

**Molnupiravir versus ritonavir-boosted nirmatrelvir; a randomised controlled adaptive trial
comparison of antiviral efficacy in early symptomatic COVID-19 (PLATCOV)**

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37

38 **Abstract**

39 **Background:**

40 Molnupiravir and ritonavir-boosted nirmatrelvir are the two leading oral COVID-19 treatments,
41 but their antiviral activities *in vivo* have not been compared directly.

42 **Methods:**

43 In an open label controlled adaptive pharmacometric platform trial, low-risk adult patients 18-
44 50 years old with early symptomatic COVID-19 (<4 days of symptoms) were randomised
45 concurrently using a mobile 'phone application to one of seven treatment arms including
46 molnupiravir, ritonavir-boosted nirmatrelvir, and no study drug, as well as
47 casirivimab/imdevimab, tixagevimab/cilgavimab, favipiravir and fluoxetine, which were not
48 included in this analysis. The primary endpoint was the rate of viral clearance assessed in a
49 modified intention-to-treat population (mITT), defined as patients with ≥ 3 days of follow-up.
50 The viral clearance rate was derived under a Bayesian hierarchical linear model fitted to the \log_{10}
51 viral densities in standardised duplicate oropharyngeal swab eluates taken daily over one week
52 (18 measurements). Treatment arms with a >0.9 probability that viral clearance was
53 accelerated by $>20\%$ compared to no drug entered a non-inferiority comparison (with a 10%
54 non-inferiority margin) compared to the platform's current most effective drug. All baseline
55 isolates and samples with Ct values <35 on days 7 or later had whole viral genome sequencing.
56 This trial is registered at ClinicalTrials.gov (NCT05041907).

57 **Findings:**

58 The three study arms randomised 209 patients concurrently in Thailand from June 2022 until
59 February 2023 when molnupiravir reached the prespecified inferiority margin of 10% compared

60 with nirmatrelvir (molnupiravir: n=65; nirmatrelvir: n=59; no study drug: n=85). The estimated
61 mean rate of SARS-CoV-2 viral clearance with molnupiravir was 37% faster (95% credible
62 Interval: 16 to 65%) faster compared to no drug but was 25% (10 to 38%) slower than with
63 nirmatrelvir. Median (interquartile range) estimated viral clearance half-lives were 8.5 (6.7 to
64 10.1) hours with nirmatrelvir; 11.6 (8.6 to 15.4) hours with molnupiravir; and 15.5 (11.9 to 21.2)
65 hours with no drug. Viral rebound occurred more frequently following nirmatrelvir (6/58: 10%)
66 compared with the no drug (1/84: 1%, p=0.02) or the molnupiravir arms (1/65: 2%, p=0.05).
67 Persistent infections following molnupiravir had more viral mutations (3/9 patients had an
68 increased number of single nucleotide polymorphisms in samples collected ≥ 7 days compared
69 to those at baseline) than after nirmatrelvir (0/3) or no study drug (0/18).

70 **Interpretation:**

71 Both molnupiravir and nirmatrelvir accelerate oropharyngeal SARS-CoV-2 viral clearance in
72 COVID-19, but the antiviral effect of nirmatrelvir is substantially greater.

73 **Funding:**

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75 antiviral pharmacodynamics in early symptomatic COVID-19 (PLAT-COV)” is supported by the
76 Wellcome Trust Grant ref: 223195/Z/21/Z through the COVID-19 Therapeutics Accelerator.

77 **Panel: Research in context**

78 **Evidence before this study**

79 Molnupiravir and ritonavir-boosted nirmatrelvir are the two leading candidate oral antiviral
80 drugs for COVID-19. We searched Pubmed for studies in English up until the 11 July 2023 using

the terms: “randomised” AND [“nirmatrelvir OR paxlovid”] AND “molnupiravir”. Both molnupiravir and nirmatrelvir have demonstrated *in vivo* antiviral activity and clinical benefit, but there have been no direct randomised head-to-head comparisons. A network meta-analysis suggested that nirmatrelvir is slightly more effective than molnupiravir. Comparisons between the pre-registration studies are confounded by substantial differences in the study populations, and timing of the studies. Associations between the use of these drugs and the risk of viral mutations (molnupiravir) and viral rebound (nirmatrelvir) have both been reported, although their incidence and impact are uncertain.

Added value of the study

For COVID-19, comparison of antiviral drugs using clinical endpoints such as hospitalisation or death now requires prohibitively large sample sizes because these outcomes have become increasingly rare. In contrast the pharmacometric approach described here provides a quantitative measure of *in vivo* antiviral effects with tractable sample sizes. This randomised study provides the first direct comparison of the *in vivo* antiviral effects of molnupiravir and nirmatrelvir. It shows that both drugs accelerate SARS-CoV-2 viral clearance but that nirmatrelvir results in faster clearance than molnupiravir; that viral rebound occurs relatively often in a healthy population following nirmatrelvir; and that mutant viruses are generated frequently following molnupiravir.

