	N/A	2.0 (2.0 to 2.0)
Days from start of symptoms to taking medication*, median(IQR)	4.0 (3.0 to 5.0)	N/A	4.0 (3.0 to 5.0)
Data unavailable, n(%)	6434 (79.5%)		6434 (39.9%)
Ethnicity category, n(%)			
White	7628 (94.3%)	7573 (94.1%)	15201 (94.2%)
Asian	233 (2.9%)	269 (3.3%)	502 (3.1%)
Mixed Race	117 (1.4%)	105 (1.3%)	222 (1.4%)
Black	53 (0.7%)	53 (0.7%)	106 (0.7%)
Other	57 (0.7%)	46 (0.6%)	103 (0.6%)
NHS priority category, n(%)			
Aged ≥80	256 (3.2%)	271 (3.4%)	527 (3.3%)
Aged ≥75 and <80	537 (6.6%)	573 (7.1%)	1110 (6.9%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1115 (13.8%)	1108 (13.8%)	2223 (13.8%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1488 (18.4%)	1463 (18.2%)	2951 (18.3%)
Aged ≥18 and <65 in an at risk group	4545 (56.2%)	4474 (55.6%)	9019 (55.9%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at risk group	37 (0.5%)	35 (0.4%)	72 (0.4%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at risk group	43 (0.5%)	56 (0.7%)	99 (0.6%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at risk group	67 (0.8%)	66 (0.8%)	133 (0.8%)
Predicted risk quintile, n(%)			
1 (lowest risk)	623 (7.7%)	633 (7.9%)	1256 (7.8%)
2	1698 (21.0%)	1660 (20.6%)	3358 (20.8%)
3	1861 (23.0%)	1898 (23.6%)	3759 (23.3%)
4	2084 (25.8%)	2063 (25.6%)	4147 (25.7%)
5 (highest risk)	1822 (22.5%)	1792 (22.3%)	3614 (22.4%)
Confirmed PCR positive, n(%)	3680 (45.5%)	3585 (44.6%)	7265 (45.0%)
IMD quintile, n(%)			
(Most deprived) 1	835 (10.3%)	808 (10.0%)	1643 (10.2%)
2	1250 (15.5%)	1265 (15.7%)	2515 (15.6%)
3	1659 (20.5%)	1629 (20.2%)	3288 (20.4%)

図2-3-2-6 PANORAMIC試験から抽出した症例の背景因子(感度分析)

	Molnupiravir plus usual care (N=8088)	Usual Care (N=8046)	Overall (N=16134)
4	2011 (24.9%)	1967 (24.4%)	3978 (24.7%)
(Least deprived) 5	2305 (28.5%)	2340 (29.1%)	4645 (28.8%)
Data unavailable, n(%)	28 (0.3%)	37 (0.5%)	65 (0.4%)
Took at least 4 doses IMP, n(%)	7495 (92.7%)		7495 (46.5%)
Received vaccination, n(%)	7994 (98.8%)	7974 (99.1%)	15968 (99.0%)
Number of COVID-19 vaccine doses, n(%)			
1	54 (0.7%)	48 (0.6%)	102 (0.6%)
2	290 (3.6%)	249 (3.1%)	539 (3.3%)
3	7440 (92.0%)	7464 (92.8%)	14904 (92.4%)
4	210 (2.6%)	213 (2.6%)	423 (2.6%)
Data unavailable, n(%)	94 (1.2%)	72 (0.9%)	166 (1.0%)
Current smoker, n(%)	787 (9.7%)	799 (9.9%)	1586 (9.8%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	3871 (47.9%)	3786 (47.1%)	7657 (47.5%)
Minor problem	2834 (35.0%)	2891 (35.9%)	5725 (35.5%)
Moderate problem	1221 (15.1%)	1198 (14.9%)	2419 (15.0%)
Major problem	162 (2.0%)	171 (2.1%)	333 (2.1%)
Fatigue, n(%)			
No problem	803 (9.9%)	788 (9.8%)	1591 (9.9%)
Minor problem	2960 (36.6%)	2952 (36.7%)	5912 (36.6%)
Moderate problem	3187 (39.4%)	3186 (39.6%)	6373 (39.5%)
Major problem	1138 (14.1%)	1120 (13.9%)	2258 (14.0%)
Muscle ache, n(%)			
No problem	2264 (28.0%)	2155 (26.8%)	4419 (27.4%)
Minor problem	2734 (33.8%)	2934 (36.5%)	5668 (35.1%)
Moderate problem	2371 (29.3%)	2290 (28.5%)	4661 (28.9%)
Major problem	719 (8.9%)	667 (8.3%)	1386 (8.6%)
Vomiting, n(%)			
No problem	6603 (81.6%)	6564 (81.6%)	13167 (81.6%)
Minor problem	1151 (14.2%)	1140 (14.2%)	2291 (14.2%)
Moderate problem	298 (3.7%)	288 (3.6%)	586 (3.6%)
Major problem	36 (0.4%)	54 (0.7%)	90 (0.6%)
Diarrhoea, n(%)			
No problem	6599 (81.6%)	6593 (81.9%)	13192 (81.8%)
Minor problem	1073 (13.3%)	1094 (13.6%)	2167 (13.4%)
Moderate problem	331 (4.1%)	296 (3.7%)	627 (3.9%)
Major problem	85 (1.1%)	63 (0.8%)	148 (0.9%)
Loss of smell or taste, n(%)			
No problem	5660 (70.0%)	5802 (72.1%)	11462 (71.0%)
Minor problem	1589 (19.6%)	1473 (18.3%)	3062 (19.0%)
Moderate problem	541 (6.7%)	512 (6.4%)	1053 (6.5%)

図2-3-2-6 PANORAMIC試験から抽出した症例の背景因子(感度分析) 続き

	Molnupiravir plus usual care (N=8088)	Usual Care (N=8046)	Overall (N=16134)
Major problem	298 (3.7%)	259 (3.2%)	557 (3.5%)
Headache, n(%)			
No problem	1753 (21.7%)	1837 (22.8%)	3590 (22.3%)
Minor problem	3293 (40.7%)	3205 (39.8%)	6498 (40.3%)
Moderate problem	2316 (28.6%)	2337 (29.0%)	4653 (28.8%)
Major problem	726 (9.0%)	667 (8.3%)	1393 (8.6%)
Dizziness, n(%)			
No problem	5306 (65.6%)	5174 (64.3%)	10480 (65.0%)
Minor problem	1946 (24.1%)	2034 (25.3%)	3980 (24.7%)
Moderate problem	701 (8.7%)	699 (8.7%)	1400 (8.7%)
Major problem	135 (1.7%)	139 (1.7%)	274 (1.7%)
Abdominal pain, n(%)			
No problem	6541 (80.9%)	6466 (80.4%)	13007 (80.6%)
Minor problem	1143 (14.1%)	1191 (14.8%)	2334 (14.5%)
Moderate problem	359 (4.4%)	351 (4.4%)	710 (4.4%)
Major problem	45 (0.6%)	38 (0.5%)	83 (0.5%)
Generally unwell, n(%)			
No problem	347 (4.3%)	345 (4.3%)	692 (4.3%)
Minor problem	3162 (39.1%)	3212 (39.9%)	6374 (39.5%)
Moderate problem	3637 (45.0%)	3591 (44.6%)	7228 (44.8%)
Major problem	942 (11.6%)	898 (11.2%)	1840 (11.4%)
Fever, n(%)			
No problem	3563 (44.1%)	3583 (44.5%)	7146 (44.3%)
Minor problem	3019 (37.3%)	3021 (37.5%)	6040 (37.4%)
Moderate problem	1375 (17.0%)	1315 (16.3%)	2690 (16.7%)
Major problem	131 (1.6%)	127 (1.6%)	258 (1.6%)
Cough, n(%)			
No problem	837 (10.3%)	802 (10.0%)	1639 (10.2%)
Minor problem	3811 (47.1%)	3805 (47.3%)	7616 (47.2%)
Moderate problem	2910 (36.0%)	2968 (36.9%)	5878 (36.4%)
Major problem	530 (6.6%)	471 (5.9%)	1001 (6.2%)
Wellness score, mean (SD) [min,max]	5.2 (1.7) [0.0 to 10.0]	5.2 (1.7) [0.0 to 10.0]	5.2 (1.7) [0.0 to 10.0]
People in household, n(%)			
0	1106 (13.7%)	1127 (14.0%)	2233 (13.8%)
1	4167 (51.5%)	4104 (51.0%)	8271 (51.3%)
2	1211 (15.0%)	1197 (14.9%)	2408 (14.9%)
3	938 (11.6%)	998 (12.4%)	1936 (12.0%)
4	446 (5.5%)	412 (5.1%)	858 (5.3%)
5	220 (2.7%)	208 (2.6%)	428 (2.7%)
Taking inhaled corticosteroids, n(%)	1607 (19.9%)	1696 (21.1%)	3303 (20.5%)
Taking inhaled corticosteroids for COVID, n(%)	93 (1.1%)	84 (1.0%)	177 (1.1%)

図2-3-2-6 PANORAMIC試験から抽出した症例の背景因子(感度分析) 続き

	Molnupiravir plus usual care (N=8088)	Usual Care (N=8046)	Overall (N=16134)
Monoclonal antibodies for COVID, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Comorbidities			
Lung disease	1620 (20.0%)	1718 (21.4%)	3338 (20.7%)
Heart disease	993 (12.3%)	952 (11.8%)	1945 (12.1%)
Kidney disease	222 (2.7%)	253 (3.1%)	475 (2.9%)
Liver disease	131 (1.6%)	119 (1.5%)	250 (1.5%)
Neurological disease	295 (3.6%)	281 (3.5%)	576 (3.6%)
Learning disability	32 (0.4%)	26 (0.3%)	58 (0.4%)
Down's syndrome'	24 (0.3%)	26 (0.3%)	50 (0.3%)
Diabetes	1473 (18.2%)	1507 (18.7%)	2980 (18.5%)
Weakened immune system	1110 (13.7%)	1055 (13.1%)	2165 (13.4%)
Transplant recipient	55 (0.7%)	69 (0.9%)	124 (0.8%)
Obesity	1957 (24.2%)	1932 (24.0%)	3889 (24.1%)
Mental illness	143 (1.8%)	159 (2.0%)	302 (1.9%)
Hypertension	2854 (35.3%)	2895 (36.0%)	5749 (35.6%)
Other vulnerability	1683 (20.8%)	1615 (20.1%)	3298 (20.4%)

*Median and interquartile range presented for non-normally distributed variables.

図2-3-2-6 PANORAMIC試験から抽出した症例の背景因子(感度分析) 続き

本解析対象者において、モルヌピラビルの標準治療に対する主要評価項目(入院又は死亡)のオッズ比は1.022 (95% CI：0.738 to 1.382)であった(図2-3-2-7)。

	Molnupiravir plus usual care (N=8088)	Usual care (N=8046)	Estimated treatment effect (95% BCI)	Probability of superiority
Hospitalization or death	81/7933 (1.0%)	78/7770 (1.0%)	1.022 (0.738 to 1.382)	0.4778
Deaths	3/7933	5/7770	Not estimable	
Hospitalizations	79/7933 (1.0%)	76/7770 (1.0%)	1.023 (0.737 to 1.385)	0.4762

*OR < 1 favours Molnupiravir

図2-3-2-7 主要評価項目の結果(感度分析)

結果の解釈

PANORAMIC試験から、本邦における重症化リスク因子の定義や標準治療の内容に合致した症例のみを抽出した上で分析を実施した。その結果、標準治療に対するモルヌピラビルの入院又は死亡におけるオッズ比は1.053 (95% CI：0.775 to 1.396)であり、点推定値ではオッズ比が1以上であった。また、その構成要素である入院のオッズ比も1.055 (95% CI：0.773 to 1.413)であり、点推定値では1を

超過していた。

諸外国の医療技術評価機関や公的機関においても、PANORAMIC試験は、モルヌピラビルの治療効果の評価として参照されており、それぞれ対応が行われている。具体的には、NICEでは、新たにSTAを実施し、その結論が出るまで最終ガイダンスは公表しないこととなっているが、評価の過程においてモルヌピラビルが標準治療に対する優越性を示していないことが指摘された。PBACにおいては、PANORAMIC試験を考慮して、ニルマトレルビル/リトナビルが禁忌または適切ではない場合のみ、モルヌピラビルによる治療を検討すべきであることが提言されている。また、EMAではMOVe-OUT試験の外的妥当性に対する課題やPANORAMIC試験の結果を受けて、モルヌピラビルの臨床的有用性が証明されていないとして、モルヌピラビルの販売承認の取下げを勧告した。

その一方で、PANORAMIC試験事後解析の解析対象者における平均年齢は56.8歳であり、本邦の実臨床における投与対象と比較して、若年で相対的に重症化リスクの低い症例が多く含まれていたことが考えられる。実際に、製造販売業者の特定使用成績調査によると、モルヌピラビルが投与された日本人患者(3,384例)における年齢の中央値は69歳であったことが示されている。そして、高齢者を多く解析対象としている、いくつかのリアルワールドデータを用いた観察研究では、モルヌピラビルは標準治療と比較して、入院又は死亡の発生を抑制しうる効果が報告されている。

例えば、米国退役軍人のデータベースを用いた観察研究では、重症化リスク因子を有するCOVID-19患者85,998例(平均年齢：67.3歳)が解析対象となったが、モルヌピラビル投与群において、30日目までの入院又は死亡の発生率が低値であったことが報告されている(RR 0.72 [95% CI：0.64 to 0.79]) (13)。また、PANORAMIC試験事後解析においても、統計学的に有意な異質性は検出されなかったが、80歳以上でのサブグループでは、入院又は死亡におけるオッズ比は0.52 (95% CI：0.17 to 1.48)であり、点推定値では全体集団よりも治療効果が改善する方向にあった。このように、臨床専門家からの示唆によれば、高齢者集団に対しては、モルヌピラビルが一定の有用性を有する可能性もあるが、多くの高齢者を解析対象として含んだ、モルヌピラビルが入院又は死亡の発生を抑制することを示唆した研究の多くは海外における大規模データベースを用いた後ろ向き観察研究であり、またPANORAMIC試験における80歳以上集団もその数が各群で数百人程度とわずかであることから、高齢者における有用性については今後のさらなるデータの蓄積や検討が必要であろう。

よって、PANORAMIC試験の事後解析結果を参照すれば、現時点では全体集団に対してモルヌピラビルが比較対照技術に対して追加的有用性を有すると判断できる明確な根拠が欠けており、追加的有用性を有すると判断することは困難であると評価した。

2.4　追加的有用性の有無に関する評価

表2-4 モルヌピラビルの追加的有用性に関する評価

対象集団	重症化リスク因子を有するSARS-CoV-2による感染症(COVID-19)患者(18歳以上) 但し、有効性が確立していないため、重症度*の高いCOVID-19患者を除く *重症度の定義は新型コロナウイルス感染症(COVID-19)診療の手引き・第8.1版に準ずる。
介入	モルヌピラビル＋標準治療* *COVID-19に対して治療の適応がある薬剤を除く、対症療法
比較対照	標準治療
アウトカム	入院又は死亡
追加的有用性の有無	□ 追加的有用性あり ■「追加的有用性なし」あるいは「ありとは判断できない」 □ その他(　　)
判断の根拠となったデータ	□ RCTのメタアナリシス　□ 単一のRCT □ 前向きの比較観察研究　□ RCTの間接比較 □ 単群試験の比較 ■ その他(単一のRCTの事後解析)
追加的有用性の有無を判断した理由	PANORAMIC試験から、本邦における重症化リスク因子の定義や標準治療の内容に合致した症例のみを抽出した上で分析を実施した。その結果、標準治療に対するモルヌピラビルの入院又は死亡におけるオッズ比は1.053 (95% CI： 0.775 to 1.396)であり、点推定値ではオッズ比が1以上であった。また、その構成要素である入院のオッズ比も1.055 (95% CI： 0.773 to 1.413)であり、点推定値では1以上であった。 ただし、多くの高齢者を解析対象として含んだ、いくつかの大規模データベースを用いた後ろ向き観察研究では、モルヌピラビルは標準治療と比較して、入院又は死亡の発生を抑制しうる効果も報告されている。また、PANORAMIC試験事後解析においても、 80歳以上でのサブグループでは、入院又は死亡におけるオッズ比は0.52 (95% CI： 0.17 to 1.48)と全体集団よりも治療効果が改善する傾向が見られた。臨床専門家からの示唆によれば、このように高齢者に対しては、モルヌピラビルが一定の有用性を有する可能性があるが、実際のエビデンスとしては限定的であることから、今後のさらなるデータの蓄積や検討が必要である。

【製造販売業者の提出資料（追加的有用性）に対するレビュー結果】

得られたデータに基づくと、評価対象技術は比較対照技術に対し

□　追加的有用性を有すると考えられたため、費用効果分析が妥当である。

■　追加的有用性を有すると判断できないため、費用最小化分析が妥当である。

□　その他(　　)

3. 費用対効果の評価

3.1.1　標準治療と比較した費用効果分析の概要

製造販売業者は、COVID-19外来患者における臨床経過をモデル化し、モルヌピラビルの費用対効果を評価した（図3-1-1-1)。COVID-19の発症から急性期治療終了までの分析期間(30日）には決定樹モデルを、その後の分析期間(生涯:死亡又は100歳まで)には1サイクルを1年としたマルコフモデルを用いた。患者の健康状態は、軽症・中等症、一般病棟、ICU、ICU+MV/ECMO、長期の後遺症、長期の後遺症なしの回復、再入院、死亡の8状態とし、治療(モルヌピラビル又は標準治療)による入院または死亡リスクの差異を考慮した。決定樹モデルは、軽症・中等症の健康状態から開始し、COVID-19重症化に伴い、外来から入院(一般病棟、ICU、ICU+MV/ECMO)への移行を仮定した。マルコフモデルでは、入院後の患者の転帰として、長期の後遺症、長期の後遺症なしの回復、再入院、死亡への移行を仮定した。

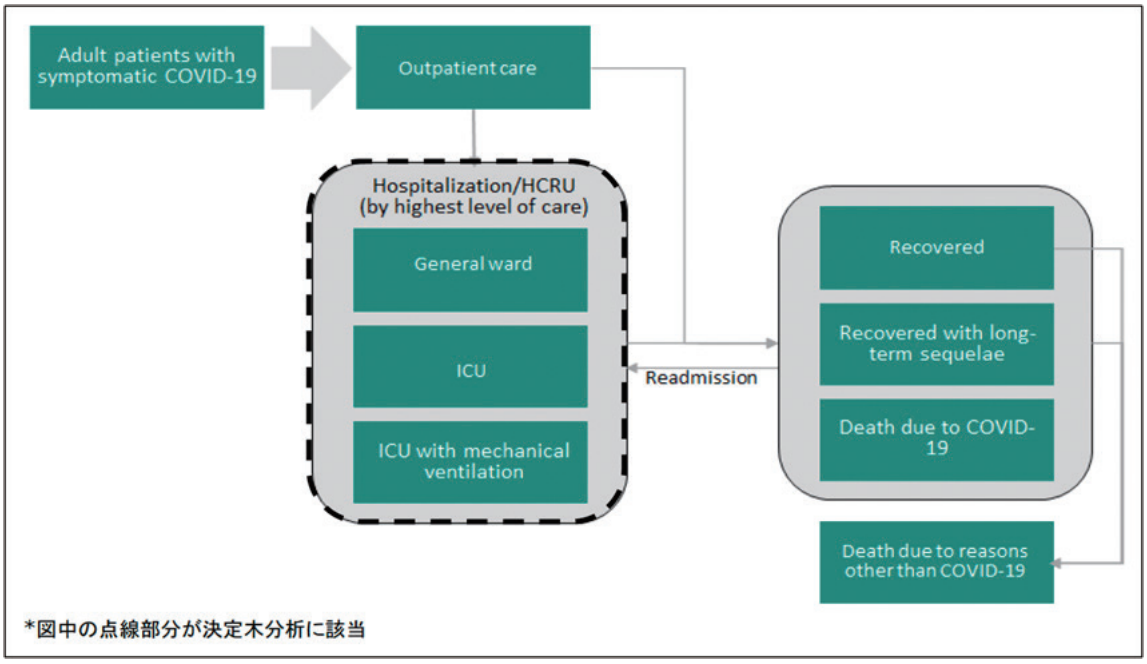

図3-1-1-1 費用効果分析のモデル構造(製造販売業者の報告書より)

モルヌピラビルの有効性(入院、入院患者の重症化及び死亡のRR)には、MOVe-OUTのデータを用いた。ベースラインの患者背景(年齢、性別)、入院患者の遷移確率、後遺症発生率、外来または入院費用等、COVID-19疾患特性に関わるパラメータには、メディカル・データ・ビジョン(MDV)社のEBM Providerの集計結果を用いた。分析対象集団におけるベースラインの入院割合には、厚生労働省「新型コロナウイルス感染症患者の療養状況等及び入院患者受入病床数等に関する調査結果」(15)における2022年各週の療養者数と入院者数から算出した入院割合の平均値を用いた。