Implications of available evidence

Ritonavir-boosted nirmatrelvir has superior *in vivo* antiviral activity in early COVID-19 compared with molnupiravir.

102 **Brief summary:**

103 Ritonavir-boosted nirmatrelvir cleared oropharyngeal SARS-CoV-2 faster than molnupiravir.
104 Viral rebound occurred more frequently following ritonavir-boosted nirmatrelvir treatment.
105 Persistent infections following molnupiravir had considerably more mutations than those
106 following nirmatrelvir or no study drug.

107 **Introduction**

108 Effective antiviral drugs and monoclonal antibodies accelerate viral clearance and prevent
109 progression to severe disease and death in early COVID-19 (1, 2). Large randomised controlled
110 trials (RCTs) have shown clinical efficacy with corresponding accelerated nasopharyngeal viral
111 clearance for monoclonal antibodies, parenteral remdesivir, and oral molnupiravir and
112 ritonavir-boosted nirmatrelvir (1, 2, 3, 4, 5). These new oral antiviral drugs have been used
113 widely, although availability in low resource settings is still limited, particularly for nirmatrelvir
114 (6). Both medications have disadvantages. For molnupiravir, there have been doubts over the
115 drug's efficacy. The initial reported clinical benefit, based on an interim analysis, was revised
116 down when further data were available, and despite approvals, some countries opted to cancel
117 their orders (7). A recent open-label randomised study of molnupiravir in the UK of 26,411 high-
118 risk vaccinated patients in the community showed no decrease in subsequent COVID-19
119 hospitalisation or death, although there were improvements in time to recovery and viral loads
120 (8). An additional concern is the creation of mutant viruses; molnupiravir is the prodrug of N⁴-
121 hydroxycytidine which causes such a high frequency of SARS-CoV-2 mutations that replication is
122 prevented ("error catastrophe") (9). Nirmatrelvir, a 3C-like ("main") protease inhibitor is a

123 potent antiviral *in vitro*, but it has been associated with high-profile viral and symptom
124 rebounds (10), although there is uncertainty whether viral rebound is more common with
125 nirmatrelvir than other antivirals (11). Significant dysgeusia is common with ritonavir-boosted
126 nirmatrelvir. Concomitant administration of ritonavir is required to “boost” nirmatrelvir levels,
127 and thereby increase exposure. Ritonavir is contraindicated in many patients because of drug-
128 drug interactions.

129 Although widely purchased by governments and promoted in the private sector, molnupiravir
130 and nirmatrelvir have not been compared directly or compared with other COVID-19
131 therapeutics. As a result, current use largely depends on availability, cost, estimates of effect
132 from pre-registration studies conducted earlier in the pandemic, and perceptions regarding
133 potential drawbacks (i.e. tolerability, viral rebound versus mutant creation).

134 Clinical outcomes depend on the clinical and immune status of the study population and the
135 virulence of the virus. COVID-19 has become substantially milder, although severe infections
136 still occur particularly in high-risk groups. But the increasing rarity of deterioration requiring
137 hospitalisation and death mean that prohibitively large comparative studies are needed to
138 detect clinically important differences. We present a randomised controlled platform trial
139 assessment of the *in vivo* antiviral activities of molnupiravir and ritonavir-boosted nirmatrelvir
140 in adults with early symptomatic COVID-19.

141 **Methods**

142 PLATCOV is an ongoing phase 2 open label, multi-centre, randomised, controlled adaptive
143 pharmacometric platform trial currently running in Thailand, Brazil, Pakistan and Lao PDR

(ClinicalTrials.gov: NCT05041907) (12). The trial provides a standardised quantitative comparative method for *in vivo* assessment of potential antiviral treatments in low-risk adults with early symptomatic COVID-19. Potential antiviral treatments enter the randomised trial when they become available and leave when pre-specified endpoints are reached. The primary outcome measure is the viral clearance rate estimated under a linear model fitted to the \log_{10} oropharyngeal viral densities over the first 7 days following randomisation (12, 13). This component of the trial was conducted in the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. After a detailed explanation of study procedures and requirements all patients provided fully informed written consent. PLATCOV is coordinated and monitored by the Mahidol Oxford Tropical Medicine Research Unit (MORU) in Bangkok. The trial was overseen by a trial steering committee (TSC), was conducted according to Good Clinical Practice principles and approved by the local IRB/EC, and its results were reviewed regularly by a data and safety monitoring board (DSMB). The ongoing platform trial is registered at ClinicalTrials.gov (NCT05041907).