製造販売業者のモデルにおける主な仮定は以下の通りであった。

- モルヌピラビル群は、モルヌピラビルの投与によって、標準治療群に比べて入院率、入院時の死亡率が低下する。
- 入院患者の健康状態は、一般病棟、ICU、ICU+MV/ECMOの3状態のいずれかに移行する。
- 有害事象(AE)または治療上緊急を要する有害事象は発生しない。
- 外来、入院患者は一定の確率で後遺症を発症する。後遺症の継続期間は初期治療終了日～30日までとし、後遺症の継続期間中はQOLの低下、診療費用が発生する。
- 再入院の健康状態におけるQOL値は、一般病棟の健康状態と同等である。

製造販売業者による基本分析の結果は以下の表3-1-1の通りであった。

表3-1-1 製造販売業者による費用効果分析の基本分析の結果

	効果(QALY)	増分効果(QALY)	費用(円)	増分費用(円)	ICER(円/QALY)
モルヌピラビル	25.596	0.044	175,291	84,391	1,930,637
標準治療	25.552		90,900		

3.1.2　標準治療群と比較した費用効果分析に対する見解

公的分析によるレビューの結果、製造販売業者が用いたモデルの構造や費用パラメータの設定方法はおおむね妥当と考えられた。一方で、以下の論点が挙げられた。

費用最小化分析の実施

上記「2.4 追加的有用性の有無に関する評価」に記載の通りモルヌピラビルは比較対照技術に対して追加的有用性を有すると判断できないと評価した。このことから、費用最小化分析の実施が適当である。

3.2　レビュー結果による再分析の必要な箇所の有無

□　特になし　→　　本節で終了
■　あり　　→　　以下に続く
□　その他(　　)

3.3　実施が必要な再分析の概要

3.3.1　再検討が必要な分析手法やパラメータなど(主要な[結果への影響が大きい]もの)

a)費用最小化分析の実施

3.3.2　再検討が必要な分析手法やパラメータなど(3.3.1 以外のもの)

該当なし

3.4　主要な点 (結果に与える影響が大きい点) についての再分析の内容

3.4.1　費用最小化分析の実施

表 3-4-1 製造販売業者による報告書の該当部分

製造販売業者の提出した報告書等における		
セクション	ページ数	開始行番号(あるいは図表番号)
5.1.1	p.65	表 21

【報告書等の記述】

	効果(QALY)	増分効果(QALY)	費用(円)	増分費用(円)	ICER(円/QALY)
モルヌピラビル	25.596	0.044	175,291	84,391	1,930,637
標準治療	25.552		90,900		

【具体的な再分析の内容】

追加的有用性の検討結果から、入院や死亡に関連する治療効果に群間差を設定せず、治療費用を比較する費用最小化分析を実施した。製造販売業者におけるモルヌピラビルの治療費用推計方法について、公的分析では妥当であると判断し、その結果を治療費用として用いた。

表 3-4-2 製造販売業者によるモルヌピラビル治療費用の推計方法

項目	費用	推計方法
モルヌピラビル治療費用	94,312 円	モルヌピラビル(ラゲブリオカプセル 200mg)の添付文書における用法及び用量として「通常、18 歳以上の患者には、モルヌピラビルとして 1 回 800mg を 1 日 2 回、 5 日間経口投与する。」とされている。このことから、分析時点の薬価(200mg カプセル： 2,357.8 円)に基づいて、 4 カプセル[1 回当たり]× 2 回[1 日当たり]× 5 日の計算から算出した。

3.5　3.4 以外に検討が必要な点における再分析の内容

該当なし

4. 分析結果

4.1　再分析における基本分析の結果

□	費用効果分析(増分費用効果比を算出する)
■	費用最小化分析(効果は同等として費用を比較する)
□	その他(　　)

4.1.1　再分析における基本分析の増分費用

表4-1-1-1 製造販売業者による基本分析の結果

	効果 (QALY)	増分効果 (QALY)	費用(円)	増分費用(円)	ICER(円/QALY)
モルヌピラビル	25.596	0.044	175,291	84,391	1,930,637
標準治療	25.552		90,900		

表4-1-1-2 再分析における基本分析の結果

	増分費用(円)
モルヌピラビル+標準治療	94,312

4.1.2　費用効果分析を実施する場合に、増分費用効果比に影響を与えうる要因

a) ベースラインの患者背景に関するモデル設定について

製造販売業者は、分析モデルに組み込むベースラインの患者背景(年齢や性別等)の分析パラメータを算出するために、重症化リスク因子の有無に関わらず、COVID-19と診断された患者をレセプトデータベースから抽出して、分析を行った。しかし、費用対効果評価専門組織において決定された分析枠組みにおける分析対象集団は、「重症化リスク因子を有するCOVID-19患者」である。重症化リスク因子の有無によって、適用すべき年齢や男女の比率は異なることが想定される。

b) 長期の後遺症について

製造販売業者は、分析モデルに組み入れられた患者がCOVID-19罹患後に一定の確率で長期の後遺症を発症することを仮定しており、後遺症の発症確率は重症度の高い状態(軽症・中等症から、一般病棟、ICU、ICU+MV/ECMO)ほど高くなる設定となっていた。つまり、分析モデルにおいて、モルヌピラビルは重症度の高い状態へ移行することを抑制する効果を有するために、間接的に長期の後遺症発症までも抑制することが仮定されていた。しかし、データソースとしたRCTにおいて、モルヌピラビルの長期の後遺症発症に対する有効性は検討されておらず、その効果を分析に組み込むにはエビデンスとして不十分である。

c) QOL値について

製造販売業者はCOVID-19関連の健康状態におけるQOL値を取得するために、ビネット(記述された健康状態について一般人にその状態を想起させることにより評価を行う手法)に基づくQOL調査データを用いた。当該データは英国の一般人を対象に、ビネットで記述された健康状態について、EQ-5D-5Lのどの選択肢に該当するかを調査したものである。得られたデータを日本の換算表を用いてQOL値に変換することにより、分析モデルに組み込んだ。しかし、費用対効果評価の分析ガイドライン第3版では、対象者本人からQOL値を得ることが困難な場合には一般の人々を対象に健康状態を想起させることにより基準的賭け法や時間得失法といった直接法の手法を用いてQOL値を測定してもよいとされているが、EQ-5D-5Lのような選好基づく尺度に回答することは学術的にも一般的ではなく、また適切な手法とも言えない。

4.2　再分析における感度分析の結果

本品目では費用最小化分析を実施したため、本項は該当しない。

4.3　再分析におけるシナリオ分析の結果

該当なし

4.4　分析結果の解釈

表4-4 分析結果の解釈

分析対象集団	重症化リスク因子を有するSARS-CoV-2による感染症(COVID-19)患者(18歳以上) 但し、有効性が確立していないため、重症度*の高いCOVID-19患者を除く *重症度の定義は新型コロナウイルス感染症(COVID-19)診療の手引き・第8.1版に準ずる。
比較対照技術	標準治療*(評価対象技術：モルヌピラビル＋標準治療) *COVID-19に対して治療の適応がある薬剤を除く、対症療法
ICERの基準値	■　通常の品目　　□　配慮が必要な品目
ICERの所属する確率が最も高いと考える区間	□　ドミナント(比較対照技術に対し効果が増加し、かつ費用が削減) □　比較対照技術に対し効果が同等であり、かつ費用が削減 □　200万円/QALY未満 □　200万円/QALY以上(200万円/QALY以上)かつ500万円/QALY未満(750万円/QALY未満) □　500万円/QALY以上(750万円/QALY以上)かつ750万円/QALY未満(1125万円/QALY未満) □　750万円/QALY以上(1125万円/QALY以上)かつ1000万円/QALY以下(1500万円/QALY未満) □　1000万円/QALY以上(1500万円/QALY以上) ■　効果が同等(あるいは劣り)、かつ費用が高い □　その他(　　)
そのように判断した理由	費用最小化分析の結果、評価対象技術は比較対照技術と比較して94,312円の費用増加であった。

4.5　価格調整率の重み

該当なし

謝辞

公的分析に際して、データをご提供いただきましたオックスフォード大学のLy-Mee YU先生、Christopher Butler先生、Victoria Harris先生、Milensu Shanyinde先生、ならびにPANORAMIC Trial Collaborative Groupの全ての先生方に厚く御礼申し上げます。

5. 参考文献

[1] National Institute for Health and Care Excellence. Molnupiravir, remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261] In development [GID-TA11297] 2023 [Available from: https://www.nice.org.uk/guidance/indevelopment/GID-TA11297.

[2] Pharmaceutical Benefits Advisory Committee. Lagevrio® (molnupiravir) Pharmaceutical Benefits Scheme Factsheet – Updated July 2023 2023 [Available from: https://www.pbs.gov.au/publication/factsheets/covid-19-treatments/Factsheet-lagevrio-molnupiravir-July-2023.pdf.

[3] Department of Health and Social Care. Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group report 2022 [Available from: https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report/defining-the-highest-risk-clinical-subgroups-upon-community-infection-with-sars-cov-2-when-considering-the-use-of-neutralising-monoclonal-antibodies.

[4] The European Medicines Agency. Lagevrio: Withdrawal of the marketing authorisation application 2023 [Available from: https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/lagevrio.

[5] Khoo SH, FitzGerald R, Saunders G, Middleton C, Ahmad S, Edwards CJ, et al. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Infect Dis. 2023;23(2):183-95.

[6] Fischer WA, 2nd, Eron JJ, Jr., Holman W, Cohen MS, Fang L, Szewczyk LJ, et al. A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Science translational medicine. 2022;14(628):eabl7430.

[7] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2022;386(6):509-20.

[8] Johnson MG, Puenpatom A, Moncada PA, Burgess L, Duke ER, Ohmagari N, et al. Effect of Mol-

nupiravir on Biomarkers, Respiratory Interventions, and Medical Services in COVID-19 : A Randomized, Placebo-Controlled Trial. Ann Intern Med. 2022;175(8):1126-34.

[9] Johnson MG, Strizki JM, Brown ML, Wan H, Shamsuddin HH, Ramgopal M, et al. Molnupiravir for the treatment of COVID-19 in immunocompromised participants: efficacy, safety, and virology results from the phase 3 randomized, placebo-controlled MOVe-OUT trial. Infection. 2023:1-12.

[10] Butler CC, Hobbs FDR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, et al. 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. Lancet. 2023;401(10373):281-93.

[11] Sinha S, N K, Suram VK, Chary SS, Naik S, Singh VB, et al. Efficacy and Safety of Molnupiravir in Mild COVID-19 Patients in India. Cureus. 2022;14(11):e31508.

[12] Zou R, Peng L, Shu D, Zhao L, Lan J, Tan G, et al. Antiviral Efficacy and Safety of Molnupiravir Against Omicron Variant Infection: A Randomized Controlled Clinical Trial. Front Pharmacol. 2022;13:939573.

[13] Xie Y, Bowe B, Al-Aly Z. Molnupiravir and risk of hospital admission or death in adults with covid-19: emulation of a randomized target trial using electronic health records. Bmj. 2023;380:e072705.

[14] 首相官邸. 新型コロナワクチンについて 2023 [Available from: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html.

[15] 厚生労働省. 療養状況等及び入院患者受入病床数等に関する調査 2022 [Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/newpage_00023.html.

STATISTICAL ANALYSIS PART 1 REPORT

Platform **A**daptive trial of **NO**vel antivi**R**als for e**A**rly treat**M**ent of covid-19 **I**n the **C**ommunity

Reference Number / Short title: PANORAMIC

MONUPIRAVIR

Ethics Ref: 21/SC/0393

IRAS Project ID: 1004274

EudraCT Number: 2021-005748-31

Based on protocol version 5.0 9th May 2022

Version 2.0 Date: 9th October 2023

Report prepared and analysis carried out by	Dr Victoria Harris, Department of Primary Care Health Sciences, University of Oxford
Report reviewed by	Dr Milensu Shanyinde, Department of Primary Care Health Sciences, University of Oxford

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1 BACKGROUND

The Center for Outcomes Research and Economic Evaluation for Health (C2H) is currently conducting a cost-effectiveness evaluation of molnupiravir as a part of the Japanese health technology assessment (HTA) process. The data from the PANORAMIC study(Butler CC, et al. Lancet. 2023:28;401:281-293) could potentially be the source to assess the additional benefit of molnupiravir in the Japanese setting. However, there are several differences between the study design of the PANORAMIC and the indication for molnupiravir in Japan. For example, molnupiravir is approved in Japan for the treatment of COVID-19 in adults with risk factors for severe COVID-19 whereas the PANORAMIC study included adults without these risk factors. Additionally, differences in the definition of standard of care also exist. In Japan, concomitant use of molnupiravir with other COVID-19 medications (e.g., remdesivir) is not recommended. Given these differences, the purpose of this report is to present the results of sub-group analysis of the PANORAMIC study in line with the indication and clinical practice of molnupiravir in Japan. The results are presented excluding both **A) participants without risk factors** and **B) participants using other COVID-19 medications at the prescription of molnupiravir**.

DISCLAIMER: Publication of the results presented in this report requires approval in writing to the Chief Investigators.

2 INTRODUCTION

This document details the analysis for the subgroup reporting results for the comparison of Molnupiravir with usual care from the PANORAMIC trial. The results reported in these papers follow the strategy set out in the statistical analysis plan. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

This report is based on the statistical analysis plan { **Subgroup analysis of PANORAMIC study in Japan_Plan2.docx**}. Any deviations from the statistical analysis plan will be described and justified in this report of the trial.

Primary Care Clinical Trials Unit

UNIVERSITY OF OXFORD

PANORAMIC-MOLNUPIRAVIR Statistical Analysis Part 2 Report Version 2.0

Trial/Study statistician(s):

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2.1 SOFTWARE EMPLOYED

Analysis was carried out using STATA v18

3 METHODS

3.1 TRIAL OVERVIEW

Despite high uptake of vaccination against COVID-19, the disease remains prevalent in the UK and in many countries around the world, with many patients continuing to require hospital admission. COVID-19 causes considerable suffering, including loss of ability to perform activities of daily living, loss of educational and work opportunities, and inability to perform caring duties, with far reaching personal and societal consequences. Many go on to experience persisting and/or relapsing symptoms. People with underlying health conditions, unvaccinated people, and those in whom the vaccine is not effective are at increased risk of more severe disease. [11] New 'vaccine escaping' variants may yet emerge, and the impact of early antiviral treatment on long COVID syndromes is as yet unknown. Early treatment with antiviral agents may prevent progression to the later phase of COVID-19. Therefore, there is an urgent need to identify treatments for COVID-19 for use in the community early on in the illness that speeds recovery and prevents the need for hospital admission.

Antiviral agents may reduce viral shedding, and use of antiviral agents may lead to the emergence of resistance to novel antiviral agents, but the impact of novel antiviral agents on shedding and resistance is not yet known.

3.2 STUDY DESIGN

PANORAMIC is an open label, prospective, individually randomised, platform, adaptive, controlled clinical trial in community care. Trial arms will include:

Intervention arms: Novel antiviral agents (or combinations) targeting SARS-CoV-2, initially specified by The UK Antivirals National Taskforce (ATF) and with capacity for sequential introduction of each treatment regimen into the trial plus Usual Care. This report presents the primary and secondary analysis for the Molnupiravir arm.

Comparator arm: Usual Care, defined as the currently recommended treatment delivered by responsible clinicians. Usual Care was not mandated by the trial, as recommended treatments may change and be tailored to individual characteristics, and self-care will vary. Use of over the counter medication as well as key medications such as inhaled steroids and monoclonal antibodies was captured. In this report only usual care participants randomised concurrently and eligible to Molnupiravir were included.

3.3 Adaptive Design

The trial design allows for interim analysis and early stopping due to futility or efficacy and the addition or removal of interventions. The number and timing of interim analyses depends on the rate of recruitment. Full details of the design and decision criteria are given in the Adaptive Design Report. Due to rapid recruitment no interim analyses were carried out on the Molnupiravir arm. Paxlovid was added as an additional arm on 21st April 2022.

3.4 Objectives

Main Trial: The primary aim is to determine the effectiveness of selected antiviral agents in preventing hospitalisation and/or death in higher-risk patients with a confirmed positive PCR or LFT SARS-CoV-2 test result (see Inclusion/Exclusion Criteria, below).

Main Study	Objectives	Endpoint Measures	Timepoint (s)
Primary	To determine whether antiviral treatment in the community safely reduces non-elective hospitalisations/ deaths in higher risk, symptomatic patients with confirmed COVID-19	All cause, non-elective hospitalisation and/or death, within 28 days of randomisation	Within 28 days of randomisation Patient report, Study Partner report, HES/ONS/medical record data linkage
Secondary	To explore whether antiviral treatment affects 1) Time to recovery (defined as the first instance that a participant report of feeling recovered from the illness)	1-3) Participant reports symptoms daily for 28 days and at 3 and 6 months.	1-3) Daily online symptom scores. Telephone call or text on days 7, 14 and 28 if data is not obtained through the online diary.

	2) Participant reported illness severity, reported by daily rating of how well participant feels, enabling identification of sustained recovery.		Also, at 3 and 6 months.
	3) Duration of severe symptoms and symptom recurrence, including time to alleviation of symptoms, time to initial reduction of severity of symptoms, time to sustained recovery, time to sustained alleviation of symptoms, number of days of severe symptoms and worsening of symptoms		
	4) Contacts with the health services	4) Contacts with health services reported by patients and/or captured by reports of patients' medical records	4) GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days. Medical notes review for up to 10 years.

	5) New infections in household	5) Reports of new infections in the household from daily diary	5) Daily online symptom scores or telephone call or text on days 7, 14 and 28
	6) To investigate the safety of antiviral agents	6) Evaluation of overall safety of drugs by the monitoring of adverse events (Aes as defined in the ISAs)	6) For the duration of the antiviral course and a defined period after the antiviral finishes (see ISAs)
	7) Longer term effects, including proportion with long covid, long covid symptoms, health care use and wellness	7) Well-being, symptoms and heath care utilisation	7) Patient contact at three and six months, electronic medical record search for up to one year
	8) Cost effectiveness	8) Resource use and cost data and EQ-5D-5L	8) Baseline and Day 28

3.5 TARGET POPULATION

The trial includes participants who test positive for SARS-CoV-2 infection and with ongoing symptoms consistent with COVID-19, not hospitalised, and who are aged 50 years and over, or 18-49 years and considered clinically vulnerable (see Inclusion Criteria below).

3.5.1 Inclusion Criteria

- Participant is able and willing to provide informed consent, or their legal representative is willing to provide informed consent
- Symptoms attributable to COVID-19 started within the past 5 days and ongoing
- A positive PCR or LFT SARS-CoV-2 test* Aged ≥50 years OR aged 18-49 years with one of the following known underlying chronic health condition considered to make them clinically vulnerable:
    - chronic respiratory disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis and asthma requiring at least daily use of preventative and/or reliever medication)
    - chronic heart or vascular disease
    - chronic kidney disease
    - chronic liver disease
    - chronic neurological disease (including dementia, stroke, epilepsy)
    - severe and profound learning disability
    - Down's syndrome
    - Diabetes mellitus (Type I or Type II)
    - immunosuppression: primary (e.g., inherited immune disorders resulting from genetic mutations, usually present at birth and diagnosed in childhood) or secondary due to disease or treatment (e.g., sickle cell, HIV, cancer, chemotherapy)
    - solid organ, bone marrow and stem cell transplant recipients
    - morbid obesity (BMI >35)
    - severe mental illness
    - care home resident
    - judged by recruiting clinician or research nurse (registered medical practitioner or trained study nurse) to be clinically vulnerable

* Any positive PCR test taken between two days before symptom onset and randomisation qualifies. A positive lateral flow test in a symptomatic person qualifies for randomisation and will be subject to pre-specified secondary analysis by type of diagnostic test.

3.5.2 Exclusion criteria

- Patient currently admitted to hospital (inpatient)
- Previous randomisation in the PANORAMIC trial
- Currently participating in a clinical trial of a therapeutic agent for acute COVID-19
- Additional exclusions specific to each intervention arm, if any, as listed in the Intervention Specific Appendices (ISA's) of currently open trial arms

3.5.3 A Risk factors

Risk factors for severe COVID-19 by the Ministry of Health, Labour and Welfare (MHLW) in Japan may not be available in the PANORAMIC study. Therefore, we propose the following 2 options to extract the data according to risk or modified risk factors that could be applicable to the Japanese setting.

1. Risk factors for severe COVID-19 defined by the Ministry of Health, Labour and Welfare (MHLW) is shown in Table 1.

TABLE 1 THE MHLW DEFINED RISK FACTORS FOR SEVERE COVID-19

Older adults aged ≥ 65 years	Hypertension	History of smoking
Malignant tumor	Dyslipidemia	Immunodeficiency after solid organ transplantation
Chronic respiratory disease (i.e., COPD)	Cardiovascular disease	Use of immunomodulatory agent or immunosuppressant
Chronic renal disease	Cerebrovascular disease	HIV infection (particularly CD4 < 200/μL)
Diabetes	Obesity (BMI ≥ 30 kg/m^2)	

Clinical Management of Patients with COVID-19 in Japan version 9.0 (In Japanese)

(https://www.mhlw.go.jp/content/000936655.pdf)

The diagnostic criteria for each risk factor have not been clearly indicated.