Randomisation and interventions

All study drugs were stored under appropriate conditions. Block randomisation was performed for each site via a centralised web-app designed by MORU software engineers using RShiny®, hosted on a MORU webserver. At enrolment, after obtaining fully informed consent and entering the patient details, the app provided the study drug allocation. The “no study drug” arm comprised a minimum proportion of 20% of patients at all times, with uniform randomisation ratios applied across the active treatment arms. All patients received standard symptomatic treatment. The platform trial began recruitment on 30 September 2021. The

166 initial drugs studied were ivermectin, favipiravir, remdesivir and the casirivimab/imdevimab
167 monoclonal antibody cocktail. All these arms have now stopped having reached the
168 prespecified endpoints for efficacy or lack of efficacy. Additional arms (molnupiravir, ritonavir-
169 boosted nirmatrelvir, fluoxetine, and the tixagevimab/cilgavimab monoclonal antibodies) were
170 introduced subsequently. The analysis reported here includes only patients from Thailand
171 enrolled between the 6 June 2022 and the 23 February 2023 (as the test drugs were unavailable
172 at the other study sites). Molnupiravir (Lagevrio™: Merck, Sharpe & Dohme), and ritonavir-
173 boosted nirmatrelvir (Paxlovid™: Pfizer) were given in standard doses (appendix page 9).
174 Molnupiravir 800mg was given twice a day for five days; nirmatrelvir 300mg with 100mg
175 ritonavir was given twice a day for five days. Both medicines were provided through the
176 Thailand Ministry of Public Health. During this period, patients were also randomised to
177 casirivimab/imdevimab (until 20 October 2022), tixagevimab/cilgavimab (ongoing), favipiravir
178 (until 30 October 2022), and fluoxetine (ongoing). The ivermectin and remdesivir treatment
179 arms had already stopped (for lack of efficacy and for efficacy respectively) (12, 14).

180 *Participants and procedures*

181 Previously healthy adults aged between 18 and 50 years were eligible for enrolment in the trial
182 if they understood the procedures and requirements of the study and were able to give fully
183 informed consent for full participation in the study, reported symptoms of COVID-19 for less
184 than 4 days (<96hrs), were SARS-CoV-2 positive, as defined either as a nasal lateral flow antigen
185 test which became positive within two minutes (STANDARD™ Q COVID-19 Ag Test, SD
186 Biosensor, Suwon-si, Korea), or a positive PCR test with a cycle threshold value (Ct) <25 (all viral
187 gene targets) within the previous 24hrs (both ensure the majority of recruited patients have

188 high viral loads), had oxygen saturation $\geq 96\%$ measured by pulse oximetry at the time of
189 screening, were unimpeded in activities of daily living, and agreed to adhere to all procedures,
190 including availability and contact information for follow-up visits. Exclusion criteria included
191 taking any concomitant medications or drugs, chronic illness or condition requiring long-term
192 treatment or other significant comorbidity, laboratory abnormalities discovered at screening
193 (haemoglobin $< 8\text{g/dL}$, platelet count $< 50,000/\text{uL}$, abnormal liver function tests, $\text{eGFR} < 70\text{ mls/}$
194 $\text{min}/1.73\text{m}^2$), pregnancy (a urinary pregnancy test was performed in females), or actively trying
195 to become pregnant, lactation, or contraindication or known hypersensitivity to any of the
196 proposed therapeutics, currently participating in a COVID-19 therapeutic or vaccine trial or
197 evidence of pneumonia (although imaging was not required).

198 Pre-screening occurred in the hospital's Acute Respiratory Infection (ARI) unit. Potentially
199 eligible participants were selected by the ARI Nurses to be contacted by the study team and
200 were screened. Enrolled patients were admitted to the study ward or managed as outpatients,
201 as per patient preference (none of the admissions were for clinical reasons, but for ease of
202 adherence with the study procedures, or for self-isolation reasons). All treatments were directly
203 observed. After randomisation and baseline procedures (appendix page 7) oropharyngeal
204 swabs (two swabs from each tonsil) were taken as follows. A flocked swab (Thermo Fisher
205 MicroTest™ and later COPAN FLOQSwabs®) was rotated against the tonsil through 360° four
206 times and placed in Thermo Fisher M4RT™ viral transport medium (3mL). Swabs were
207 transferred at $4-8^\circ\text{C}$, aliquoted, and then frozen at -80°C within 48hrs. Separate swabs from
208 each tonsil were taken once daily from day 0 to day 7, day 10 and on day 14. Each swab was
209 processed and tested separately. Vital signs were recorded three times daily by the patient

210 (initial vital signs on the first day were recorded by the study team), and symptoms and any
211 adverse effects were recorded daily.

212 The TaqCheck™ SARS-CoV-2 Fast PCR Assay (Applied Biosystems®, Thermo Fisher Scientific,
213 Waltham, Massachusetts) quantitated viral loads (RNA copies per mL). The laboratory team was
214 blinded to treatment allocation and the clinical investigators were blinded to the virology
215 results until the study arm was terminated. This multiplexed real-time PCR method detects the
216 SARS-CoV-2 N and S genes, and human RNase P gene in a single reaction. RNase P was used in
217 the linear model to adjust for variation in sample human cell content (see Statistical Analysis
218 Plan [SAP]). Viral loads were quantified against ATCC® heat-inactivated SARS-CoV-2 (VR-
219 1986HK™ strain 2019-nCoV/USA-WA1/2020) standards. Whole genome sequencing was
220 performed to identify viral variants and allocate genotypes (appendix pages 15-16). Adverse
221 events were graded according to the Common Terminology Criteria for Adverse Events v.5.0
222 (CTCAE). Summaries were generated if the adverse event was \geq grade 3 and was new, or had
223 increased in intensity. Serious adverse events were recorded separately and reported to the
224 DSMB.

225 *Outcome measures and statistical analysis*

226 The primary outcome measure was the rate of viral clearance. This was expressed as a slope
227 coefficient and estimated under a Bayesian hierarchical linear model (random effect terms for
228 the individual patient slope and intercept) (12). The model was fitted to the daily \log_{10} viral load
229 measurements between days 0 and 7 (18 measurements per patient), using weakly informative
230 priors and treating non-detectable viral loads (CT value=40) as left-censored (appendix pages
231 22-24) (13). The treatment effect was defined as the multiplicative change (%) in the viral

clearance rate, either relative to the no study drug arm (when determining if an intervention had an antiviral effect), or relative to the positive control arm (nirmatrelvir) (13). The viral clearance rate (i.e. slope coefficient from the model fit) can also be expressed as a clearance half-life ($t_{1/2} = \log_{10} 0.5/\text{slope}$). A 50% increase in clearance rate equals a 33% reduction in clearance half-life. All cause hospitalisation for clinical deterioration (until day 28) was a secondary endpoint. For each studied intervention the sample size was adaptive based on prespecified futility and success stopping rules (appendix pages 25-26). Time to resolution of fever and time to resolution of symptoms were assessed using survival methods as the data were right-censored at the last visit. Patients are defined as febrile at baseline if at least one axillary temperature measurement within 24 hours of randomisation was $\geq 37.5^{\circ}\text{C}$. Resolution of fever was defined as an axillary temperature $\leq 37.0^{\circ}\text{C}$ for at least 24 hours. Resolution of symptoms is defined as no reported symptoms. Comparison of times to resolution of fever and resolution of symptoms between different treatment arms used the log-rank test. Viral rebound was defined as a mean daily oropharyngeal viral load which had declined to <100 genomes per mL for ≥ 2 consecutive days, followed by a viral load >1000 genomes per mL at any timepoint thereafter. Comparison of proportions was done using the Fisher exact test.

New interventions entering the platform trial go through two consecutive comparisons. Initially, all interim analyses compare the new intervention against the no study drug arm. The intervention is “dropped” for futility when there is >0.9 probability that the acceleration in viral clearance is $<20\%$ (this threshold was increased from 12.5% in January 2023, SAP version 3.0). If the new intervention reaches the success threshold (i.e. probability >0.9 of acceleration in viral clearance $>20\%$ relative to no study drug), it is then compared with the positive control. This

254 comparison terminates when the intervention is shown to be inferior, non-inferior, or superior
255 to the positive control arm using a 10% non-inferiority margin. If the intervention is superior, it
256 then replaces the positive control arm (Figure S3 appendix page 26). The non-inferiority
257 component of the trial was added to the SAP in January 2023 (version 3.0). All stopping
258 decisions are made using data from contemporaneously randomised patients only. Apart from
259 the trial statistician (JAW), the clinical investigators were all blinded to the qPCR results, and the
260 laboratory was blinded to the treatment allocations.