2. The modified definition of risk factors for severe COVID-19 is shown in Table 2. By reviewing the article of the PANORAMIC study, we believe that we could define the modified risk factors as follows:

TABLE 2 THE MODIFIED DEFINITION OF RISK FACTORS FOR SEVERE COVID-19

Risk factor	Details
Age	● Older adults aged ≥ 65 years
Asthma	
Cancer	● Hematologic malignancies
Cerebrovascular disease	
Chronic kidney disease	● People receiving dialysis
Chronic lung diseases limited to:	● Bronchiectasis ● COPD (Chronic obstructive pulmonary disease) ● Interstitial lung disease ● Pulmonary embolism ● Pulmonary hypertension
Chronic liver diseases limited to:	● Cirrhosis ● Non-alcoholic fatty liver disease ● Alcoholic liver disease ● Autoimmune hepatitis
Cystic fibrosis	
Diabetes mellitus, type 1	
Diabetes mellitus, type 2	
Down syndrome	
Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)	
HIV (Human immunodeficiency virus)	
Mental health conditions limited to:	● Mood disorders, including depression ● Schizophrenia spectrum disorders
Neurologic conditions limited to dementia	
Obesity	● BMI ≥ 30 kg/m^2
Physical inactivity	

Primary immunodeficiencies

Smoking, current and former

Solid organ or blood stem cell transplantation

Tuberculosis

Use of corticosteroids or other immunosuppressive medications

Risk factors have been defined by CDC criteria(https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html). We only extracted factors categorized into "Higher Risk (conclusive)" from the CDC criteria.

Clinical Management of Patients with COVID-19 in Japan version 10.0 (001136687.pdf (mhlw.go.jp))(In Japanese).

Disabilities were excluded from a risk factor.

a: Obesity was originally defined as BMI ≥ 35 kg/m^2 in the PANORAMIC study.

TABLE 3 THE DIAGNOSTIC CRITERIA FOR EACH RISK FACTOR IN THE PANORAMIC STUDY

Risk factor	Diagnostic criteria or definition
Older adults aged ≥ 65 years	Aged ≥ 65 years
Asthma	From free text and collected under lung disease.
Cancer (Hematologic malignancies)	From free text only. Mentions "blood cancer".
Cerebrovascular disease	From free text, mentions "stroke" or "cerebral aneurysm"
Chronic kidney disease (People receiving dialysis)	Collected as "long term kidney disease", not clear if receiving dialysis. Have counted anyone who has this checked.
Bronchiectasis	Collect "long term lung disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis or asthma requiring at least daily use of inhalers)".
COPD (Chronic obstructive pulmonary disease)	Collected as lung disease
Interstitial lung disease	Collected as lung disease
Pulmonary embolism	Collected as lung disease
Pulmonary hypertension	Collected as lung disease
Cirrhosis	Collected as liver disease
Non-alcoholic fatty liver disease	Collected as liver disease
Alcoholic liver disease	Collected as liver disease
Autoimmune hepatitis	Collected as liver disease
Cystic fibrosis	Collected as lung disease
Diabetes mellitus, type 1	Collected as diabetes, not separated by type.
Diabetes mellitus, type 2	Collected as diabetes, not separated by type.
Down syndrome	Down syndrome
Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)	Defined as long term heart or vascular disease
HIV (Human immunodeficiency virus)	Comes under weakened immune system or free text mentions HIV
Mood disorders, including depression	Collected under severe mental health disorder
Schizophrenia spectrum disorders	Free text mentions "Schizoaffective disorder" or collected under severe mental health disorder
Neurologic conditions limited to dementia	Collected as long term neurological disease (including dementia, stroke, epilepsy).
Obesity (BMI ≥ 30 kg/m^2)	Defined as BMI≥ 35 kg/m^2
Physical inactivity	Not collected
Primary immunodeficiencies	Collected as weakened immune system due to a condition you were born with or due to disease or treatment (e.g. sickle cell, HIV, cancer, chemotherapy)
Smoking, current and former	Current only
Solid organ or blood stem cell transplantation	Collected as transplant
Tuberculosis	Not collected, no free text.
Use of corticosteroids or other immunosuppressive medications	Free text mentions "steroids" or "immunosuppressant"

3.5.4 CONCOMITANT USE OF OTHER COVID-19 MEDICATIONS

In Japan, concomitant use of molnupiravir with other COVID-19 medications (e.g., remdesivir) is not recommended. We would like to exclude adults taking the following medications at the prescription of molnupiravir (Table 4) from the dataset. On the other hand, we consider that adults using the following medications **after the completion of treatment with molnupiravir** should not be excluded from the analysis because they are most likely to have progressed to severe COVID-19 (e.g., adults prescribed the following medications 10 days after a prescription for molnupiravir, adults who stopped treatment with molnupiravir within 5 days and subsequently received the following medications).

TABLE 4 THE DEFINITION OF OTHER COVID-19 MEDICATIONS

Remdesivir	Tixagevimab/cilgavimab	Any other neutralizing antibody for COVID-19
Nirmatrelvir/ritonavir	Tocilizumab	Any other immunosuppressive medications for COVID-19
Ensitrelvir	Baricitinib	Favipiravir
Casirivimab/imdevimab	Dexamethasone	Ivermectin
Sotrovimab	Any other antiviral medications for COVID-19	

3.6 INTERVENTIONS

Based on version 5.0 of the Protocol, the main randomisation was between the following treatment arms (although not all treatments were available at all times and not all participants were eligible for all treatments). However, the trial design accommodates interventions being added and dropped as appropriate.

- Usual care
- Molnupiravir (recruitment between 8th December 2021 and 27th April 2022)
- PAXLOVID (recruitment started 21st April 2022)

3.7 OUTCOMES

3.7.1 PRIMARY OUTCOME

The primary outcome is all-cause, non-elective hospitalisation and/or death within 28 days of randomisation.

3.7.2 SECONDARY OUTCOMES

Secondary outcomes include time to self-reported recovery defined as the first instance that a participant reports feeling fully recovered from the illness; duration of symptoms; symptom recurrence; daily rating of feeling well reported by participants; healthcare service use; participant reported household infection rate; safety outcomes and cost-effectiveness outcomes; symptoms and well-being at three and six months (with determination of proportion with Long Covid) from randomisation.

3.7.2.1 TIME TO RECOVERY

Time to recovery from COVID-19 infection within 28 days from randomisation, where recovery is defined as the first instance that a participant reported feeling recovered.

3.7.2.2 PATIENT REPORTED ILLNESS SEVERITY

Participants are asked to rate how well they are feeling overall each day on a scale of 1-10 (1 being the worst and 10 being the best). This is captured on the patients' daily diaries and the Call CRF.

3.7.2.3 DURATION OF SEVERE SYMPTOMS AND SYMPTOM RECURRENCE

Participants are asked to rate their symptoms of fever, cough, shortness of breath, fatigue (tiredness), muscle ache, nausea / vomiting, diarrhoea, loss of smell and/or taste, headache, dizziness, abdominal pain and generally feeling unwell on a four point scale from 0=no problem, 1=mild problem, 2=moderate problem and 3=major problem.

This is captured on patients' daily diaries and Call CRF.

The outcomes to be analysed include time to alleviation of symptoms, time to initial reduction in severe symptoms, time to sustained recovery, time to sustained alleviation of symptoms, number of days of severe symptoms, number reporting severe symptoms at days 7, 14 and 28, symptom recurrence and worsening of symptoms.

3.7.2.4 CONTACTS WITH HEALTH SERVICES BETWEEN RANDOMISATION AND DAY 28 OF FOLLOW-UP (FU).

This is captured on patients' daily diaries and telephone call CRFs.

3.7.2.5 NEW INFECTIONS IN THE HOUSEHOLD

Number of new infections within the household are captured within the participant daily diaries and call CRF.

3.7.2.6 SAFETY OF ANTIVIRAL AGENTS

Common side effects, according to the SmPC, include dizziness, headache, diarrhoea, and nausea. These symptoms, potential medication side-effects and Serious Adverse Events (SAE) were collected from participant daily diaries, calls to participants/Study Partners, face-to-face visits with Hub clinicians, medical records, notes reviews, NHS Digital data extracts and RCGP data downloads.

Pregnancy was recorded as an AE of Special Interest and was monitored from the start of treatment for the 28-day trial duration.

3.7.2.7 LONGER TERM EFFECTS: SYMPTOMS AND WELL-BEING AT 3 AND 6 MONTHS

The primary analysis is based on data collected through 28 days from randomisation; however additional outcomes will be collected at 3 and 6 months follow-up to capture the

long term outcomes of participants. This report covers outcomes for the first 28 days follow-up. The long term follow-up analysis will be covered in a future report.

3.7.2.8 HEALTHCARE MEASURES (EQ-5D-5L)

The EQ-5D-5L is a questionnaire consisting of 5 items (crosswalk) and a scale from 0 to 100 (VAS) defining overall health. These were captured in participant's daily diaries and call CRF. Cost effectiveness outcomes will be reported in a separate health economic analysis report and the analysis of this outcome will be described in a separate health economic analysis plan.

3.8 SAMPLE SIZE

The sample size calculation as stated in the protocol:

An estimated maximum of approximately 5300 participants per arm will be required to provide approximately 90% power for detecting a 33% relative reduction in the hospitalisation/death in an experimental arm relative to Usual Care, based on the assumption of an underlying 3% combined hospitalisation/death rate in the Usual Care arm, and an intervention lowering the hospitalisation/death rate to 2%. We expect fewer participants will be needed to detect the same relative reduction if the event rate is larger than 3% in the Usual Care arm, or if there is a greater reduction in the relative risk of hospitalisation/death for a given intervention. However, should the event rate be lower than expected, then the target sample size will be increased to reflect this.

We recruited 25783 for the comparison of Molnupiravir with Usual Care.

3.9 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

Participants were randomised using a secure, fully validated and compliant web-based randomisation system. Once deemed eligible, the medically qualified clinician or research nurse from the central clinical team or Hub (as documented on the delegation log) randomised the participant. Participants were randomised to one study arm using equal allocation ratios corresponding to the number of arms they were eligible for that were recruiting in the trial at that time. This started as 1:1 Molnupiravir:Usual Care, and once Paxlovid was introduced on 21st April 2022 changed to 1:1:1 Molnupiravir:Usual Care:Paxlovid. Patients had to be eligible for at least two arms (Usual Care and at least one novel antiviral intervention). Stratification was by age (< 50/ ≥ 50 years) and vaccination status (see 2.2.3).

The randomisation database automatically alerted the relevant IMP distributor and the participant, trial team and legal representative if applicable were notified electronically of the treatment allocation. If the participant did not have an email address, they were notified by telephone.

3.10 Definition of population for analysis

The analysis population will include participants as defined by the protocol eligibility criteria and having at least one of the vulnerabilities as listed in Table 3.

As per ICH E9 guidance the following participants will be excluded from the analysis population;

(a) Participants randomised but subsequently found to be not eligible for randomization

(b) Participants previously randomised to an arm in the PANORAMIC trial (subsequent randomisations will be excluded)

In addition, the following participants will be excluded;

(c) Participants who withdraw consent for data linkage and notes review and for whom no outcome data has been collected.

(d) Participants taking medications listed in Table 4

3.10.1.1 Primary analysis population

The primary analysis population is defined as participants who were randomised to Molnupiravir or usual care and were eligible for randomisation to Molnupiravir, during the same time frame when Molnupiravir was actively randomising (i.e. Concurrent Randomised and Eligible Analysis Population). That is, participants who were eligible for Molnupiravir and randomised to either Molnupiravir or usual care between 8th December 2021 and 27th April 2022.

This includes participants for whom data are available with participants analysed according to the groups they were randomly allocated to, regardless of deviation from protocol.

3.10.1.2 SECONDARY ANALYSIS POPULATION

Analysis of the secondary outcomes for a given intervention will be based on the same population as the primary analysis.

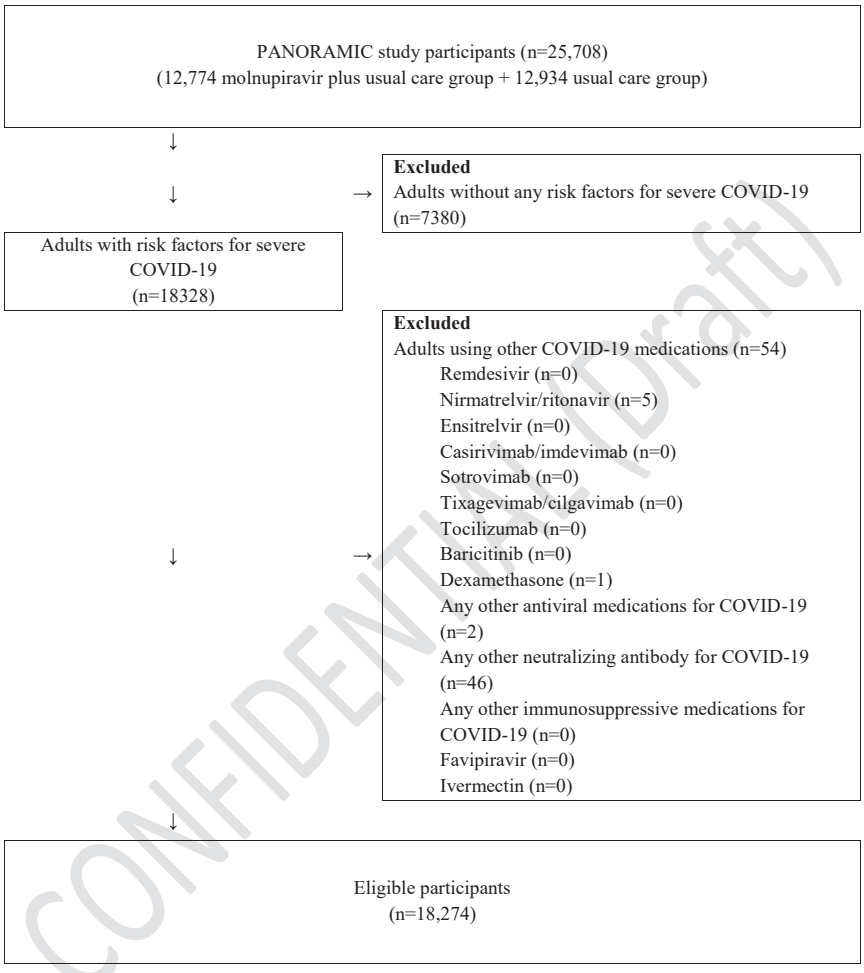
4 RESULTS

4.1 RECRUITMENT

Randomisation to the Molnupiravir arm was stopped on 27th April 2022. Participants randomised to the Molnupiravir arm and Usual Care between 8th December 2021 and 27th April 2022 (inclusive) are included in this report (see SAP for more details). During this time 111,383 participants were screened, 44,073 of whom were not eligible on screening and a further 41,517 were excluded after GP eligibility check (see CONSORT in appendix for reasons). 25,793 in total were randomised, of which 25,783 were randomised between Molnupiravir and Usual Care and were eligible for randomisation to Molnupiravir. 504 participants were randomised to other arms or randomised to Usual Care and not eligible for Molnupiravir. 75 participants were excluded from the analysis population as they were found to be ineligible after randomisation, leaving 25,708 participants in the analysis population.

Figure 2 shows the flow of participants for the subgroup analysis as presented in this report. 7380 participants were excluded as they did not have any risk factors for severe COVID-19 and a further 54 were excluded due to taking other medications. This leaves 18,274 in the subgroup analysis population.

FIGURE 1 FLOW DIAGRAM OF TRIAL PARTICIPANTS FOR THE SUBGROUP POPULATION



4.2 BASELINE CHARACTERISTICS OF PARTICIPANTS

Baseline characteristics by randomised group and overall are given in Table 5 for the concurrent and eligible population.

TABLE 5 BASELINE CHARACTERISTIC BY RANDOMISED GROUP

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
Age, mean(SD) [min,max]	56.7 (12.5) [18.0 to 99.0]	56.5 (12.7) [18.0 to 98.0]	56.6 (12.6) [18.0 to 99.0]
Sex, n(%)			
Female	7451 (58.1%)	7650 (59.0%)	15101 (58.6%)
Male	5367 (41.9%)	5308 (41.0%)	10675 (41.4%)
Other	3 (0.0%)	4 (0.0%)	7 (0.0%)
Days from randomisation to reporting receipt of medication*, median(IQR)	2.0 (2.0 to 2.0)	N/A	2.0 (2.0 to 2.0)
Days from start of symptoms to taking medication*, median(IQR)	5.0 (4.0 to 6.0)	N/A	5.0 (4.0 to 6.0)
Missing, n(%)	288 (1.1%)		
Ethnicity category, n(%)			
White	12088 (94.3%)	12182 (94.0%)	24270 (94.1%)
Asian	366 (2.9%)	434 (3.3%)	800 (3.1%)
Mixed Race	203 (1.6%)	189 (1.5%)	392 (1.5%)
Black	78 (0.6%)	77 (0.6%)	155 (0.6%)
Other	86 (0.7%)	80 (0.6%)	166 (0.6%)
NHS priority category, n(%)			
Aged ≥80	259 (2.0%)	272 (2.1%)	531 (2.1%)
Aged ≥75 and <80	539 (4.2%)	577 (4.5%)	1116 (4.3%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1117 (8.7%)	1114 (8.6%)	2231 (8.7%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1496 (11.7%)	1464 (11.3%)	2960 (11.5%)
Aged ≥18 and <65 in an at risk group	6541 (51.0%)	6591 (50.8%)	13132 (50.9%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at risk group	746 (5.8%)	768 (5.9%)	1514 (5.9%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at risk group	997 (7.8%)	1063 (8.2%)	2060 (8.0%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at risk group	1126 (8.8%)	1113 (8.6%)	2239 (8.7%)
Predicted risk quintile, n(%)			
1 (lowest risk)	2491 (19.4%)	2558 (19.7%)	5049 (19.6%)
2	2679 (20.9%)	2636 (20.3%)	5315 (20.6%)
3	2524 (19.7%)	2660 (20.5%)	5184 (20.1%)
4	2784 (21.7%)	2767 (21.3%)	5551 (21.5%)

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
5 (highest risk)	2343 (18.3%)	2341 (18.1%)	4684 (18.2%)
Confirmed PCR positive, n(%)	5965 (46.5%)	5902 (45.5%)	11867 (46.0%)
IMD quintile, n(%)			
(Most deprived) 1	1234 (9.6%)	1182 (9.1%)	2416 (9.4%)
2	1913 (14.9%)	1956 (15.1%)	3869 (15.0%)
3	2569 (20.0%)	2592 (20.0%)	5161 (20.0%)
4	3216 (25.1%)	3213 (24.8%)	6429 (24.9%)
(Least deprived) 5	3839 (29.9%)	3960 (30.6%)	7799 (30.2%)
Missing, n(%)	50 (0.4%)	59 (0.5%)	109 (0.4%)
Took at least 4 doses IMP, n(%)	11892 (92.8%)	N/A	11892 (46.1%)
Received vaccination, n(%)	12678 (98.9%)	12830 (99.0%)	25508 (98.9%)
Number of COVID-19 vaccine doses, n(%)			
1	87 (0.7%)	88 (0.7%)	175 (0.7%)
2	519 (4.0%)	458 (3.5%)	977 (3.8%)
3	11836 (92.3%)	12044 (92.9%)	23880 (92.6%)
4	236 (1.8%)	240 (1.9%)	476 (1.8%)
Data unavailable, n(%)	143 (1.1%)	132 (1.0%)	275 (1.1%)
Smoker, n(%)	795 (6.2%)	805 (6.2%)	1600 (6.2%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	6111 (47.7%)	6125 (47.3%)	12236 (47.5%)
Minor problem	4514 (35.2%)	4684 (36.1%)	9198 (35.7%)
Moderate problem	1936 (15.1%)	1896 (14.6%)	3832 (14.9%)
Major problem	260 (2.0%)	257 (2.0%)	517 (2.0%)
Fatigue, n(%)			
No problem	1251 (9.8%)	1216 (9.4%)	2467 (9.6%)
Minor problem	4721 (36.8%)	4853 (37.4%)	9574 (37.1%)
Moderate problem	5083 (39.6%)	5127 (39.6%)	10210 (39.6%)
Major problem	1766 (13.8%)	1766 (13.6%)	3532 (13.7%)
Muscle ache, n(%)			
No problem	3479 (27.1%)	3425 (26.4%)	6904 (26.8%)
Minor problem	4504 (35.1%)	4791 (37.0%)	9295 (36.1%)
Moderate problem	3763 (29.4%)	3684 (28.4%)	7447 (28.9%)
Major problem	1075 (8.4%)	1062 (8.2%)	2137 (8.3%)
Vomiting, n(%)			
No problem	10440 (81.4%)	10503 (81.0%)	20943 (81.2%)
Minor problem	1847 (14.4%)	1913 (14.8%)	3760 (14.6%)
Moderate problem	478 (3.7%)	477 (3.7%)	955 (3.7%)
Major problem	56 (0.4%)	69 (0.5%)	125 (0.5%)
Diarrhoea, n(%)			
No problem	10600 (82.7%)	10732 (82.8%)	21332 (82.7%)
Minor problem	1649 (12.9%)	1681 (13.0%)	3330 (12.9%)

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
Moderate problem	471 (3.7%)	457 (3.5%)	928 (3.6%)
Major problem	101 (0.8%)	92 (0.7%)	193 (0.7%)
Loss of smell or taste, n(%)			
No problem	9066 (70.7%)	9402 (72.5%)	18468 (71.6%)
Minor problem	2484 (19.4%)	2368 (18.3%)	4852 (18.8%)
Moderate problem	825 (6.4%)	800 (6.2%)	1625 (6.3%)
Major problem	446 (3.5%)	392 (3.0%)	838 (3.3%)
Headache, n(%)			
No problem	2702 (21.1%)	2820 (21.8%)	5522 (21.4%)
Minor problem	5194 (40.5%)	5215 (40.2%)	10409 (40.4%)
Moderate problem	3783 (29.5%)	3838 (29.6%)	7621 (29.6%)
Major problem	1142 (8.9%)	1089 (8.4%)	2231 (8.7%)
Dizziness, n(%)			
No problem	8446 (65.9%)	8382 (64.7%)	16828 (65.3%)
Minor problem	3087 (24.1%)	3295 (25.4%)	6382 (24.8%)
Moderate problem	1096 (8.5%)	1087 (8.4%)	2183 (8.5%)
Major problem	192 (1.5%)	198 (1.5%)	390 (1.5%)
Abdominal pain, n(%)			
No problem	10391 (81.0%)	10440 (80.5%)	20831 (80.8%)
Minor problem	1834 (14.3%)	1920 (14.8%)	3754 (14.6%)
Moderate problem	524 (4.1%)	542 (4.2%)	1066 (4.1%)
Major problem	72 (0.6%)	60 (0.5%)	132 (0.5%)
Generally unwell, n(%)			
No problem	525 (4.1%)	535 (4.1%)	1060 (4.1%)
Minor problem	5028 (39.2%)	5145 (39.7%)	10173 (39.5%)
Moderate problem	5789 (45.2%)	5838 (45.0%)	11627 (45.1%)
Major problem	1479 (11.5%)	1444 (11.1%)	2923 (11.3%)
Fever, n(%)			
No problem	5670 (44.2%)	5765 (44.5%)	11435 (44.4%)
Minor problem	4813 (37.5%)	4955 (38.2%)	9768 (37.9%)
Moderate problem	2107 (16.4%)	2042 (15.8%)	4149 (16.1%)
Major problem	231 (1.8%)	200 (1.5%)	431 (1.7%)
Cough, n(%)			
No problem	1410 (11.0%)	1343 (10.4%)	2753 (10.7%)
Minor problem	6153 (48.0%)	6384 (49.3%)	12537 (48.6%)
Moderate problem	4502 (35.1%)	4509 (34.8%)	9011 (34.9%)
Major problem	756 (5.9%)	726 (5.6%)	1482 (5.7%)
Wellness score, mean(SD) [min,max]	5.1 (1.7) [0.0 to 10.0]	5.2 (1.7) [0.0 to 10.0]	5.1 (1.7) [0.0 to 10.0]
People in household, n(%)			
0	1660 (12.9%)	1660 (12.8%)	3320 (12.9%)
1	6113 (47.7%)	6019 (46.4%)	12132 (47.1%)

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
2	2129 (16.6%)	2176 (16.8%)	4305 (16.7%)
3	1765 (13.8%)	1979 (15.3%)	3744 (14.5%)
4	808 (6.3%)	772 (6.0%)	1580 (6.1%)
Taking inhaled corticosteroids, n(%)	2990 (23.3%)	3152 (24.3%)	6142 (23.8%)
Taking inhaled corticosteroids for COVID, n(%)	183 (1.4%)	158 (1.2%)	341 (1.3%)
Monoclonal antibodies for COVID, n(%)	26 (0.2%)	19 (0.1%)	45 (0.2%)
Comorbidities			
Lung disease	3014 (23.5%)	3171 (24.5%)	6185 (24.0%)
Heart disease	1000 (7.8%)	957 (7.4%)	1957 (7.6%)
Kidney disease	227 (1.8%)	253 (2.0%)	480 (1.9%)
Liver disease	159 (1.2%)	144 (1.1%)	303 (1.2%)
Neurological disease	430 (3.4%)	438 (3.4%)	868 (3.4%)
Learning disability	36 (0.3%)	27 (0.2%)	63 (0.2%)
Down's syndrome'	24 (0.2%)	30 (0.2%)	54 (0.2%)
Diabetes	1483 (11.6%)	1512 (11.7%)	2995 (11.6%)
Weakened immune system	1125 (8.8%)	1070 (8.3%)	2195 (8.5%)
Transplant recipient	57 (0.4%)	71 (0.5%)	128 (0.5%)
Obesity	1968 (15.3%)	1944 (15.0%)	3912 (15.2%)
Mental illness	198 (1.5%)	220 (1.7%)	418 (1.6%)
Hypertension	2880 (22.5%)	2902 (22.4%)	5782 (22.4%)
Other vulnerability	2295 (17.9%)	2341 (18.1%)	4636 (18.0%)

*Median and interquartile range presented for non-normally distributed variables.

TABLE 6 BASELINE CHARACTERISTIC OF THE SUBGROUP POPULATION BY RANDOMISED GROUP

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
Age, mean(SD) [min,max]	56.9 (14.4) [18.0 to 99.0]	56.7 (14.7) [18.0 to 98.0]	56.8 (14.5) [18.0 to 99.0]
Sex, n(%)			
Female	5267 (57.8%)	5319 (58.1%)	10586 (57.9%)
Male	3851 (42.2%)	3832 (41.9%)	7683 (42.0%)
Other	2 (0.0%)	3 (0.0%)	5 (0.0%)
Days from randomisation to reporting receipt of medication*, median(IQR)	2.0 (2.0 to 2.0) [0.0 to 7.0]	N/A	2.0 (2.0 to 2.0) [0.0 to 7.0]
Days from start of symptoms to taking medication*, median(IQR)	4.0 (3.0 to 5.0) [1.0 to 29.0]	N/A	4.0 (3.0 to 5.0) [1.0 to 29.0]
Data unavailable, n(%)	7163 (78.5%)	0 (0.0%)	7163 (39.2%)
Ethnicity category, n(%)			
White	8589 (94.2%)	8596 (93.9%)	17185 (94.0%)
Asian	257 (2.8%)	318 (3.5%)	575 (3.1%)
Mixed Race	150 (1.6%)	138 (1.5%)	288 (1.6%)
Black	54 (0.6%)	52 (0.6%)	106 (0.6%)
Other	70 (0.8%)	50 (0.5%)	120 (0.7%)
NHS priority category, n(%)			
Aged ≥80	256 (2.8%)	271 (3.0%)	527 (2.9%)
Aged ≥75 and <80	537 (5.9%)	573 (6.3%)	1110 (6.1%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1115 (12.2%)	1108 (12.1%)	2223 (12.2%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1488 (16.3%)	1463 (16.0%)	2951 (16.1%)
Aged ≥18 and <65 in an at risk group	5577 (61.2%)	5582 (61.0%)	11159 (61.1%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at risk group	37 (0.4%)	35 (0.4%)	72 (0.4%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at risk group	43 (0.5%)	56 (0.6%)	99 (0.5%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at risk group	67 (0.7%)	66 (0.7%)	133 (0.7%)
Predicted risk quintile, n(%)			
1 (lowest risk)	623 (6.8%)	633 (6.9%)	1256 (6.9%)
2	1810 (19.8%)	1780 (19.4%)	3590 (19.6%)
3	2108 (23.1%)	2157 (23.6%)	4265 (23.3%)
4	2442 (26.8%)	2439 (26.6%)	4881 (26.7%)
5 (highest risk)	2137 (23.4%)	2145 (23.4%)	4282 (23.4%)
Confirmed PCR positive, n(%)	4267 (46.8%)	4161 (45.5%)	8428 (46.1%)
IMD quintile, n(%)			
(Most deprived) 1	985 (10.8%)	930 (10.2%)	1915 (10.5%)
2	1427 (15.6%)	1466 (16.0%)	2893 (15.8%)
3	1838 (20.2%)	1833 (20.0%)	3671 (20.1%)

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
4	2248 (24.6%)	2238 (24.4%)	4486 (24.5%)
(Least deprived) 5	2590 (28.4%)	2640 (28.8%)	5230 (28.6%)
Data unavailable, n(%)	32 (0.4%)	47 (0.5%)	79 (0.4%)
Took at least 4 doses IMP, n(%)	8412 (92.2%)		8412 (46.0%)
Received vaccination, n(%)	9015 (98.8%)	9064 (99.0%)	18079 (98.9%)
Number of COVID-19 vaccine doses, n(%)			
1	67 (0.7%)	72 (0.8%)	139 (0.8%)
2	369 (4.0%)	329 (3.6%)	698 (3.8%)
3	8361 (91.7%)	8440 (92.2%)	16801 (91.9%)
4	218 (2.4%)	223 (2.4%)	441 (2.4%)
Data unavailable, n(%)	105 (1.2%)	90 (1.0%)	195 (1.1%)
Smoker, n(%)	787 (8.6%)	799 (8.7%)	1586 (8.7%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	4011 (44.0%)	3948 (43.1%)	7959 (43.6%)
Minor problem	3289 (36.1%)	3393 (37.1%)	6682 (36.6%)
Moderate problem	1585 (17.4%)	1577 (17.2%)	3162 (17.3%)
Major problem	235 (2.6%)	236 (2.6%)	471 (2.6%)
Fatigue, n(%)			
No problem	853 (9.4%)	836 (9.1%)	1689 (9.2%)
Minor problem	3251 (35.6%)	3254 (35.5%)	6505 (35.6%)
Moderate problem	3672 (40.3%)	3694 (40.4%)	7366 (40.3%)
Major problem	1344 (14.7%)	1370 (15.0%)	2714 (14.9%)
Muscle ache, n(%)			
No problem	2501 (27.4%)	2384 (26.0%)	4885 (26.7%)
Minor problem	3051 (33.5%)	3295 (36.0%)	6346 (34.7%)
Moderate problem	2724 (29.9%)	2649 (28.9%)	5373 (29.4%)
Major problem	844 (9.3%)	826 (9.0%)	1670 (9.1%)
Vomiting, n(%)			
No problem	7361 (80.7%)	7340 (80.2%)	14701 (80.4%)
Minor problem	1339 (14.7%)	1381 (15.1%)	2720 (14.9%)
Moderate problem	380 (4.2%)	371 (4.1%)	751 (4.1%)
Major problem	40 (0.4%)	62 (0.7%)	102 (0.6%)
Diarrhoea, n(%)			
No problem	7414 (81.3%)	7476 (81.7%)	14890 (81.5%)
Minor problem	1237 (13.6%)	1249 (13.6%)	2486 (13.6%)
Moderate problem	380 (4.2%)	358 (3.9%)	738 (4.0%)
Major problem	89 (1.0%)	71 (0.8%)	160 (0.9%)
Loss of smell or taste, n(%)			
No problem	6379 (69.9%)	6567 (71.7%)	12946 (70.8%)
Minor problem	1791 (19.6%)	1686 (18.4%)	3477 (19.0%)
Moderate problem	614 (6.7%)	600 (6.6%)	1214 (6.6%)

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
Major problem	336 (3.7%)	301 (3.3%)	637 (3.5%)
Headache, n(%)			
No problem	1912 (21.0%)	2015 (22.0%)	3927 (21.5%)
Minor problem	3630 (39.8%)	3570 (39.0%)	7200 (39.4%)
Moderate problem	2718 (29.8%)	2734 (29.9%)	5452 (29.8%)
Major problem	860 (9.4%)	835 (9.1%)	1695 (9.3%)
Dizziness, n(%)			
No problem	5820 (63.8%)	5748 (62.8%)	11568 (63.3%)
Minor problem	2286 (25.1%)	2373 (25.9%)	4659 (25.5%)
Moderate problem	855 (9.4%)	864 (9.4%)	1719 (9.4%)
Major problem	159 (1.7%)	169 (1.8%)	328 (1.8%)
Abdominal pain, n(%)			
No problem	7311 (80.2%)	7280 (79.5%)	14591 (79.8%)
Minor problem	1329 (14.6%)	1410 (15.4%)	2739 (15.0%)
Moderate problem	417 (4.6%)	417 (4.6%)	834 (4.6%)
Major problem	63 (0.7%)	47 (0.5%)	110 (0.6%)
Generally unwell, n(%)			
No problem	383 (4.2%)	381 (4.2%)	764 (4.2%)
Minor problem	3449 (37.8%)	3521 (38.5%)	6970 (38.1%)
Moderate problem	4160 (45.6%)	4138 (45.2%)	8298 (45.4%)
Major problem	1128 (12.4%)	1114 (12.2%)	2242 (12.3%)
Fever, n(%)			
No problem	3990 (43.8%)	4052 (44.3%)	8042 (44.0%)
Minor problem	3428 (37.6%)	3481 (38.0%)	6909 (37.8%)
Moderate problem	1541 (16.9%)	1464 (16.0%)	3005 (16.4%)
Major problem	161 (1.8%)	157 (1.7%)	318 (1.7%)
Cough, n(%)			
No problem	1004 (11.0%)	937 (10.2%)	1941 (10.6%)
Minor problem	4242 (46.5%)	4352 (47.5%)	8594 (47.0%)
Moderate problem	3277 (35.9%)	3291 (36.0%)	6568 (35.9%)
Major problem	597 (6.5%)	574 (6.3%)	1171 (6.4%)
Wellness score, mean(SD) [min,max]	5.1 (1.7) [0.0 to 10.0]	5.1 (1.7) [0.0 to 10.0]	5.1 (1.7) [0.0 to 10.0]
People in household, n(%)			
0	1245 (13.7%)	1236 (13.5%)	2481 (13.6%)
1	4489 (49.2%)	4368 (47.7%)	8857 (48.5%)
2	1376 (15.1%)	1409 (15.4%)	2785 (15.2%)
3	1156 (12.7%)	1309 (14.3%)	2465 (13.5%)
4	580 (6.4%)	547 (6.0%)	1127 (6.2%)
5	274 (3.0%)	285 (3.1%)	559 (3.1%)
Taking inhaled corticosteroids, n(%)	2848 (31.2%)	3010 (32.9%)	5858 (32.1%)

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
Taking inhaled corticosteroids for COVID, n(%)	159 (1.7%)	143 (1.6%)	302 (1.7%)
Monoclonal antibodies for COVID, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Comorbidities			
Lung disease	2989 (32.8%)	3161 (34.5%)	6150 (33.7%)
Heart disease	993 (10.9%)	952 (10.4%)	1945 (10.6%)
Kidney disease	222 (2.4%)	253 (2.8%)	475 (2.6%)
Liver disease	158 (1.7%)	143 (1.6%)	301 (1.6%)
Neurological disease	423 (4.6%)	432 (4.7%)	855 (4.7%)
Learning disability	33 (0.4%)	27 (0.3%)	60 (0.3%)
Down's syndrome'	24 (0.3%)	29 (0.3%)	53 (0.3%)
Diabetes	1473 (16.2%)	1507 (16.5%)	2980 (16.3%)
Weakened immune system	1110 (12.2%)	1055 (11.5%)	2165 (11.8%)
Transplant recipient	50 (0.5%)	60 (0.7%)	110 (0.6%)
Obesity	1957 (21.5%)	1932 (21.1%)	3889 (21.3%)
Mental illness	196 (2.1%)	220 (2.4%)	416 (2.3%)
Hypertension	2285 (25.1%)	2303 (25.2%)	4588 (25.1%)
Other vulnerability	1886 (20.7%)	1883 (20.6%)	3769 (20.6%)

*Median and interquartile range presented for non-normally distributed variables.

TABLE 7 PREVALENCE OF RISK FACTORS FOR SEVERE COVID-19 (MODIFIED DEFINITION) AMONG ELIGIBLE PARTICIPANTS

	Molnupiravir plus usual care (n=9120)	Usual care (n=9154)
Risk factors		
Older adults aged ≥ 65 years	3396 (37.2%)	3415 (37.3%)
Asthma	233 (2.6%)	290 (3.2%)
Cancer (Hematologic malignancies)	1 (0.0%)	1 (0.0%)
Stroke	16 (0.2%)	24 (0.3%)
Aneurysm	1 (0.0%)	0 (0.0%)
Kidney disease	222 (2.4%)	253 (2.8%)
Lung disease	2989 (32.8%)	3161 (34.5%)
Liver disease	158 (1.7%)	143 (1.6%)
Diabetes	1473 (16.2%)	1507 (16.5%)
Down syndrome	24 (0.3%)	29 (0.3%)
Heart disease	993 (10.9%)	952 (10.4%)
Immune disease	1110 (12.2%)	1055 (11.5%)
Mental illness	196 (2.1%)	220 (2.4%)
Neurologic conditions	423 (4.6%)	432 (4.7%)
Obesity (BMI ≥ 35 kg/m^2)	1957 (21.5%)	1932 (21.1%)
Current smoker	787 (8.6%)	799 (8.7%)
Transplant	50 (0.5%)	60 (0.7%)
Use of corticosteroids or other immunosuppressive medications	28 (0.3%)	37 (0.4%)

4.3 Number analysed

Of the 18274 participants included in the subgroup analysis 17754 (97.2%) had data collected on hospitalisation/death and so could be included in the primary analysis. 17334 (94.9%) completed any diaries or calls and so could be included in the secondary analysis.

4.4 Primary Analyses

4.4.1 Primary outcome

The primary outcome is defined as all cause unplanned hospitalisation or death from randomisation to 28 days follow-up. Data is derived from participant daily diaries, phone calls, and routine electronic data. If a primary endpoint is reported from any data source then this outcome is counted as "yes". If the participant has completed 28 days follow-up and is not hospitalised or is lost to follow-up but has been checked against routine electronic data and no hospitalisation or death is found then this outcome is coded "no". An odds ratio<1 suggests fewer hospitalisations/deaths in the Molnupiravir arm. The results show probability of superiority below 0.5, indicating no benefit of Molnupiravir compared to Usual Care.

TABLE 8 PRIMARY OUTCOME

	Molnupiravir plus usual care (N=9120)	Usual care (N=9154)	Estimated treatment effect (95% BCI)	Probability of superiority
Hospitalization or death	92/8932 (1.0%)	87/8822 (1.0%)	1.053 (0.775 to 1.396)	0.3919
Deaths	3/8932	5/8822	Not estimable	
Hospitalizations	90/8932 (1.0%)	85/8822 (1.0%)	1.055 (0.773 to 1.413)	0.3963

*OR < 1 favours molnupiravir

4.4.2 SECONDARY OUTCOMES

Definition of outcomes:

1. Time to recovery: time to first reporting of feeling recovered in diary or call. A hazard ratio>1 suggests faster recovery in the Molnupiravir arm.
2. Time to sustained recovery: time to reporting recovery in diary or call followed by no subsequent relapse. A hazard ratio>1 favours Monupiravir.
3. Early sustained recovery: reported recovered within the first 14 days with no subsequent relapse. An odds ratio >1 favours Molnupiravir.
4. Alleviation of symptoms: Time to first rating of symptoms as mild/none. If all symptoms are rated mild/none at baseline then the participant is censored at day 0. A hazard ratio>1 favours Molnupiravir.
5. Sustained alleviation of symptoms: Time to rating of symptoms as mild/none followed by no subsequent relapse. If all symptoms are rated mild/none at baseline then the participant is censored at day 0. A hazard ratio>1 favours Molnupiravir.
6. Reduction of symptoms: Time to reduction of all symptoms by at least one grade. A hazard ratio>1 favours Molnupiravir.
7. Rating of how well participant feels (1 worst, 10 best): Participant rating of wellness at each day. Estimates represent the mean differences and a values >0 favours Molnupiravir.
8. Household infections: Participant reported another member of their household becoming unwell with COVID-19. Participants who live alone at baseline are excluded. An odds ratio <1 favours Molnupiravir (fewer household infections). For number of infections a rate ratio <1 favours Molnupiravir.

The following assumptions have been made in the following analysis:

1. For time to event outcomes participants are censored at the last point of contact or 28 days, whichever is sooner. For time to sustained recovery if a participant reported feeling recovered and is subsequently lost to follow-up it is assumed they remained recovered (last

observation carried forward). A similar principle is used for time to sustained alleviation of symptoms. Therefore the only missing data for time to event outcomes is participants who completed no diary data

2. For early sustained recovery if a participant is lost to follow-up, such that it is not possible to establish if they remained recovered, then this outcome is treated as missing.
3. For time to alleviation and time to reduction of symptoms if a symptom is missing but the participant reported feeling recovered, that symptom is assumed to be rated "none".
4. For household infections if a participant has incomplete diaries but has not stated that they have an infection within the household this outcome is assumed to be zero. Participants who live alone at baseline are excluded from the analysis.
5. Analysis of daily symptom scores uses a frequentist mixed model, due to the computational difficultly running the Bayesian model with the number of parameters.

Results in Table 9 have showed estimated median (95% BCI) time to first reported recovery from the Bayesian model were 10.381 (10.137 to 10.640) days and 14.853 (14.383 to 15.345) days, respectively, which suggested that Molnupiravir has a 4.5 days benefit in TTR compared with Usual Care.

There was a significant benefit in early sustained recovery by 9.7%, i.e. recovered within the first 14 days and remained well until day 28 from randomisation, in Molnupiravir group (31.4%) compared to Usual Care (21.7%) (OR = 1.7; 95% BCI (1.56 to 1.81)).