261 All analyses were done in a modified intention-to-treat (mITT) population, comprising patients
262 who had >2 days follow-up data. A sensitivity analysis was performed using a non-linear model
263 fitted to the serial viral densities, which allows for an initial increase followed by a log-linear
264 decrease (exact specification is given in the appendix pages 22-24). All models included the
265 virus variant (main lineages as given in Table 1) as a covariate for the slope and intercept
266 (Figure S4, S5 appendix pages 27-28). Model fits were compared using approximate leave-one-
267 out comparison as implemented in the package *loo*. All data analysis was done in R version
268 4.0.2. Posterior distributions were approximated using Hamiltonian Monte Carlo in *stan* via the
269 *rstan* interface (15). 4000 iterations were run over 4 independent chains with 2000 iterations
270 for burn-in. Convergence was assessed visually from the trace plots (Figure S9 appendix page
271 32) and using the R-hat statistic (a value <1.1 considered acceptable convergence) (16).
272 Goodness of fit was assessed by plotting the residuals over time and comparing the daily
273 median model predictions with the observed values (Figure S10 appendix page 33). All point
274 estimates are given with 95% credible intervals (CI), defined by the 2.5% and the 97.5%

275 quantiles of the posterior distribution. All code and data are openly accessible via a GitHub
276 repository:

277 <https://github.com/jwatowatson/PLATCOV-Molnupiravir>

278 *Role of the funding source*

279 The funder of the study had no role in study design, data collection, data analysis, data
280 interpretation, or writing of the report. The corresponding author had full access to all the data
281 in the study and had final responsibility for the decision to submit for publication.

282 **Results**

283 The molnupiravir and nirmatrelvir arms started enrolment on 6 June 2022 when both drugs
284 became available in Thailand. Initially, the pre-specified interim analyses compared each drug
285 individually to the concurrent no study drug arm. By the 5th interim analysis (22 August 2022,
286 using data from 12 patients randomised to ritonavir-boosted nirmatrelvir and 20 concurrent
287 controls) nirmatrelvir had met the stopping rule for success (probability >0.9 that viral
288 clearance was increased by >12.5%). As a result, nirmatrelvir remained in the platform trial but
289 then became the positive control. Molnupiravir met the stopping rule for success at the 6th
290 interim analysis (19 October 2022; 28 patients had been randomised to molnupiravir with 37
291 concurrent controls). Molnupiravir stayed in the trial, but then entered into a non-inferiority
292 comparison with nirmatrelvir (Figure S3 appendix page 26). Molnupiravir was removed from
293 the platform when the pre-specified inferiority margin was crossed (23 February 2023; 7th
294 interim analysis) indicating that molnupiravir was inferior to nirmatrelvir by at least 10%. By
295 then 59 patients had been randomised to nirmatrelvir, 65 to molnupiravir, and 85 to no study

296 drug. Two patients were excluded from the analyses because they withdrew from the study on
297 day 0 (Figure 1), resulting in a mITT population of 207. No patients developed severe disease or
298 were hospitalised. There were no significant differences in fever clearance across the three
299 intervention arms (although power was low as only a third of patients had fever at baseline;
300 Figure S6 appendix page 29). Time to symptom resolution was faster in the molnupiravir and
301 nirmatrelvir groups compared to the no study drug arm ($p=0.01$; Figure S7 appendix page 30).

302 *Virological responses*

303 In the mITT population there were 3,704 qPCR viral density measurements (a median of 18 viral
304 load estimates per patient over 8 days) of which 2,977 [80%] were above the lower limit of
305 quantification). The median baseline oropharyngeal sample viral density was $10^{5.5}$ SARS-CoV-2
306 genomes/ml (range: $10^{1.4}$ to $10^{8.3}$). Both drugs accelerated viral clearance compared with no
307 treatment. Compared to patients receiving no study drug, by day 4 the median viral densities
308 were 10-fold lower in the molnupiravir arm and 100-fold lower in the nirmatrelvir arm (Figure 2
309 panel a). Under a linear model fitted to all viral load data up to day 7, relative to the no study
310 drug arm the rates of viral clearance were 37% (95% CI: 16 to 65%) faster with molnupiravir and
311 84% (95% CI: 54 to 119%) faster with nirmatrelvir. In the non-inferiority comparison, viral
312 clearance was 25% (95% CI: 10 to 38%) slower with molnupiravir than nirmatrelvir; probability
313 less than the non-inferiority margin of 10%: 0.98. The non-linear model gave near identical
314 results (Figure 2b).

315 Median estimated viral clearance half-lives under the linear model were 8.5 hours (interquartile
316 range: IQR: 6.7 to 10.1) with nirmatrelvir; 11.6 hours (IQR: 8.6 to 15.4) with molnupiravir; and
317 15.5 hours (IQR: 11.9 to 21.2) in the contemporaneous no study drug arm. I.e. median virus

clearance half-life was nearly halved by nirmatrelvir and reduced by one third by molnupiravir (Figure 3).