TABLE 9 SECONDARY OUTCOMES

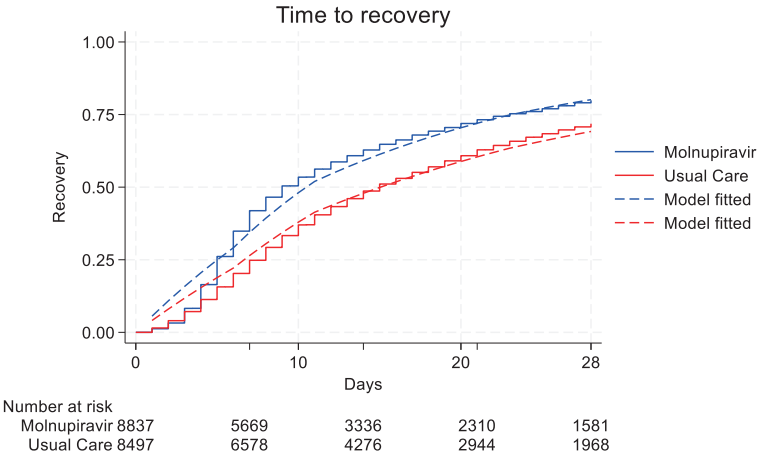
	Molnupiravir plus usual care	Usual care	Estimated treatment effect (95% BCI)	Estimated benefit (95% BCI)	Probability of superiority
First reported recovery	6860/8837 (77.6%)	5722/8497 (67.3%)			
Days to first reported recovery	10.381 (10.137 to 10.640)	14.853 (14.383 to 15.345)	1.374 (1.326 to 1.423) *	-4.472 (-5.001 to -3.953) †	>0.99
Early sustained recovery	2530/8062 (31.4%)	1625/7495 (21.7%)	1.679 (1.558 to 1.807) **		>0.99
Sustained recovery	5995/8837 (67.8%)	4950/8497 (58.3%)			
Days to sustained recovery	20.215 (19.771 to 20.686)	23.746 (23.430 to 24.066)	1.262 (1.213 to 1.310) *	-3.533 (-4.055 to -2.978) †	>0.99
Alleviation of all symptoms	6447/6997 (92.1%)	5839/6720 (86.9%)			
Days to alleviations of all symptoms	3.794 (3.691 to 3.896)	4.625 (4.493 to 4.770)	1.220 (1.177 to 1.263) *	-0.833 (-0.993 to -0.676) †	>0.99
Sustained alleviation of all symptoms	5799/6997 (82.9%)	5187/6720 (77.2%)			
Days to sustained alleviation of all symptoms	9.912 (9.533 to 10.304)	11.956 (11.489 to 12.442)	1.158 (1.117 to 1.202) *	-2.040 (-2.592 to -1.505) †	>0.99
Initial reduction of symptom severity	7634/8820 (86.6%)	6732/8487 (79.3%)			
Days to initial reduction of symptom severity	7.500 (7.333 to 7.673)	9.435 (9.202 to 9.672)	1.292 (1.248 to 1.336) *	-1.934 (-2.204 to -1.666) †	>0.99
Participant rating of wellness					
Day 7	7.3 (1.8) [8396]	6.7 (1.8) [7800]	0.5 (0.5 to 0.6) ¶		P<0.001 ‖
Day 14	7.8 (1.7) [8142]	7.5 (1.8) [7422]	0.3 (0.2 to 0.3) ¶		P<0.001 ‖
Day 21	8.1 (1.7) [7535]	7.9 (1.7) [6602]	0.2 (0.1 to 0.2) ¶		P<0.001 ‖
Day 28	8.3 (1.6) [7515]	8.2 (1.6) [6731]	0.2 (0.1 to 0.2) ¶		P<0.001 ‖
New infections in household	2852/7630 (37.4%)	2803/7307 (38.4%)	0.960 (0.898 to 1.025) **		0.8879
Contact with health and social care services					
NHS 111	487/8835 (5.5%)	614/8492 (7.2%)	0.746 (0.660 to 0.843) **		>0.99
General practitioner	2009/8835 (22.7%)	2332/8493 (27.5%)	0.774 (0.721 to 0.830) **		>0.99
Ambulance service (not hospitalised)	256/8831 (2.9%)	233/8479 (2.7%)	1.060 (0.881 to 1.267) **		0.2847

Community nurse	226/8835 (2.6%)	243/8489 (2.9%)	0.894 (0.736 to 1.073) **	0.8927
Physiotherapist	115/8835 (1.3%)	66/8489 (0.8%)	1.696 (1.239 to 2.277) **	0.0006
Counsellor	72/8835 (0.8%)	89/8489 (1.0%)	0.784 (0.565 to 1.063) **	0.9464
Social worker	21/8835 (0.2%)	27/8489 (0.3%)	0.774 (0.420 to 1.296) **	0.8498
Home carer	82/8834 (0.9%)	77/8487 (0.9%)	1.027 (0.747 to 1.397) **	0.4688
Occupational therapist	191/8834 (2.2%)	169/8489 (2.0%)	1.095 (0.884 to 1.338) **	0.2049
Hospital emergency department	512/8835 (5.8%)	489/8490 (5.8%)	1.009 (0.886 to 1.144) **	0.4584
Outpatient respiratory clinic	208/8835 (2.4%)	218/8489 (2.6%)	0.914 (0.751 to 1.101) **	0.8319
Hospital at home for COVID-19	298/8835 (3.4%)	356/8489 (4.2%)	0.798 (0.679 to 0.930) **	0.9980
Other services	485/8835 (5.5%)	539/8488 (6.4%)	0.856 (0.751 to 0.970) **	0.9926

*Estimated HR derived from a piecewise exponential model adjusted for age, comorbidity and vaccination status. HR > 1 favours Molnupiravir.
†Model based estimated benefit median time to event <0 favours Molnupiravir.
‖ Frequentist model estimates display p-value rather than a probability
¶Linear mixed effect model adjusted for age, comorbidity and vaccination status. Participant fitted as a random effect. Estimated mean difference > 0 favours Molnupiravir.
**Bayesian logistic regression, adjusted for, age, comorbidity and vaccination status

The following plot shows the actual data for time to recovery (solid lines) and the model based estimates (dashed lines). The model based estimates are derived from the piecewise exponential where all the standardised covariates are set to zero (corresponding to the sample average).

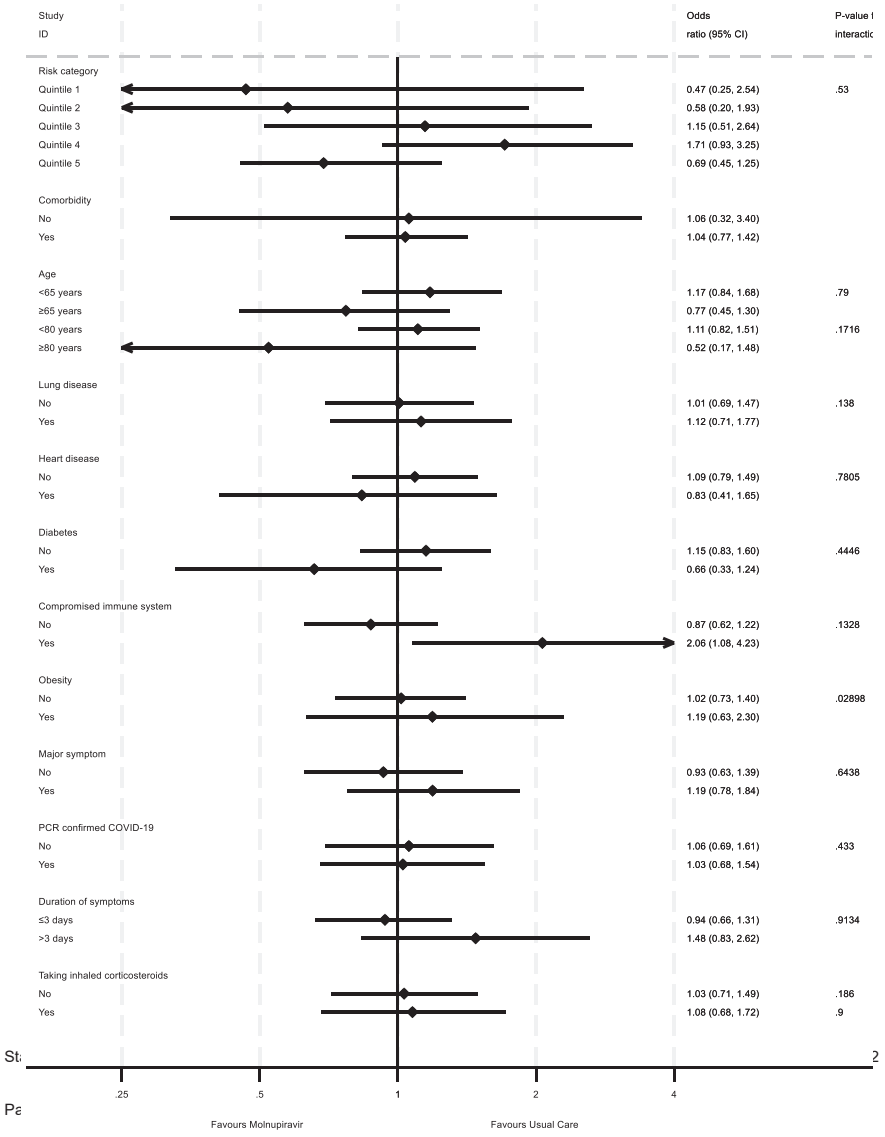
FIGURE 2 KAPLAN-MEIER CURVE AND MODEL ESTIMATES FOR TIME TO RECOVERY



4.5 SUBGROUP ANALYSES

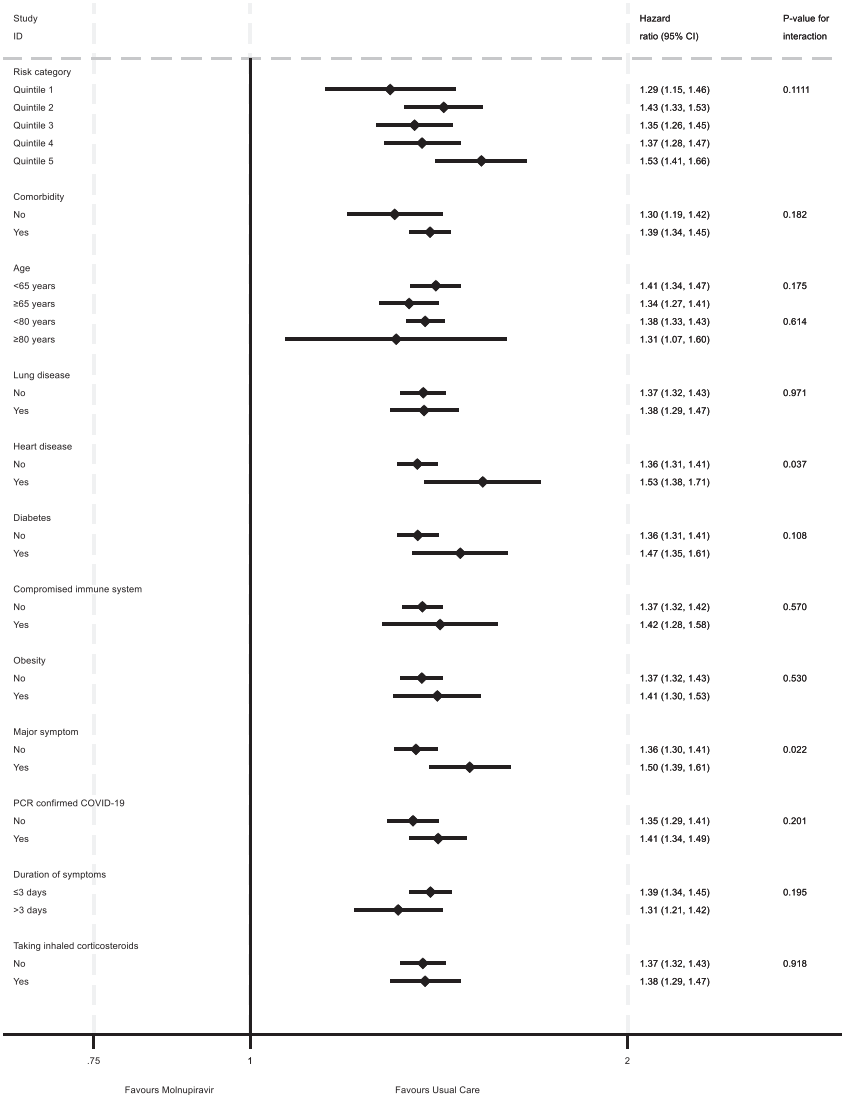
Frequentist model estimates are presented for the moderation analysis of the primary outcome. An odds ratio<1 favours Molnupiravir. P-values indicate the test for the interaction and statistically significant p-value suggests a differential effect size between subgroups.

FIGURE 3 FOREST PLOT OF SUBGROUP ANALYSIS OF PRIMARY OUTCOME



Frequentist model estimates are presented for the moderation analysis of time to recovery. A hazard ratio>1 favours Molnupiravir. P-values indicate the test for the interaction and a statistically significant p-value suggests a differential effect size between subgroups.

FIGURE 4 FOREST PLOT OF SUBGROUP ANALYSIS OF TIME TO RECOVERY



4.6 VIROLOGY SUB-STUDY ANALYSIS

TABLE 10 SUMMARY OF VIROLOGY SUB-STUDY

	Molnupiravir	Usual Care	Total
Number of participants, n			
Intensive samples cohort	22	28	50
Less intensive samples cohort	142	163	305
At least 7 samples received from intensive samples cohort, n/N (%)	22/22 (100.0%)	27/28 (96.4%)	49/50 (98.0%)
At least 2 samples received from less intensive sample cohort, n/N (%)	142/142 (100.0%)	163/163 (100.0%)	305/305 (100.0%)
Female, n/N (%)			
Intensive samples cohort	12/22 (54.5%)	14/28 (50.0%)	26/50 (52.0%)
Less intensive samples cohort	80/142 (56.3%)	102/163 (62.6%)	182/305 (59.7%)
Overall	92/164 (56.1%)	116/191 (60.7%)	208/355 (58.6%)
Age, mean (SD)			
Intensive samples cohort	58.1 (12.0) [27.0 to 79.0]	64.1 (9.6) [34.0 to 74.0]	61.4 (11.0) [27.0 to 79.0]
Less intensive samples cohort	59.2 (11.9) [29.0 to 82.0]	59.5 (13.0) [22.0 to 86.0]	59.4 (12.5) [22.0 to 86.0]
Overall	59.1 (11.9) [27.0 to 82.0]	60.2 (12.7) [22.0 to 86.0]	59.7 (12.3) [22.0 to 86.0]

TABLE 11 VIROLOGY SUBSTUDY

	Molnupiravir plus usual care	Usual care	Estimated treatment effect (95% CI)	P value
Intensive samples				
Undetectable viral load				
Day 2	0/22	0/27		
Day 3	0/22	0/27		
Day 4	1/22 (4.5%)	0/28		
Day 5	3/22 (13.6%)	0/27		
Day 6	4/22 (18.2%)	1/28 (3.6%)	4.605 (0.579 to 36.623) †	0.1489
Day 7*	5/22 (22.7%)	1/28 (3.6%)	5.769 (0.797 to 41.752) †	0.0827
Viral load, mean(SD)				
Day 1	7.268 (1.252)	7.303 (1.309)		
Day 2	6.764 (1.422)	7.083 (1.187)	-0.352 (-0.952 to 0.247) ‡	0.2498
Day 3	6.258 (1.353)	6.474 (1.149)	-0.250 (-0.849 to 0.350) ‡	0.4145
Day 4	5.350 (1.437)	5.919 (1.299)	-0.586 (-1.182 to 0.009) ‡	0.0537
Day 5	4.435 (1.518)	5.786 (1.113)	-1.385 (-1.984 to -0.785) ‡	<0.0001
Day 6	4.020 (1.552)	5.457 (1.380)	-1.454 (-2.049 to -0.858) ‡	<0.0001
Day 7	3.633 (1.392)	5.048 (1.379)	-1.432 (-2.027 to -0.836) ‡	<0.0001
All samples				
Undetectable viral load				
Day 5	14/160 (8.8%)	4/185 (2.2%)	6.038 (1.513 to 24.094) **	0.0109
Day 14	64/138 (46.4%)	75/154 (48.7%)	0.867 (0.436 to 1.721) **	0.6826
Viral load, mean(SD)				
Day 5	4.409 (1.527)	5.607 (1.323)	-1.201 (-1.609 to -0.794) ‡	<0.0001
Day 14	2.828 (1.335)	2.530 (1.113)	0.277 (-0.035 to 0.589) ‡	0.0821

* Primary outcome
† Firth logistic regression adjusting for sex, age, and baseline $\log_{10}$(viral load). Adjusted OR > 1 favours molnupiravir
‡Mixed effect model adjusting for sex, age, and baseline $\log_{10}$(viral load); adjusted difference < 0 favours molnupiravir

** Mixed effects logistic regression adjusting for sex, age, and baseline $\log_{10}$(viral load). Adjusted OR > 1 favours molnupiravir

~~~ END OF REPORT ~~~

STATISTICAL ANALYSIS PART 1 REPORT

Platform **A**daptive trial of **NO**vel antivi**R**als for e**A**rly treat**M**ent of covid-19 **I**n the **C**ommunity

Reference Number / Short title: PANORAMIC

MOLNUPIRAVIR

Ethics Ref: 21/SC/0393

IRAS Project ID: 1004274

EudraCT Number: 2021-005748-31

Based on protocol version 5.0 9th May 2022

Version 1.0 Date: 22nd September 2023

Report prepared and analysis carried out by	Dr Victoria Harris, Department of Primary Care Health Sciences, University of Oxford
Report reviewed by	Dr Milensu Shanyinde, Department of Primary Care Health Sciences, University of Oxford

2 CONTENTS

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1 BACKGROUND

The Center for Outcomes Research and Economic Evaluation for Health (C2H) is currently conducting a cost-effectiveness evaluation of Molnupiravir as a part of the Japanese health technology assessment (HTA) process. The data from the PANORAMIC study[Butler CC, et al. Lancet. 2023:28;401:281-293] could potentially be the source to assess the additional benefit of Molnupiravir in the Japanese setting. However, there are several differences between the study design of the PANORAMIC and the indication for Molnupiravir in Japan. For example, Molnupiravir is approved in Japan for the treatment of COVID-19 in adults with risk factors for severe COVID-19 whereas the PANORAMIC study included adults without these risk factors. Additionally, differences in the definition of standard of care also exist. In Japan, concomitant use of Molnupiravir with other COVID-19 medications (e.g., remdesivir) is not recommended. Given these differences, the purpose of this report is to present the results of sub-group analysis of the PANORAMIC study in line with the indication and clinical practice of Molnupiravir in Japan. The results are presented excluding both **A) participants without risk factors;** and **B) participants using other COVID-19 medications at the prescription of Molnupiravir** .

DISCLAIMER: Publication of the results presented in this report requires approval in writing to the Chief Investigators.

2 INTRODUCTION

This document details the analysis for the subgroup reporting results for the comparison of Molnupiravir with usual care from the PANORAMIC trial. The results reported in these papers follow the strategy set out in the statistical analysis plan. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

This report is based on the statistical analysis plan { **Subgroup analysis of PANORAMIC study in Japan_Plan1.docx**}. Any deviations from the statistical analysis plan will be described and justified in this report of the trial.

Trial/Study statistician(s):

Dr Victoria Harris

Lead Trial Statisticians Professor Ly-Mee Yu and Dr Ben Saville

Co-chief Investigator:

Professor Chris Butler, Professor Paul Little, and Professor Richard Hobbs

Senior Trial Manager: Lucy Cureton

Senior Data Manager: Meena Patil

2.1 SOFTWARE EMPLOYED

Analysis was carried out using STATA v18

3 METHODS

3.1 TRIAL OVERVIEW

Despite high uptake of vaccination against COVID-19, the disease remains prevalent in the UK and in many countries around the world, with many patients continuing to require hospital admission. COVID-19 causes considerable suffering, including loss of ability to perform activities of daily living, loss of educational and work opportunities, and inability to perform caring duties, with far reaching personal and societal consequences. Many go on to experience persisting and/or relapsing symptoms. People with underlying health conditions, unvaccinated people, and those in whom the vaccine is not effective are at increased risk of more severe disease. [11] New 'vaccine escaping' variants may yet emerge, and the impact of early antiviral treatment on long COVID syndromes is as yet unknown. Early treatment with antiviral agents may prevent progression to the later phase of COVID-19. Therefore, there is an urgent need to identify treatments for COVID-19 for use in the community early on in the illness that speeds recovery and prevents the need for hospital admission.

Antiviral agents may reduce viral shedding, and use of antiviral agents may lead to the emergence of resistance to novel antiviral agents, but the impact of novel antiviral agents on shedding and resistance is not yet known.

3.2 STUDY DESIGN

PANORAMIC is an open label, prospective, individually randomised, platform, adaptive, controlled clinical trial in community care. Trial arms will include:

Intervention arms: Novel antiviral agents (or combinations) targeting SARS-CoV-2, initially specified by The UK Antivirals National Taskforce (ATF) and with capacity for sequential introduction of each treatment regimen into the trial plus Usual Care. This report presents the primary and secondary analysis for the Molnupiravir arm.

Comparator arm: Usual Care, defined as the currently recommended treatment delivered by responsible clinicians. Usual Care was not mandated by the trial, as recommended treatments may change and be tailored to individual characteristics, and self-care will vary. Use of over the counter medication as well as key medications such as inhaled steroids and monoclonal antibodies was captured. In this report only usual care participants randomised concurrently and eligible to Molnupiravir were included.

3.3 Adaptive Design

The trial design allows for interim analysis and early stopping due to futility or efficacy and the addition or removal of interventions. The number and timing of interim analyses depends on the rate of recruitment. Full details of the design and decision criteria are given in the Adaptive Design Report. Due to rapid recruitment no interim analyses were carried out on the Molnupiravir arm. Paxlovid was added as an additional arm on 21st April 2022.

3.4 Objectives

Main Trial: The primary aim is to determine the effectiveness of selected antiviral agents in preventing hospitalisation and/or death in higher-risk patients with a confirmed positive PCR or LFT SARS-CoV-2 test result (see Inclusion/Exclusion Criteria, below).

Main Study	Objectives	Endpoint Measures	Timepoint (s)
Primary	To determine whether antiviral treatment in the community safely reduces non-elective hospitalisations/ deaths in higher risk, symptomatic patients with confirmed COVID-19	All cause, non-elective hospitalisation and/or death, within 28 days of randomisation	Within 28 days of randomisation Patient report, Study Partner report, HES/ONS/medical record data linkage
Secondary	To explore whether antiviral treatment affects 1) Time to recovery (defined as the first instance that a participant report of feeling recovered from the illness)	1-3) Participant reports symptoms daily for 28 days and at 3 and 6 months.	1-3) Daily online symptom scores. Telephone call or text on days 7, 14 and 28 if data is not obtained through the online diary.

	2) Participant reported illness severity, reported by daily rating of how well participant feels, enabling identification of sustained recovery.		Also, at 3 and 6 months.
	3) Duration of severe symptoms and symptom recurrence, including time to alleviation of symptoms, time to initial reduction of severity of symptoms, time to sustained recovery, time to sustained alleviation of symptoms, number of days of severe symptoms and worsening of symptoms		
	4) Contacts with the health services	4) Contacts with health services reported by patients and/or captured by reports of patients' medical records	4) GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days. Medical notes

			review for up to 10 years.
	5) New infections in household	5) Reports of new infections in the household from daily diary	5) Daily online symptom scores or telephone call or text on days 7, 14 and 28
	6) To investigate the safety of antiviral agents	6) Evaluation of overall safety of drugs by the monitoring of adverse events (AEs as defined in the ISAs)	6) For the duration of the antiviral course and a defined period after the antiviral finishes (see ISAs)
	7) Longer term effects, including proportion with long covid, long covid symptoms, health care use and wellness	7) Well-being, symptoms and heath care utilisation	7) Patient contact at three and six months, electronic medical record search for up to one year
	8) Cost effectiveness	8) Resource use and cost data and EQ-5D-5L	8) Baseline and Day 28

3.5 TARGET POPULATION

The trial includes participants who test positive for SARS-CoV-2 infection and with ongoing symptoms consistent with COVID-19, not hospitalised, and who are aged 50 years and over, or 18-49 years and considered clinically vulnerable (see Inclusion Criteria below).

3.5.1 Inclusion Criteria

- Participant is able and willing to provide informed consent, or their legal representative is willing to provide informed consent
- Symptoms attributable to COVID-19 started within the past 5 days and ongoing
- A positive PCR or LFT SARS-CoV-2 test* Aged ≥50 years OR aged 18-49 years with one of the following known underlying chronic health condition considered to make them clinically vulnerable:
    - chronic respiratory disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis and asthma requiring at least daily use of preventative and/or reliever medication)
    - chronic heart or vascular disease
    - chronic kidney disease
    - chronic liver disease
    - chronic neurological disease (including dementia, stroke, epilepsy)
    - severe and profound learning disability
    - Down's syndrome
    - Diabetes mellitus (Type I or Type II)
    - immunosuppression: primary (e.g., inherited immune disorders resulting from genetic mutations, usually present at birth and diagnosed in childhood) or secondary due to disease or treatment (e.g., sickle cell, HIV, cancer, chemotherapy)
    - solid organ, bone marrow and stem cell transplant recipients
    - morbid obesity (BMI >35)
    - severe mental illness
    - care home resident
    - judged by recruiting clinician or research nurse (registered medical practitioner or trained study nurse) to be clinically vulnerable

* Any positive PCR test taken between two days before symptom onset and randomisation qualifies. A positive lateral flow test in a symptomatic person qualifies for randomisation and will be subject to pre-specified secondary analysis by type of diagnostic test.

3.5.2 Exclusion criteria

- Patient currently admitted to hospital (inpatient)
- Previous randomisation in the PANORAMIC trial
- Currently participating in a clinical trial of a therapeutic agent for acute COVID-19
- Additional exclusions specific to each intervention arm, if any, as listed in the Intervention Specific Appendices (ISA's) of currently open trial arms

3.5.3 A Risk factors

Risk factors for severe COVID-19 by the Ministry of Health, Labour and Welfare (MHLW) in Japan may not be available in the PANORAMIC study. Therefore, we propose the following 2 options to extract the data according to risk or modified risk factors that could be applicable to the Japanese setting.

1. Risk factors for severe COVID-19 defined by the Ministry of Health, Labour and Welfare (MHLW) is shown in Table 1.

TABLE 1 THE MINISTRY OF HEALTH, LABOUR AND WELFARE DEFINED RISK FACTORS FOR SEVERE COVID-19

Older adults aged ≥ 65 years	Hypertension	History of smoking
Malignant tumor	Dyslipidemia	Immunodeficiency after solid organ transplantation
Chronic respiratory disease (i.e., COPD)	Cardiovascular disease	Use of immunomodulatory agent or immunosuppressant
Chronic renal disease	Cerebrovascular disease	HIV infection (particularly CD4 < 200/μL)
Diabetes	Obesity (BMI ≥ 30 kg/m^2)	

Clinical Management of Patients with COVID-19 in Japan version 9.0 (In Japanese)

(https://www.mhlw.go.jp/content/000936655.pdf)

The diagnostic criteria for each risk factor have not been clearly indicated.

2. The modified definition of risk factors for severe COVID-19 is shown in Table 2. By reviewing the article of the PANORAMIC study, we believe that we could define the modified risk factors as follows:

TABLE 2 THE MODIFIED DEFINITION OF RISK FACTORS FOR SEVERE COVID-19

Older adults aged ≥ 65 years	Hypertension (high blood pressure)	Current smoker
Cancer or chemotherapy	Chronic heart or vascular disease	Solid organ, bone marrow and stem cell transplant recipients
Chronic respiratory disease	Stroke	Immunosuppression
Chronic kidney disease	Obesity (BMI ≥ 30 kg/m^2)[a]	HIV infection
Diabetes		

a: Obesity was originally defined as BMI ≥ 35 kg/m^2 in the PANORAMIC study.

TABLE 3 THE DIAGNOSTIC CRITERIA FOR EACH RISK FACTOR IN THE PANORAMIC STUDY

Risk factor	Diagnostic criteria or definition
Older adults aged ≥ 65 years	Aged ≥ 65 years
Cancer or chemotherapy	Free text field mentions "cancer". Only current cancers included.
Chronic respiratory disease	Self-reported long term lung disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis or asthma requiring at least daily use of inhalers)
Chronic kidney disease	Self-reported long term kidney disease
Diabetes	Self-reported diabetes
Hypertension (high blood pressure)	Self-reported high blood pressure
Chronic heart or vascular disease	Self-reported long term heart or vascular disease
Stroke	Self-reported long term neurological disease (including dementia, stroke, epilepsy) or free text mentions stroke
Obesity (BMI ≥ 30 kg/m^2)	BMI ≥ 35 kg/m^2
Current smoker	Current smoker
Solid organ, bone marrow and stem cell transplant recipients	Self-report have had a transplant (e.g. kidney, liver, heart, lung, bone marrow or stem cells)
Immunosuppression	Self-reported weakened immune system due to a condition you were born with or due to disease or treatment (e.g. sickle cell, HIV, cancer, chemotherapy)
HIV infection	Collected under immunosuppression.

3.5.4 CONCOMITANT USE OF OTHER COVID-19 MEDICATIONS

In Japan, concomitant use of Molnupiravir with other COVID-19 medications (e.g., remdesivir) is not recommended. We would like to exclude adults taking the following medications at the prescription of Molnupiravir (Table 4) from the dataset. On the other hand, we consider that adults using the following medications **after the completion of treatment with Molnupiravir** should not be excluded from the analysis because they are most likely to have progressed to severe COVID-19 (e.g., adults prescribed the following medications 10 days after a prescription for Molnupiravir , adults who stopped treatment with Molnupiravir within 5 days and subsequently received the following medications).

TABLE 4 THE DEFINITION OF OTHER COVID-19 MEDICATIONS

Remdesivir	Tixagevimab/cilgavimab	Any other neutralizing antibody for COVID-19
Nirmatrelvir/ritonavir	Tocilizumab	Any other immunosuppressive medications for COVID-19
Ensitrelvir	Baricitinib	Favipiravir
Casirivimab/imdevimab	Dexamethasone	Ivermectin
Sotrovimab	Any other antiviral medications for COVID-19	

3.6 INTERVENTIONS

Based on version 5.0 of the Protocol, the main randomisation was between the following treatment arms (although not all treatments were available at all times and not all participants were eligible for all treatments). However, the trial design accommodates interventions being added and dropped as appropriate.

- Usual care
- Molnupiravir (recruitment between 8th December 2021 and 27th April 2022)
- PAXLOVID (recruitment started 21st April 2022)

3.7 OUTCOMES

3.7.1 PRIMARY OUTCOME

The primary outcome is all-cause, non-elective hospitalisation and/or death within 28 days of randomisation.

3.7.2 SECONDARY OUTCOMES

Secondary outcomes include time to self-reported recovery defined as the first instance that a participant reports feeling fully recovered from the illness; duration of symptoms; symptom recurrence; daily rating of feeling well reported by participants; healthcare service use; participant reported household infection rate; safety outcomes and cost-effectiveness outcomes; symptoms and well-being at three and six months (with determination of proportion with Long Covid) from randomisation.

3.7.2.1 TIME TO RECOVERY

Time to recovery from COVID-19 infection within 28 days from randomisation, where recovery is defined as the first instance that a participant reports feeling recovered.

3.7.2.2 PATIENT REPORTED ILLNESS SEVERITY

Participants are asked to rate how well they are feeling overall each day on a scale of 1-10 (1 being the worst and 10 being the best). This is captured on the patients' daily diaries and the Call CRF.

3.7.2.3 DURATION OF SEVERE SYMPTOMS AND SYMPTOM RECURRENCE

Participants are asked to rate their symptoms of fever, cough, shortness of breath, fatigue (tiredness), muscle ache, nausea / vomiting, diarrhoea, loss of smell and/or taste, headache, dizziness, abdominal pain and generally feeling unwell on a four point scale from 0=no problem, 1=mild problem, 2=moderate problem and 3=major problem.