Viral rebound

In an exploratory analysis of viral rebound, there was a higher proportion of rebound in the nirmatrelvir arm (6/58: 10%) compared with the no study drug (1/84: 1%, $p=0.02$) or the molnupiravir arms (1/65: 2%, $p=0.05$). Of these patients, 3/8 reported evidence of symptom rebound, all in the nirmatrelvir arm.

Adverse effects

The oropharyngeal swabbing procedure and all treatments were well-tolerated. Patients receiving ritonavir-boosted nirmatrelvir commonly complained of dysgeusia but none discontinued treatment as a result. There were no treatment related serious adverse events (Table 1 and table S1 appendix pages 11-13).

Individual patient data meta-analysis

To compare antiviral effects of all the unblinded small molecule drugs tested in the PLATCOV platform trial, we performed an individual patient data meta-analysis using patients recruited to the same centre in Thailand. This comprised recipients of ivermectin (12), remdesivir (14), favipiravir (17), molnupiravir, nirmatrelvir, or no study drug (fluoxetine remains blinded). The analysis population comprised 447 patients randomised between 30 September 2021 and 7 February 2023 with a total of 8,032 qPCR measurements (86% above the lower limit of quantification). As the interventions were not randomised concurrently, and thus temporal confounding is expected, the analysis adjusted both for calendar time (by adding a covariate on

the slope and intercept) and for virus lineage. The no study drug arm spanned the entire study period. Under the linear model the two interventions reported previously to have no clinical antiviral effect, ivermectin and favipiravir (12, 17), had very similar virus clearance rates to the no study drug arm (Figure 5). Remdesivir, previously reported to have a moderate effect on viral clearance (14), was estimated to increase viral clearance relative to no study drug by 33% (95% CI: 9 to 59). In comparison, molnupiravir was estimated to increase viral clearance by 37% (95% CI: 16 to 61%), with a probability of superiority compared to remdesivir of 0.61 (i.e. very similar treatment effects). In the overall comparison, nirmatrelvir accelerated viral clearance relative to no study drug by 88% (95% CI: 59 to 123%, probability of superiority compared to remdesivir = 1). Symptom clearance is shown in Figure S8 appendix page 31.

Whole genome sequencing of serial viral samples

61 samples (1-6 per individual) taken on day 7 or later, from 31 individuals with persistent oropharyngeal swab Ct values <35, were sequenced successfully. Three received nirmatrelvir, nine molnupiravir, and 18 no study drug. All baseline isolates were also sequenced. An increased number of single nucleotide polymorphisms (SNPs) relative to baseline was found in 3 of the 9 molnupiravir \geq day 7 isolates and none in the nirmatrelvir or no study drug samples (Figure S2A appendix page 19).

Among these three isolates, there were three branches containing 10 or more SNPs. A previously identified mutational signature associated with molnupiravir is characterised by excess transition mutations which are mainly C to T and G to A mutations (9). All the SNPs identified on these branches were transitions, with C to T and G to A being the dominant mutations (Figure S2B appendix page 19). In one case the consensus genome at day 7 had 19

361 extra mutations compared to day 0. In another, two separate consensus genomes with excess
362 mutations were observed; at day 7 with 16 mutations and day 14 with 29 mutations (Figure S2C
363 and S2D appendix page 19).

364 A search of publicly available genome databases did not find any evidence of onward
365 transmission of these strains. Using public datasets on predicted fitness effects of amino acid
366 mutations there were a small number of mutations with elevated predicted fitness, but all
367 three strains scored lower than the parent day 0 strain (Table S2 appendix page 17-18).

368 **Discussion**

369 The main indication for oral antiviral treatment in COVID-19 is prevention of disease
370 progression (1, 4, 5, 18). As with other potentially serious infections, the earlier in the course of
371 disease that effective antiviral drugs are given, the greater is the clinical benefit (19). Several
372 different antiviral medicines have proved effective in COVID-19 but there have been no direct
373 comparisons between them. It has become increasingly difficult to conduct the large clinical
374 trials with clinical endpoints in COVID-19 that have been used to inform treatment policies. The
375 low rates of hospitalisation and death, and the imprecision of clinical and laboratory measures
376 of recovery have resulted in the failure of large outpatient-based studies to reach their
377 prespecified endpoints. Acceleration of SARS-CoV-2 clearance correlates with prevention of
378 hospitalisation and death (1, 4, 5, 18), and it provides an efficient pharmacodynamic measure of
379 comparative antiviral efficacy. Compared with trials with clinical endpoints, the
380 pharmacometric approach used here requires two orders of magnitude fewer enrolled patients
381 to provide comparative assessments, and it delivers results rapidly in real time.

382 This first comparative *in vivo* pharmacodynamic assessment of COVID-19 antiviral treatments
383 confirms that both molnupiravir and nirmatrelvir accelerate viral clearance in early COVID-19.
384 This supports the results of previous clinical trials and studies with sparse viral sampling. The
385 antiviral effect of nirmatrelvir was substantially greater than that of molnupiravir. This
386 corresponds approximately with the differences in clinical benefits reported in earlier
387 randomised and observational studies (3, 4, 5, 20). It suggests that inhibiting the main viral
388 protease provides the most potent inhibition of viral replication in COVID-19. Other main
389 protease inhibitors, which do not require pharmacokinetic boosting by ritonavir, are in
390 pharmaceutical development (21, 22). The meta-analysis of this platform trial indicated that the
391 molnupiravir effect was very similar to parenteral remdesivir, although this comparison is less
392 robust as the two drugs were not compared contemporaneously (14).

393 A mutational signature associated with molnupiravir treated SARS-CoV-2 viruses has been
394 identified previously in the AGILE CST-2 clinical trial (23), and sequence branches suggestive of
395 this signature have been seen in global surveillance samples (9). We show that viral genomes
396 with this signature can be isolated from patients treated with molnupiravir, and are present in
397 patients at allele frequencies high enough to be detected by the consensus sequences seen in
398 global surveillance. Despite the decreased viral load resulting from molnupiravir treatment, a
399 few individuals did maintain oropharyngeal viral loads high enough to perform whole genome
400 sequencing at later timepoints. The highly mutated sequences were detectable for up to 9 days
401 after stopping treatment. However, no evidence of onward transmission of any of these
402 variants could be found in the publicly available databases, and the predicted fitness effects of
403 these mutations were deleterious overall.

404 Despite characterising comparative antiviral efficacy satisfactorily with small patient numbers,
405 this study has several limitations. It is a single-centre study. Population differences in immune
406 status and pharmacokinetics may affect therapeutic responses. We intentionally evaluated the
407 interventions in low-risk adults with high viral burdens in order to optimise the comparative
408 assessment of the different drugs, and not in high-risk patients or the elderly who are at
409 greatest risk of disease progression. Protection against severe disease could not be assessed in
410 this study as no-one was hospitalised, and while the rates of symptom resolution and viral
411 clearance were correlated, only one third of patients were febrile initially, so correlates of fever
412 clearance were not established reliably. Viral rebound was noted although the study was not
413 designed to characterise this fully. The analysis population was described as a modified ITT,
414 which excluded randomised patients who provided insufficient data for analysis of viral
415 clearance (only two were excluded). This could in theory introduce bias by selecting on a post-
416 randomisation event, however the primary endpoint was virological (and blinded to the
417 investigators), so this is highly unlikely.

418 The considerable intra-individual variability in nasopharyngeal (or oropharyngeal) viral loads
419 results in a low signal-to-noise ratio. Frequent sampling over five to seven days is therefore
420 required to measure clearance rates. Oropharyngeal sampling is well-tolerated, whereas
421 frequent nasopharyngeal sampling is not. This simple approach allows pharmacometric
422 characterisation and comparison of antivirals with patient numbers usually of between 30 and
423 100 per arm (12, 13). It is readily conducted anywhere where accurate qPCR viral quantitation
424 can be performed. Pharmacometric assessment can also be used to characterise dose-response
425 relationships, thereby informing dosing and therapeutic practice in real time. Regulatory

426 authority and treatment guideline decisions should be based primarily upon *in vivo* evidence
427 and should consider viral clearance as a surrogate for clinical antiviral activity.

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442 *Author's contributions*

443 WHKS- funding acquisition, investigation, methodology, project administration, supervision,
444 validation and writing- original draft. PJ- investigation, methodology, project administration,
445 supervision, validation and writing- original draft. PJ and WHKS contributed equally. JAW-
446 conceptualisation, data curation, formal analysis, funding acquisition, methodology,

447 visualisation and writing- original draft. SB- investigation, methodology, project administration,
448 writing- original draft. VL, TS, TN- Investigation, methodology, supervision. EMB- data curation,
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450 administration. TN- data curation, software, supervision. WM, JK, KS, WP, NP- investigation,
451 methodology. PH, BH, KP, VC- investigation, supervision. MP, AS, BL- resources. WRJT-
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453 AMD, MMT, WP, WP- methodology, investigation, resources, supervision. NPJD- funding
454 acquisition, methodology, investigation, resources, supervision. NJW- conceptualisation,
455 funding acquisition, methodology, supervision, validation and writing- original draft.

456 All Authors were involved in writing- review & editing.

457 JAW, WHKS, EMB, TN, MI and NJW have directly accessed and verified the underlying data
458 reported in the manuscript.