This is captured on patients' daily diaries and Call CRF.

The outcomes to be analysed include time to alleviation of symptoms, time to initial reduction in severe symptoms, time to sustained recovery, time to sustained alleviation of symptoms, number of days of severe symptoms, number reporting severe symptoms at days 7, 14 and 28, symptom recurrence and worsening of symptoms.

3.7.2.4 CONTACTS WITH HEALTH SERVICES BETWEEN RANDOMISATION AND DAY 28 OF FOLLOW-UP (FU).

This is captured on patients' daily diaries and telephone call CRFs.

3.7.2.5 NEW INFECTIONS IN THE HOUSEHOLD

Number of new infections within the household are captured within the participant daily diaries and call CRF.

3.7.2.6 SAFETY OF ANTIVIRAL AGENTS

Common side effects, according to the SmPC, include dizziness, headache, diarrhoea, and nausea. These symptoms, potential medication side-effects and Serious Adverse Events (SAE) were collected from participant daily diaries, calls to participants/Study Partners, face-to-face visits with Hub clinicians, medical records, notes reviews, NHS Digital data extracts and RCGP data downloads.

Pregnancy was recorded as an AE of Special Interest and was monitored from the start of treatment for the 28-day trial duration.

3.7.2.7 LONGER TERM EFFECTS: SYMPTOMS AND WELL-BEING AT 3 AND 6 MONTHS

The primary analysis is based on data collected through 28 days from randomisation; however additional outcomes will be collected at 3 and 6 months follow-up to capture the

long term outcomes of participants. This report covers outcomes for the first 28 days follow-up. The long term follow-up analysis will be covered in a future report.

3.7.2.8 HEALTHCARE MEASURES (EQ-5D-5L)

The EQ-5D-5L is a questionnaire consisting of 5 items (crosswalk) and a scale from 0 to 100 (VAS) defining overall health. These were captured in participant's daily diaries and call CRF. Cost effectiveness outcomes will be reported in a separate health economic analysis report and the analysis of this outcome will be described in a separate health economic analysis plan.

3.8 SAMPLE SIZE

The sample size calculation as stated in the protocol:

An estimated maximum of approximately 5300 participants per arm will be required to provide approximately 90% power for detecting a 33% relative reduction in the hospitalisation/death in an experimental arm relative to Usual Care, based on the assumption of an underlying 3% combined hospitalisation/death rate in the Usual Care arm, and an intervention lowering the hospitalisation/death rate to 2%. We expect fewer participants will be needed to detect the same relative reduction if the event rate is larger than 3% in the Usual Care arm, or if there is a greater reduction in the relative risk of hospitalisation/death for a given intervention. However, should the event rate be lower than expected, then the target sample size will be increased to reflect this.

We recruited 25783 for the comparison of Molnupiravir with Usual Care.

3.9 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

Participants were randomised using a secure, fully validated and compliant web-based randomisation system. Once deemed eligible, the medically qualified clinician or research nurse from the central clinical team or Hub (as documented on the delegation log) randomised the participant. Participants were randomised to one study arm using equal allocation ratios corresponding to the number of arms they were eligible for that were recruiting in the trial at that time. This started as 1:1 Molnupiravir :Usual Care, and once Paxlovid was introduced on 21st April 2022 changed to 1:1:1 Molnupiravir :Usual Care:Paxlovid. Patients had to be eligible for at least two arms (Usual Care and at least one novel antiviral intervention). Stratification was by age (< 50/ ≥ 50 years) and vaccination status (see 2.2.3).

The randomisation database automatically alerted the relevant IMP distributor and the participant, trial team and legal representative if applicable were notified electronically of the treatment allocation. If the participant did not have an email address, they were notified by telephone.

3.10 Definition of population for analysis

The analysis population will include participants as defined by the protocol eligibility criteria and having at least one of the vulnerabilities as listed in Table 3.

As per ICH E9 guidance the following participants will be excluded from the analysis population;

(a) Participants randomised but subsequently found to be not eligible for randomization

(b) Participants previously randomised to an arm in the PANORAMIC trial (subsequent randomisations will be excluded)

In addition, the following participants will be excluded;

(c) Participants who withdraw consent for data linkage and notes review and for whom no outcome data has been collected.

(d) Participants taking medications listed in Table 4

3.10.1.1 Primary analysis population

The primary analysis population is defined as participants who were randomised to Molnupiravir or usual care and were eligible for randomisation to Molnupiravir , during the same time frame when Molnupiravir was actively randomising (i.e. Concurrent Randomised and Eligible Analysis Population). That is, participants who were eligible for Molnupiravir and randomised to either Molnupiravir or usual care between 8th December 2021 and 27th April 2022.

This includes participants for whom data are available with participants analysed according to the groups they were randomly allocated to, regardless of deviation from protocol.

3.10.1.2 SECONDARY ANALYSIS POPULATION

Analysis of the secondary outcomes for a given intervention will be based on the same population as the primary analysis.

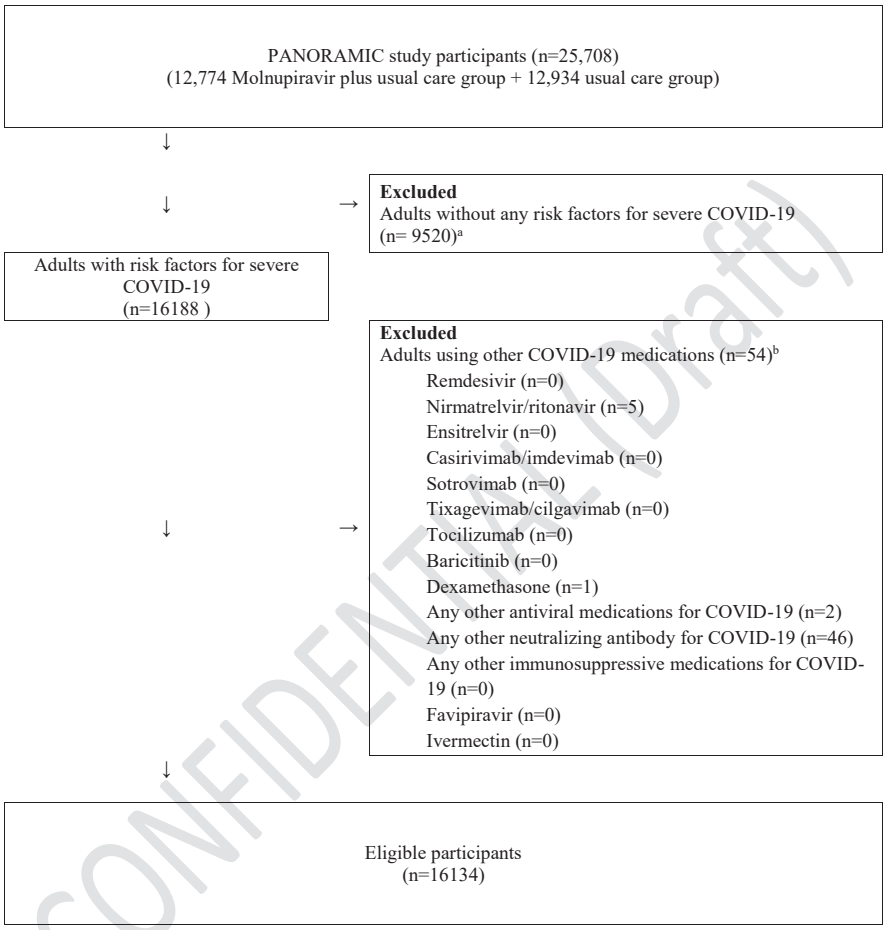
4 RESULTS

4.1 RECRUITMENT

Randomisation to the Molnupiravir arm was stopped on 27th April 2022. Participants randomised to the Molnupiravir arm and Usual Care between 8th December 2021 and 27th April 2022 (inclusive) are included in this report (see SAP for more details). During this time 111,383 participants were screened, 44,073 of whom were not eligible on screening and a further 41,517 were excluded after GP eligibility check (see CONSORT in appendix for reasons). 25,793 in total were randomised, of which 25,783 were randomised between Molnupiravir and Usual Care and were eligible for randomisation to Molnupiravir. 504 participants were randomised to other arms or randomised to Usual Care and not eligible for Molnupiravir. 75 participants were excluded from the analysis population as they were found to be ineligible after randomisation, leaving 25,708 participants in the analysis population.

Figure 2 shows the flow of participants for the subgroup analysis as presented in this report. 9520 participants were excluded as they did not have any risk factors for severe COVID-19 and a further 54 were excluded due to taking other medications. This leaves 16,134 in the subgroup analysis population.

FIGURE 1 FLOW DIAGRAM OF TRIAL PARTICIPANTS FOR THE SUBGROUP POPULATION



4.2 BASELINE CHARACTERISTICS OF PARTICIPANTS

Baseline characteristics by randomised group and overall are given in Table 5 for the concurrent and eligible population.

TABLE 5 BASELINE CHARACTERISTIC BY RANDOMISED GROUP FOR THE CONCURRENT AND ELIGIBLE POPULATION

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
Age, mean(SD) [min,max]	56.7 (12.5) [18.0 to 99.0]	56.5 (12.7) [18.0 to 98.0]	56.6 (12.6) [18.0 to 99.0]
Sex, n(%)			
Female	7451 (58.1%)	7650 (59.0%)	15101 (58.6%)
Male	5367 (41.9%)	5308 (41.0%)	10675 (41.4%)
Other	3 (0.0%)	4 (0.0%)	7 (0.0%)
Days from randomisation to reporting receipt of medication*, median(IQR)	2.0 (2.0 to 2.0)	N/A	2.0 (2.0 to 2.0)
Days from start of symptoms to taking medication*, median(IQR)	5.0 (4.0 to 6.0)	N/A	5.0 (4.0 to 6.0)
Data unavailable, n(%)	288 (1.1%)		
Ethnicity category, n(%)			
White	12088 (94.3%)	12182 (94.0%)	24270 (94.1%)
Asian	366 (2.9%)	434 (3.3%)	800 (3.1%)
Mixed Race	203 (1.6%)	189 (1.5%)	392 (1.5%)
Black	78 (0.6%)	77 (0.6%)	155 (0.6%)
Other	86 (0.7%)	80 (0.6%)	166 (0.6%)
NHS priority category, n(%)			
Aged ≥80	259 (2.0%)	272 (2.1%)	531 (2.1%)
Aged ≥75 and <80	539 (4.2%)	577 (4.5%)	1116 (4.3%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1117 (8.7%)	1114 (8.6%)	2231 (8.7%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1496 (11.7%)	1464 (11.3%)	2960 (11.5%)
Aged ≥18 and <65 in an at risk group	6541 (51.0%)	6591 (50.8%)	13132 (50.9%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at risk group	746 (5.8%)	768 (5.9%)	1514 (5.9%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at risk group	997 (7.8%)	1063 (8.2%)	2060 (8.0%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at risk group	1126 (8.8%)	1113 (8.6%)	2239 (8.7%)
Predicted risk quintile, n(%)			
1 (lowest risk)	2491 (19.4%)	2558 (19.7%)	5049 (19.6%)
2	2679 (20.9%)	2636 (20.3%)	5315 (20.6%)
3	2524 (19.7%)	2660 (20.5%)	5184 (20.1%)
4	2784 (21.7%)	2767 (21.3%)	5551 (21.5%)

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
5 (highest risk)	2343 (18.3%)	2341 (18.1%)	4684 (18.2%)
Confirmed PCR positive, n(%)	5965 (46.5%)	5902 (45.5%)	11867 (46.0%)
IMD quintile, n(%)			
(Most deprived) 1	1234 (9.6%)	1182 (9.1%)	2416 (9.4%)
2	1913 (14.9%)	1956 (15.1%)	3869 (15.0%)
3	2569 (20.0%)	2592 (20.0%)	5161 (20.0%)
4	3216 (25.1%)	3213 (24.8%)	6429 (24.9%)
(Least deprived) 5	3839 (29.9%)	3960 (30.6%)	7799 (30.2%)
Data unavailable, n(%)	50 (0.4%)	59 (0.5%)	109 (0.4%)
Took at least 4 doses IMP, n(%)	11892 (92.8%)	N/A	11892 (46.1%)
Received vaccination, n(%)	12678 (98.9%)	12830 (99.0%)	25508 (98.9%)
Number of COVID-19 vaccine doses, n(%)			
1	87 (0.7%)	88 (0.7%)	175 (0.7%)
2	519 (4.0%)	458 (3.5%)	977 (3.8%)
3	11836 (92.3%)	12044 (92.9%)	23880 (92.6%)
4	236 (1.8%)	240 (1.9%)	476 (1.8%)
Data unavailable, n(%)	143 (1.1%)	132 (1.0%)	275 (1.1%)
Current smoker, n(%)	795 (6.2%)	805 (6.2%)	1600 (6.2%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	6111 (47.7%)	6125 (47.3%)	12236 (47.5%)
Minor problem	4514 (35.2%)	4684 (36.1%)	9198 (35.7%)
Moderate problem	1936 (15.1%)	1896 (14.6%)	3832 (14.9%)
Major problem	260 (2.0%)	257 (2.0%)	517 (2.0%)
Fatigue, n(%)			
No problem	1251 (9.8%)	1216 (9.4%)	2467 (9.6%)
Minor problem	4721 (36.8%)	4853 (37.4%)	9574 (37.1%)
Moderate problem	5083 (39.6%)	5127 (39.6%)	10210 (39.6%)
Major problem	1766 (13.8%)	1766 (13.6%)	3532 (13.7%)
Muscle ache, n(%)			
No problem	3479 (27.1%)	3425 (26.4%)	6904 (26.8%)
Minor problem	4504 (35.1%)	4791 (37.0%)	9295 (36.1%)
Moderate problem	3763 (29.4%)	3684 (28.4%)	7447 (28.9%)
Major problem	1075 (8.4%)	1062 (8.2%)	2137 (8.3%)
Vomiting, n(%)			
No problem	10440 (81.4%)	10503 (81.0%)	20943 (81.2%)
Minor problem	1847 (14.4%)	1913 (14.8%)	3760 (14.6%)
Moderate problem	478 (3.7%)	477 (3.7%)	955 (3.7%)
Major problem	56 (0.4%)	69 (0.5%)	125 (0.5%)
Diarrhoea, n(%)			
No problem	10600 (82.7%)	10732 (82.8%)	21332 (82.7%)
Minor problem	1649 (12.9%)	1681 (13.0%)	3330 (12.9%)

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
Moderate problem	471 (3.7%)	457 (3.5%)	928 (3.6%)
Major problem	101 (0.8%)	92 (0.7%)	193 (0.7%)
Loss of smell or taste, n(%)			
No problem	9066 (70.7%)	9402 (72.5%)	18468 (71.6%)
Minor problem	2484 (19.4%)	2368 (18.3%)	4852 (18.8%)
Moderate problem	825 (6.4%)	800 (6.2%)	1625 (6.3%)
Major problem	446 (3.5%)	392 (3.0%)	838 (3.3%)
Headache, n(%)			
No problem	2702 (21.1%)	2820 (21.8%)	5522 (21.4%)
Minor problem	5194 (40.5%)	5215 (40.2%)	10409 (40.4%)
Moderate problem	3783 (29.5%)	3838 (29.6%)	7621 (29.6%)
Major problem	1142 (8.9%)	1089 (8.4%)	2231 (8.7%)
Dizziness, n(%)			
No problem	8446 (65.9%)	8382 (64.7%)	16828 (65.3%)
Minor problem	3087 (24.1%)	3295 (25.4%)	6382 (24.8%)
Moderate problem	1096 (8.5%)	1087 (8.4%)	2183 (8.5%)
Major problem	192 (1.5%)	198 (1.5%)	390 (1.5%)
Abdominal pain, n(%)			
No problem	10391 (81.0%)	10440 (80.5%)	20831 (80.8%)
Minor problem	1834 (14.3%)	1920 (14.8%)	3754 (14.6%)
Moderate problem	524 (4.1%)	542 (4.2%)	1066 (4.1%)
Major problem	72 (0.6%)	60 (0.5%)	132 (0.5%)
Generally unwell, n(%)			
No problem	525 (4.1%)	535 (4.1%)	1060 (4.1%)
Minor problem	5028 (39.2%)	5145 (39.7%)	10173 (39.5%)
Moderate problem	5789 (45.2%)	5838 (45.0%)	11627 (45.1%)
Major problem	1479 (11.5%)	1444 (11.1%)	2923 (11.3%)
Fever, n(%)			
No problem	5670 (44.2%)	5765 (44.5%)	11435 (44.4%)
Minor problem	4813 (37.5%)	4955 (38.2%)	9768 (37.9%)
Moderate problem	2107 (16.4%)	2042 (15.8%)	4149 (16.1%)
Major problem	231 (1.8%)	200 (1.5%)	431 (1.7%)
Cough, n(%)			
No problem	1410 (11.0%)	1343 (10.4%)	2753 (10.7%)
Minor problem	6153 (48.0%)	6384 (49.3%)	12537 (48.6%)
Moderate problem	4502 (35.1%)	4509 (34.8%)	9011 (34.9%)
Major problem	756 (5.9%)	726 (5.6%)	1482 (5.7%)
Wellness score, mean(SD) [min,max]	5.1 (1.7) [0.0 to 10.0]	5.2 (1.7) [0.0 to 10.0]	5.1 (1.7) [0.0 to 10.0]
People in household, n(%)			
0	1660 (12.9%)	1660 (12.8%)	3320 (12.9%)
1	6113 (47.7%)	6019 (46.4%)	12132 (47.1%)

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
2	2129 (16.6%)	2176 (16.8%)	4305 (16.7%)
3	1765 (13.8%)	1979 (15.3%)	3744 (14.5%)
4	808 (6.3%)	772 (6.0%)	1580 (6.1%)
Taking inhaled corticosteroids, n(%)	2990 (23.3%)	3152 (24.3%)	6142 (23.8%)
Taking inhaled corticosteroids for COVID, n(%)	183 (1.4%)	158 (1.2%)	341 (1.3%)
Monoclonal antibodies for COVID, n(%)	26 (0.2%)	19 (0.1%)	45 (0.2%)
Comorbidities			
Lung disease	3014 (23.5%)	3171 (24.5%)	6185 (24.0%)
Heart disease	1000 (7.8%)	957 (7.4%)	1957 (7.6%)
Kidney disease	227 (1.8%)	253 (2.0%)	480 (1.9%)
Liver disease	159 (1.2%)	144 (1.1%)	303 (1.2%)
Neurological disease	430 (3.4%)	438 (3.4%)	868 (3.4%)
Learning disability	36 (0.3%)	27 (0.2%)	63 (0.2%)
Down's syndrome'	24 (0.2%)	30 (0.2%)	54 (0.2%)
Diabetes	1483 (11.6%)	1512 (11.7%)	2995 (11.6%)
Weakened immune system	1125 (8.8%)	1070 (8.3%)	2195 (8.5%)
Transplant recipient	57 (0.4%)	71 (0.5%)	128 (0.5%)
Obesity	1968 (15.3%)	1944 (15.0%)	3912 (15.2%)
Mental illness	198 (1.5%)	220 (1.7%)	418 (1.6%)
Hypertension	2880 (22.5%)	2902 (22.4%)	5782 (22.4%)
Other vulnerability	2295 (17.9%)	2341 (18.1%)	4636 (18.0%)

*Median and interquartile range presented for non-normally distributed variables.

TABLE 6 BASELINE CHARACTERISTIC OF THE SUBGROUP POPULATION BY RANDOMISED GROUP

	Molnupiravir plus usual care (N=8088)	Usual Care (N=8046)	Overall (N=16134)
Age, mean(SD) [min,max]	59.2 (13.4) [18.0 to 99.0]	59.2 (13.6) [18.0 to 98.0]	59.2 (13.5) [18.0 to 99.0]
Sex, n(%)			
Female	4452 (55.0%)	4450 (55.3%)	8902 (55.2%)
Male	3634 (44.9%)	3595 (44.7%)	7229 (44.8%)
Other	2 (0.0%)	1 (0.0%)	3 (0.0%)
Days from randomisation to reporting receipt of medication*, median(IQR)	2.0 (2.0 to 2.0)	N/A	2.0 (2.0 to 2.0)
Days from start of symptoms to taking medication*, median(IQR)	4.0 (3.0 to 5.0)	N/A	4.0 (3.0 to 5.0)
Data unavailable, n(%)	6434 (79.5%)		6434 (39.9%)
Ethnicity category, n(%)			
White	7628 (94.3%)	7573 (94.1%)	15201 (94.2%)
Asian	233 (2.9%)	269 (3.3%)	502 (3.1%)
Mixed Race	117 (1.4%)	105 (1.3%)	222 (1.4%)
Black	53 (0.7%)	53 (0.7%)	106 (0.7%)
Other	57 (0.7%)	46 (0.6%)	103 (0.6%)
NHS priority category, n(%)			
Aged ≥80	256 (3.2%)	271 (3.4%)	527 (3.3%)
Aged ≥75 and <80	537 (6.6%)	573 (7.1%)	1110 (6.9%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1115 (13.8%)	1108 (13.8%)	2223 (13.8%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1488 (18.4%)	1463 (18.2%)	2951 (18.3%)
Aged ≥18 and <65 in an at risk group	4545 (56.2%)	4474 (55.6%)	9019 (55.9%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at risk group	37 (0.5%)	35 (0.4%)	72 (0.4%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at risk group	43 (0.5%)	56 (0.7%)	99 (0.6%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at risk group	67 (0.8%)	66 (0.8%)	133 (0.8%)
Predicted risk quintile, n(%)			
1 (lowest risk)	623 (7.7%)	633 (7.9%)	1256 (7.8%)
2	1698 (21.0%)	1660 (20.6%)	3358 (20.8%)
3	1861 (23.0%)	1898 (23.6%)	3759 (23.3%)
4	2084 (25.8%)	2063 (25.6%)	4147 (25.7%)
5 (highest risk)	1822 (22.5%)	1792 (22.3%)	3614 (22.4%)
Confirmed PCR positive, n(%)	3680 (45.5%)	3585 (44.6%)	7265 (45.0%)
IMD quintile, n(%)			
(Most deprived) 1	835 (10.3%)	808 (10.0%)	1643 (10.2%)
2	1250 (15.5%)	1265 (15.7%)	2515 (15.6%)
3	1659 (20.5%)	1629 (20.2%)	3288 (20.4%)

	Molnupiravir plus usual care (N=8088)	Usual Care (N=8046)	Overall (N=16134)
4	2011 (24.9%)	1967 (24.4%)	3978 (24.7%)
(Least deprived) 5	2305 (28.5%)	2340 (29.1%)	4645 (28.8%)
Data unavailable, n(%)	28 (0.3%)	37 (0.5%)	65 (0.4%)
Took at least 4 doses IMP, n(%)	7495 (92.7%)		7495 (46.5%)
Received vaccination, n(%)	7994 (98.8%)	7974 (99.1%)	15968 (99.0%)
Number of COVID-19 vaccine doses, n(%)			
1	54 (0.7%)	48 (0.6%)	102 (0.6%)
2	290 (3.6%)	249 (3.1%)	539 (3.3%)
3	7440 (92.0%)	7464 (92.8%)	14904 (92.4%)
4	210 (2.6%)	213 (2.6%)	423 (2.6%)
Data unavailable, n(%)	94 (1.2%)	72 (0.9%)	166 (1.0%)
Current smoker, n(%)	787 (9.7%)	799 (9.9%)	1586 (9.8%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	3871 (47.9%)	3786 (47.1%)	7657 (47.5%)
Minor problem	2834 (35.0%)	2891 (35.9%)	5725 (35.5%)
Moderate problem	1221 (15.1%)	1198 (14.9%)	2419 (15.0%)