459 *Data sharing statement*

460 All code and de-identified participant data required for replication of the study's endpoints are
461 openly accessible via GitHub, as well as the study protocol and statistical analysis plan, from
462 publication date onwards: <https://github.com/jwatowatson/PLATCOV-Molnupiravir>. Individual
463 Patient Data can be requested and may be shared according to the terms defined in the MORU
464 data sharing policy with other researchers to use in the future from the date of publication.
465 Further information on how to apply is found here: [https://www.tropmedres.ac/units/moru-](https://www.tropmedres.ac/units/moru-bangkok/bioethics-engagement/data-sharing)
466 [bangkok/bioethics-engagement/data-sharing](https://www.tropmedres.ac/units/moru-bangkok/bioethics-engagement/data-sharing).

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523 95.

524

525

| Baseline characteristics in mITT population and safety information in ITT population | | | | |
|--|----------------------------------|---------|------------------------|-------------------------|
| | Nirmatrelvir/ritonavir (n=58) | | Molnupiravir (n=65) | No Study Drug (n=84) |
| Age (years) | 29 (26-35) | | 30 (26-36) | 29 (24-36) |
| BMI (kg/m ²) | 22.5 (21.0-24.5) | | 22.3 (20.3-25.8) | 22.5 (20.0-25.4) |
| Oropharyngeal viral load (log ₁₀ copies per mL) | 5.4 (4.7-6.3) | | 5.8 (5.0-6.4) | 5.6 (4.7-6.3) |
| Male sex (%) | 23 (40) | | 28 (43) | 27 (32) |
| SARS-CoV-2 variant (N, %) | | | | |
| BA.2 | 1 (2) | | 5 (8) | 10 (12) |
| BA.5 | 25 (43) | | 28 (43) | 37 (44) |
| BA.4 | 3 (5) | | 2 (3) | 2 (2) |
| BA.2.75 | 27 (47) | | 27 (42) | 33 (39) |
| BQ.1 | 1 (2) | | 0 (0) | 1 (1) |
| XBB | 1 (2) | | 3 (5) | 1 (1) |
| Duration of symptoms (days) | 2 (2-2) | | 2 (2-2) | 2 (1-3) |
| Any vaccine received | 58 (100) | | 64 (99) | 84 (100) |
| Number of mRNA vaccine doses N (%) | 0 | 7 (12) | 9 (14) | 7 (8) |
| | 1 | 25 (43) | 27 (42) | 26 (31) |
| | 2 | 22 (38) | 23 (36) | 43 (51) |
| | 3 | 4 (7) | 6 (9) | 8 (10) |
| Any adverse event (grade ≥ 3) | | 0 | 0 | 0 |
| Serious adverse event reported | | 0 | 0 | 0 |

526

527 **Table 1:** Baseline patient characteristics in the mITT population, and safety information in the
528 ITT population. For continuous variables we show the median (interquartile range); for
529 categorical variables we show the number (%).

530

531 **Figure 1:** Study CONSORT diagram for the molnupiravir versus nirmatrelvir versus no study drug
532 analysis. *Pre-screening occurred in the hospital's Acute Respiratory Infection (ARI) unit.
533 Potentially eligible participants were selected by the ARI Nurses to be contacted by the study
534 team, therefore, a high proportion of those assessed for eligibility participated in the study.
535 **SARS CoV-2 Antigen Test Kit (STANDARD Q COVID-19 Ag Test, SD Biosensor, Suwon-si,
536 Republic of Korea). mITT, modified intention-to-treat.

537

538 **Figure 2:** SARS-CoV-2 oropharyngeal viral clearance following no study drug, molnupiravir, and
539 nirmatrelvir. The left panel shows the median viral loads over time in the three
540 contemporaneous randomised arms (individual data points shown as circles). The right panel
541 shows the estimated treatment effects relative to nirmatrelvir under the linear and non-linear
542 models (the grey zone shows the inferiority zone relative to nirmatrelvir).

543

544 **Figure 3:** Individual patient estimated virus clearance half-lives grouped by treatment arm
545 (point estimates and 80% credible intervals are shown for legibility). The vertical dashed lines
546 show the median half-lives in each group.

547

548 **Figure 4:** Exploratory analysis of viral rebound. Individual oropharyngeal viral load profiles in
549 patients who had a viral rebound under the pre-specified definition (viral load <100 genomes/ml
550 for \geq two consecutive days, followed by a viral load >1000 genomes/ml at any later timepoint).

551

552 **Figure 5:** Meta-analysis of oropharyngeal viral clearance in 447 patients enrolled in the same
553 site in Thailand (not all concurrently). Left panel: daily median oropharyngeal viral loads by
554 treatment group; right panel: estimated treatment effect on viral clearance rate relative to no
555 study drug under a model adjusting for study epoch and virus variant.