Major problem	162 (2.0%)	171 (2.1%)	333 (2.1%)
Fatigue, n(%)			
No problem	803 (9.9%)	788 (9.8%)	1591 (9.9%)
Minor problem	2960 (36.6%)	2952 (36.7%)	5912 (36.6%)
Moderate problem	3187 (39.4%)	3186 (39.6%)	6373 (39.5%)
Major problem	1138 (14.1%)	1120 (13.9%)	2258 (14.0%)
Muscle ache, n(%)			
No problem	2264 (28.0%)	2155 (26.8%)	4419 (27.4%)
Minor problem	2734 (33.8%)	2934 (36.5%)	5668 (35.1%)
Moderate problem	2371 (29.3%)	2290 (28.5%)	4661 (28.9%)
Major problem	719 (8.9%)	667 (8.3%)	1386 (8.6%)
Vomiting, n(%)			
No problem	6603 (81.6%)	6564 (81.6%)	13167 (81.6%)
Minor problem	1151 (14.2%)	1140 (14.2%)	2291 (14.2%)
Moderate problem	298 (3.7%)	288 (3.6%)	586 (3.6%)
Major problem	36 (0.4%)	54 (0.7%)	90 (0.6%)
Diarrhoea, n(%)			
No problem	6599 (81.6%)	6593 (81.9%)	13192 (81.8%)
Minor problem	1073 (13.3%)	1094 (13.6%)	2167 (13.4%)
Moderate problem	331 (4.1%)	296 (3.7%)	627 (3.9%)
Major problem	85 (1.1%)	63 (0.8%)	148 (0.9%)
Loss of smell or taste, n(%)			
No problem	5660 (70.0%)	5802 (72.1%)	11462 (71.0%)
Minor problem	1589 (19.6%)	1473 (18.3%)	3062 (19.0%)
Moderate problem	541 (6.7%)	512 (6.4%)	1053 (6.5%)

	Molnupiravir plus usual care (N=8088)	Usual Care (N=8046)	Overall (N=16134)
Major problem	298 (3.7%)	259 (3.2%)	557 (3.5%)
Headache, n(%)			
No problem	1753 (21.7%)	1837 (22.8%)	3590 (22.3%)
Minor problem	3293 (40.7%)	3205 (39.8%)	6498 (40.3%)
Moderate problem	2316 (28.6%)	2337 (29.0%)	4653 (28.8%)
Major problem	726 (9.0%)	667 (8.3%)	1393 (8.6%)
Dizziness, n(%)			
No problem	5306 (65.6%)	5174 (64.3%)	10480 (65.0%)
Minor problem	1946 (24.1%)	2034 (25.3%)	3980 (24.7%)
Moderate problem	701 (8.7%)	699 (8.7%)	1400 (8.7%)
Major problem	135 (1.7%)	139 (1.7%)	274 (1.7%)
Abdominal pain, n(%)			
No problem	6541 (80.9%)	6466 (80.4%)	13007 (80.6%)
Minor problem	1143 (14.1%)	1191 (14.8%)	2334 (14.5%)
Moderate problem	359 (4.4%)	351 (4.4%)	710 (4.4%)
Major problem	45 (0.6%)	38 (0.5%)	83 (0.5%)
Generally unwell, n(%)			
No problem	347 (4.3%)	345 (4.3%)	692 (4.3%)
Minor problem	3162 (39.1%)	3212 (39.9%)	6374 (39.5%)
Moderate problem	3637 (45.0%)	3591 (44.6%)	7228 (44.8%)
Major problem	942 (11.6%)	898 (11.2%)	1840 (11.4%)
Fever, n(%)			
No problem	3563 (44.1%)	3583 (44.5%)	7146 (44.3%)
Minor problem	3019 (37.3%)	3021 (37.5%)	6040 (37.4%)
Moderate problem	1375 (17.0%)	1315 (16.3%)	2690 (16.7%)
Major problem	131 (1.6%)	127 (1.6%)	258 (1.6%)
Cough, n(%)			
No problem	837 (10.3%)	802 (10.0%)	1639 (10.2%)
Minor problem	3811 (47.1%)	3805 (47.3%)	7616 (47.2%)
Moderate problem	2910 (36.0%)	2968 (36.9%)	5878 (36.4%)
Major problem	530 (6.6%)	471 (5.9%)	1001 (6.2%)
Wellness score, mean (SD) [min,max]	5.2 (1.7) [0.0 to 10.0]	5.2 (1.7) [0.0 to 10.0]	5.2 (1.7) [0.0 to 10.0]
People in household, n(%)			
0	1106 (13.7%)	1127 (14.0%)	2233 (13.8%)
1	4167 (51.5%)	4104 (51.0%)	8271 (51.3%)
2	1211 (15.0%)	1197 (14.9%)	2408 (14.9%)
3	938 (11.6%)	998 (12.4%)	1936 (12.0%)
4	446 (5.5%)	412 (5.1%)	858 (5.3%)
5	220 (2.7%)	208 (2.6%)	428 (2.7%)
Taking inhaled corticosteroids, n(%)	1607 (19.9%)	1696 (21.1%)	3303 (20.5%)
Taking inhaled corticosteroids for COVID, n(%)	93 (1.1%)	84 (1.0%)	177 (1.1%)

	Molnupiravir plus usual care (N=8088)	Usual Care (N=8046)	Overall (N=16134)
Monoclonal antibodies for COVID, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Comorbidities			
Lung disease	1620 (20.0%)	1718 (21.4%)	3338 (20.7%)
Heart disease	993 (12.3%)	952 (11.8%)	1945 (12.1%)
Kidney disease	222 (2.7%)	253 (3.1%)	475 (2.9%)
Liver disease	131 (1.6%)	119 (1.5%)	250 (1.5%)
Neurological disease	295 (3.6%)	281 (3.5%)	576 (3.6%)
Learning disability	32 (0.4%)	26 (0.3%)	58 (0.4%)
Down's syndrome'	24 (0.3%)	26 (0.3%)	50 (0.3%)
Diabetes	1473 (18.2%)	1507 (18.7%)	2980 (18.5%)
Weakened immune system	1110 (13.7%)	1055 (13.1%)	2165 (13.4%)
Transplant recipient	55 (0.7%)	69 (0.9%)	124 (0.8%)
Obesity	1957 (24.2%)	1932 (24.0%)	3889 (24.1%)
Mental illness	143 (1.8%)	159 (2.0%)	302 (1.9%)
Hypertension	2854 (35.3%)	2895 (36.0%)	5749 (35.6%)
Other vulnerability	1683 (20.8%)	1615 (20.1%)	3298 (20.4%)

*Median and interquartile range presented for non-normally distributed variables.

TABLE 7 PREVALENCE OF RISK FACTORS FOR SEVERE COVID-19 (MODIFIED DEFINITION) AMONG ELIGIBLE PARTICIPANTS

	Molnupiravir plus usual care (n=8088)	Usual care (n=8046)
Risk factors		
Older adults aged ≥ 65 years	3396 (42.0%)	3415 (42.4%)
Cancer or chemotherapy	10 (0.1%)	14 (0.2%)
Chronic respiratory disease	1620 (20.0%)	1718 (21.4%)
Chronic kidney disease	222 (2.7%)	253 (3.1%)
Diabetes	1473 (18.2%)	1507 (18.7%)
Hypertension (high blood pressure)	2854 (35.3%)	2895 (36.0%)
Chronic heart or vascular disease	993 (12.3%)	952 (11.8%)
Stroke	16 (0.2%)	24 (0.3%)
Obesity (BMI ≥ 35 kg/m^2)	1957 (24.2%)	1932 (24.0%)
Current smoker	787 (9.7%)	799 (9.9%)
Solid organ, bone marrow and stem cell transplant recipients	55 (0.7%)	69 (0.9%)
Immunosuppression and HIV infection	1110 (13.7%)	1055 (13.1%)

4.3 Number analysed

Of the 16134 participants included in the subgroup analysis 15703 (97.3%) had data collected on hospitalisation/death and so could be included in the primary analysis. 15324 (95.0%) completed any diaries or calls and so could be included in the secondary analysis.

4.4 Primary Analyses

4.4.1 Primary outcome

The primary outcome is defined as all cause unplanned hospitalisation or death from randomisation to 28 days follow-up. Data is derived from participant daily diaries, phone calls, and routine electronic data. If a primary endpoint is reported from any data source then this outcome is counted as "yes". If the participant has completed 28 days follow-up and is not hospitalised or is lost to follow-up but has been checked against routine electronic data and no hospitalisation or death is found then this outcome is coded "no". An odds ratio<1 suggests fewer hospitalisations/deaths in the Molnupiravir arm. The results show probability of superiority just below 0.5, indicating equivalence of Molnupiravir with Usual Care.

TABLE 8 PRIMARY OUTCOME

	Molnupiravir plus usual care (N=8088)	Usual care (N=8046)	Estimated treatment effect (95% BCI)	Probability of superiority
Hospitalization or death	81/7933 (1.0%)	78/7770 (1.0%)	1.022 (0.738 to 1.382)	0.4778
Deaths	3/7933	5/7770	Not estimable	
Hospitalizations	79/7933 (1.0%)	76/7770 (1.0%)	1.023 (0.737 to 1.385)	0.4762

*OR < 1 favours Molnupiravir

4.4.2 SECONDARY OUTCOMES

Definition of outcomes:

1. Time to recovery: time to first reporting of feeling recovered in diary or call. A hazard ratio>1 suggests faster recovery in the Molnupiravir arm
2. Time to sustained recovery: time to reporting recovery in diary or call followed by no subsequent relapse. A hazard ratio>1 favours Molnupiravir.
3. Early sustained recovery: reported recovered within the first 14 days with no subsequent relapse. An odds ratio >1 favours Molnupiravir.
4. Alleviation of symptoms: Time to first rating of symptoms as mild/none. If all symptoms are rated mild/none at baseline then the participant is censored at day 0. A hazard ratio>1 favours Molnupiravir.
5. Sustained alleviation of symptoms: Time to rating of symptoms as mild/none followed by no subsequent relapse. If all symptoms are rated mild/none at baseline then the participant is censored at day 0. A hazard ratio>1 favours Molnupiravir.
6. Reduction of symptoms: Time to reduction of all symptoms by at least one grade. A hazard ratio>1 favours Molnupiravir.
7. Rating of how well participant feels (1 worst, 10 best): Participant rating of wellness at each day. Estimates represent the mean differences and a values >0 favours Molnupiravir.
8. Household infections: Participant reported another member of their household becoming unwell with COVID-19. Participants who live alone at baseline are excluded. An odds ratio <1 favours Molnupiravir (fewer household infections). For number of infections a rate ratio <1 favours Molnupiravir.

The following assumptions have been made in the following analysis:

1. For time to event outcomes participants are censored at the last point of contact or 28 days, whichever is sooner. For time to sustained recovery if a participant reported feeling recovered and is subsequently lost to follow-up it is assumed they remained recovered (last

observation carried forward). A similar principle is used for time to sustained alleviation of symptoms. Therefore the only missing data for time to event outcomes is participants who completed no diary data

2. For early sustained recovery if a participant is lost to follow-up, such that it is not possible to establish if they remained recovered, then this outcome is treated as missing.
3. For time to alleviation and time to reduction of symptoms if a symptom is missing but the participant reported feeling recovered, that symptom is assumed to be rated "none".
4. For household infections if a participant has incomplete diaries but has not stated that they have an infection within the household this outcome is assumed to be zero. Participants who live alone at baseline are excluded from the analysis.
5. Analysis of daily symptom scores uses a frequentist mixed model, due to the computational difficultly running the Bayesian model with the number of parameters.

Results in Table 9 have showed that the estimated median (95% BCI) TTR from the Bayesian model were 10.022 (9.775 to 10.274) days and 13.940 (13.447 to 14.445) days, respectively, which suggested that Molnupiravir has a nearly 4 days benefit in TTR compared with Usual Care.

There was a significant benefit in early sustained recovery by 9.5%, i.e. recovered within the first 14 days and remained well until day 28 from randomisation, in Molnupiravir group (32.8%) compared to Usual Care (23.3%) (OR = 1.6; 95% BCI (1.52 to 1.77)).

TABLE 9 SECONDARY OUTCOMES

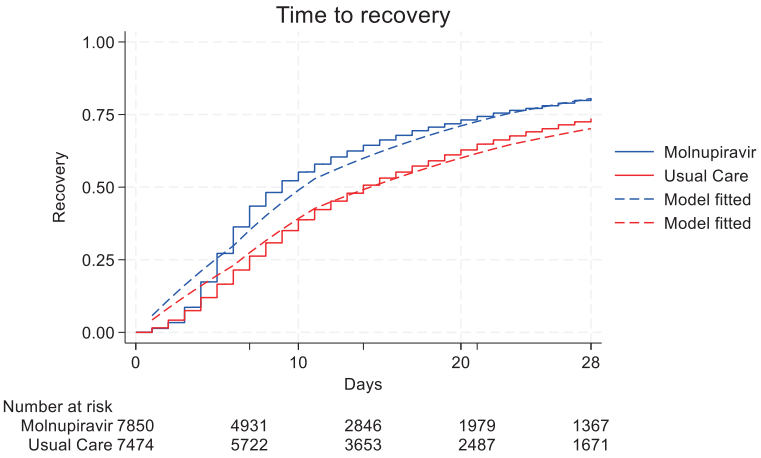
	Molnupiravir plus usual care (N=8088)	Usual care (N=8046)	Estimated treatment effect (95% BCI)	Estimated benefit (95% BCI)	Probability of superiority
First reported recovery	6177/7850 (78.7%)	5195/7474 (69.5%)			
Days to first reported recovery	10.022 (9.775 to 10.274)	13.940 (13.447 to 14.445)	1.353 (1.301 to 1.403) *	-3.920 (-4.453 to -3.384) †	>0.99
Early sustained recovery	2360/7188 (32.8%)	1547/6649 (23.3%)	1.638 (1.517 to 1.768) **		>0.99
Sustained recovery	5401/7850 (68.8%)	4512/7474 (60.4%)			
Days to sustained recovery	19.746 (19.275 to 20.232)	23.272 (22.882 to 23.611)	1.237 (1.189 to 1.288) *	-3.524 (-4.093 to -2.926) †	>0.99
Alleviation of all symptoms	5674/6132 (92.5%)	5136/5816 (88.3%)			
Days to alleviations of all symptoms	3.694 (3.589 to 3.802)	4.388 (4.252 to 4.535)	1.188 (1.143 to 1.234) *	-0.695 (-0.856 to -0.535) †	>0.99
Sustained alleviation of all symptoms	5125/6132 (83.6%)	4609/5816 (79.2%)			
Days to sustained alleviation of all symptoms	9.374 (8.974 to 9.799)	11.038 (10.585 to 11.525)	1.134 (1.090 to 1.178) *	-1.669 (-2.221 to -1.111) †	>0.99
Initial reduction of symptom severity	6821/7835 (87.1%)	6010/7464 (80.5%)			
Days to initial reduction of symptom severity	7.349 (7.167 to 7.534)	9.162 (8.929 to 9.404)	1.278 (1.234 to 1.322) *	-1.812 (-2.086 to -1.537) †	>0.99
Participant rating of wellness					
Day 7	7.3 (1.8) [7471]	6.8 (1.8) [6927]	0.5 (0.5 to 0.6) ¶		P<0.001‖
Day 14	7.8 (1.7) [7276]	7.6 (1.7) [6605]	0.3 (0.2 to 0.3) ¶		P<0.001‖
Day 21	8.1 (1.7) [6782]	7.9 (1.7) [5927]	0.1 (0.1 to 0.2) ¶		P<0.001‖
Day 28	8.4 (1.6) [6746]	8.2 (1.6) [6062]	0.1 (0.1 to 0.2) ¶		P<0.001‖
New infections in household	2542/ (31.4%)	2469/ (30.7%)	0.961 (0.896 to 1.025) **		0.8873
Contact with health and social care services					
NHS 111	404/7849 (5.1%)	510/7470 (6.8%)	0.738 (0.645 to 0.841) **		>0.99

	Molnupiravir plus usual care (N=8088)	Usual care (N=8046)	Estimated treatment effect (95% BCI)	Estimated benefit (95% BCI)	Probability of superiority
General practitioner	1673/7848 (21.3%)	1885/7470 (25.2%)	0.797 (0.738 to 0.860) **		>0.99
Ambulance service (not hospitalised)	225/7845 (2.9%)	203/7460 (2.7%)	1.060 (0.868 to 1.281) **		0.2966
Community nurse	193/7849 (2.5%)	216/7468 (2.9%)	0.854 (0.696 to 1.035) **		0.9466
Physiotherapist	98/7849 (1.2%)	57/7468 (0.8%)	1.659 (1.184 to 2.270) **		0.0020
Counsellor	53/7849 (0.7%)	66/7468 (0.9%)	0.762 (0.520 to 1.071) **		0.9419
Social worker	18/7849 (0.2%)	24/7468 (0.3%)	0.736 (0.384 to 1.281) **		0.8785
Home carer	74/7848 (0.9%)	73/7466 (1.0%)	0.973 (0.695 to 1.328) **		0.5979
Occupational therapist	167/7848 (2.1%)	146/7468 (2.0%)	1.100 (0.870 to 1.366) **		0.2201
Hospital emergency department	445/7849 (5.7%)	401/7468 (5.4%)	1.056 (0.916 to 1.213) **		0.2334
Outpatient respiratory clinic	152/7849 (1.9%)	173/7467 (2.3%)	0.835 (0.665 to 1.038) **		0.9492
Hospital at home for COVID-19	253/7849 (3.2%)	298/7468 (4.0%)	0.803 (0.673 to 0.947) **		0.9960
Other services	429/7849 (5.5%)	469/7467 (6.3%)	0.862 (0.751 to 0.985) **		0.9849

*Estimated HR derived from a piecewise exponential model adjusted for age, comorbidity and vaccination status. HR > 1 favours Molnupiravir.
†Model based estimated benefit median time to event > 0 favours Molnupiravir.
‖ Frequentist model estimates display p-value rather than a probability.
¶Linear mixed effect model adjusted for age, comorbidity and vaccination status. Participant fitted as a random effect. Estimated mean difference > 0 favours Molnupiravir.
**Bayesian logistic regression, adjusted for, age, comorbidity and vaccination status

The following plot shows the actual data for time to recovery (solid lines) and the model-based estimates (dashed lines). The model-based estimates are derived from the piecewise exponential where all the standardised covariates are set to zero (corresponding to the sample average).

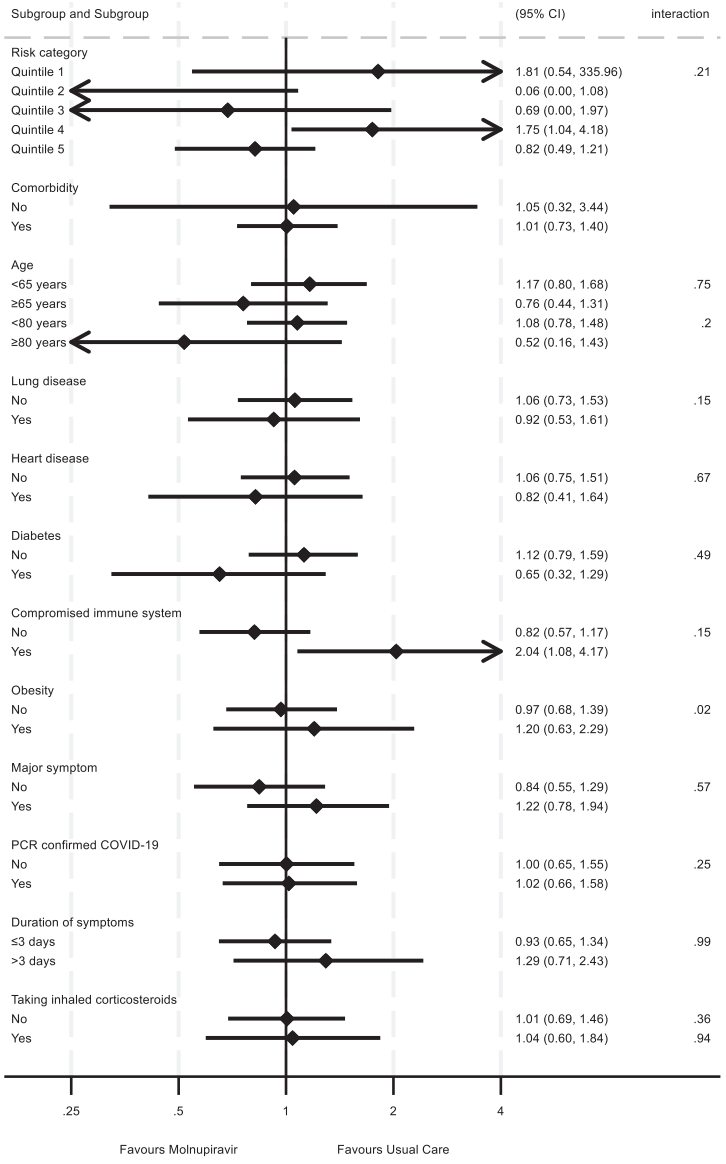
FIGURE 2 KAPLAN-MEIER CURVE AND MODEL ESTIMATES FOR TIME TO RECOVERY



4.5 SUBGROUP ANALYSES

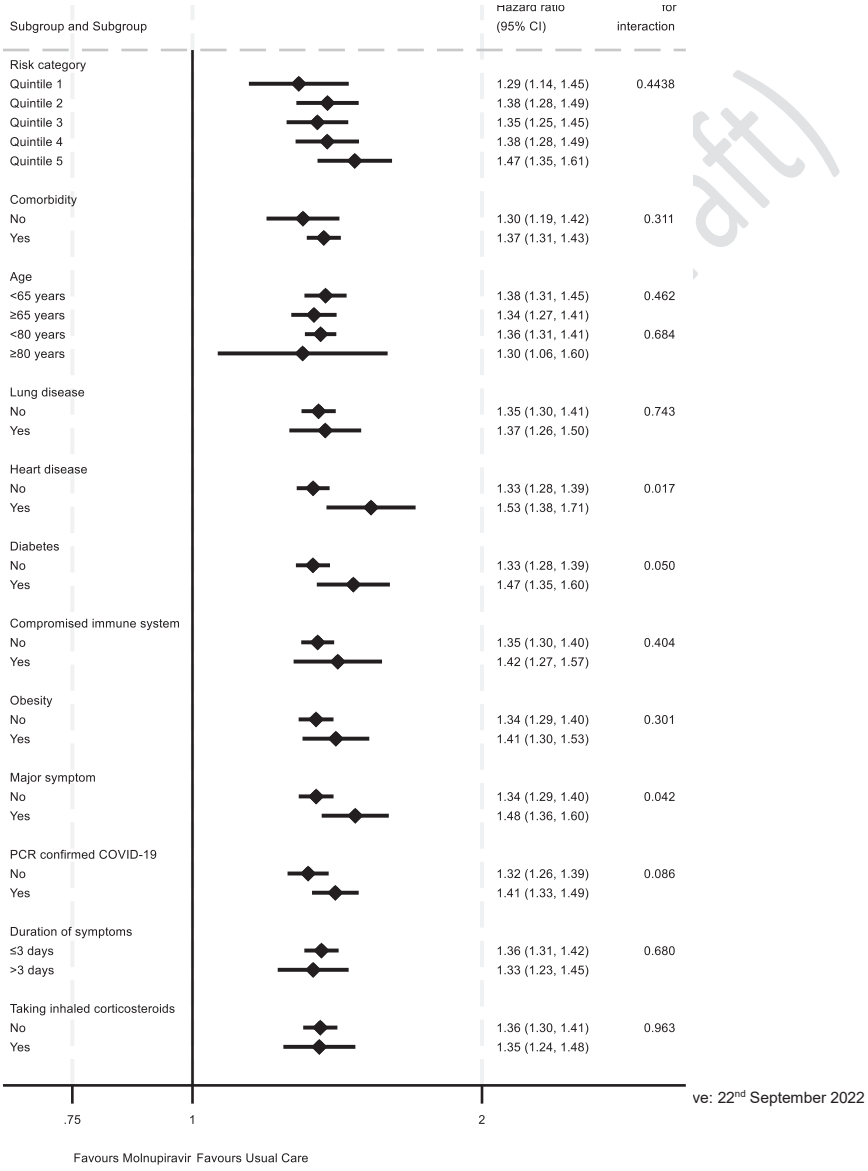
Frequentist model estimates are presented for the moderation analysis of the primary outcome. An odds ratio<1 favours Molnupiravir. P-values indicate the test for the interaction and statistically significant p-value suggests a differential effect size between subgroups.

FIGURE 3 FOREST PLOT OF SUBGROUP ANALYSIS OF PRIMARY OUTCOME



Frequentist model estimates are presented for the moderation analysis of time to recovery. A hazard ratio>1 favours Molnupiravir. P-values indicate the test for the interaction and a statistically significant p-value suggests a differential effect size between subgroups.

FIGURE 4 FOREST PLOT OF SUBGROUP ANALYSIS OF TIME TO RECOVERY



ve: 22nd September 2022

4.6 VIROLOGY SUB-STUDY ANALYSIS

TABLE 10 SUMMARY OF VIROLOGY SUB-STUDY

	Molnupiravir plus usual care	Usual Care	Total
Number of participants, n			
Intensive samples cohort	23	30	53
Less intensive samples cohort	126	149	275
At least 7 samples received from intensive samples cohort, n/N (%)	23/23 (100%)	29/30 (96.7%)	52/53 (98.1%)
At least 2 samples received from less intensive sample cohort, n/N (%)	126/126 (100%)	149/149 (100%)	275/275 (100%)
Female, n/N (%)			
Intensive samples cohort	11/23 (47.8%)	16/30 (53.3%)	27/53 (50.9%)
Less intensive samples cohort	67/126 (53.2%)	87/129 (58.4%)	154/255 (56.0%)
Overall	78/149 (52.3%)	103/159 (57.5%)	181/308 (55.2%)
Age, mean (SD)			
Intensive samples cohort	61.0 (8.7)	63.6 (9.5)	62.5 (9.1)
Less intensive samples cohort	61.3 (11.0)	62.0 (11.4)	61.7 (11.2)
Overall	61.2 (10.7)	62.3 (11.1)	61.8 (10.9)

TABLE 11 VIROLOGY SUBSTUDY

	Molnupiravir plus usual care	Usual care	Estimated treatment effect (95% CI)	P value
Intensive samples				
Undetectable viral load, n/N(%)				
Day 2	0/23	0/29		
Day 3	0/23	0/29		
Day 4	1/22 (0.5%)	0/30		
Day 5	3/20 (15%)	0/29		
Day 6	3/20 (15 %)	1/29 (0.3%)	5.508 (0.501 to 60.549) †	0.1630
Day 7*	3/20 (15 %)	1/29 (0.3%)	6.041 (0.306 to 119.352) †	0.2374
Viral load, mean(sd)				
Day 1	7.318 (1.173)	7.346 (1.266)		
Day 2	6.794 (1.457)	7.077 (1.144)	-0.342 (-0.908 to 0.225) ‡	0.2368
Day 3	6.196 (1.408)	6.435 (1.148)	-0.270 (-0.831 to 0.292) ‡	0.3464
Day 4	5.409 (1.541)	6.000 (1.182)	-0.606 (-1.164 to -0.048) ‡	0.0333
Day 5	4.590 (1.574)	5.781 (1.133)	-1.221 (-1.782 to -0.660) ‡	<0.0001
Day 6	4.276 (1.477)	5.412 (1.340)	-1.151 (-1.709 to -0.593) ‡	0.0001
Day 7	3.959 (1.245)	4.930 (1.413)	-0.986 (-1.543 to -0.428) ‡	0.0005
All samples				
Undetectable viral load, n/N(%)				
Day 5	11/144 (7.6%)	5/167 (3.0%)	3.684 (0.920 to 14.763)**	0.0655
Day 14	55/123 (44.7%)	78/152 (51.3%)	0.664 (0.307 to 1.435)**	0.2972
Viral load, mean(sd)				
Day 5	4.473 (1.567)	5.576 (1.300)	-1.133 (-1.548 to -0.718) ‡	<0.0001
Day 14	2.940 (1.357)	2.526 (1.145)	0.318 (-0.008 to 0.644) ‡	0.0556

* Primary outcome
† Firth logistic regression adjusting for sex, age, and baseline $\log_{10}$(viral load). Adjusted OR > 1 favours Molnupiravir
‡Mixed effect model adjusting for sex, age, and baseline $\log_{10}$(viral load); adjusted difference < 0 favours Molnupiravir
** Mixed effects logistic regression adjusting for sex, age, and baseline $\log_{10}$(viral load). Adjusted OR > 1 favours Molnupiravir

~~~ END OF REPORT ~~~