Antiviral efficacy of oral ensitrelvir versus oral ritonavir-boosted nirmatrelvir in COVID-19 (PLATCOV): an open-label, phase 2, randomised, controlled, adaptive trial

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Summary

Background Ensitrelvir is an oral antiviral treatment for COVID-19 with the same molecular target (the main protease) as ritonavir-boosted nirmatrelvir—the current oral first-line treatment. We aimed to compare the clinical antiviral effects of the two drugs.

Methods In an open-label, phase 2, randomised, controlled, adaptive pharmacometric platform trial, low-risk adult outpatients aged 18–60 years with early symptomatic COVID-19 (<4 days of symptoms) were recruited from hospital acute respiratory infection clinics in Thailand and Laos. Patients were randomly assigned in blocks (block sizes depended on the number of interventions available) to one of eight treatment groups, including oral ensitrelvir and oral ritonavir-boosted nirmatrelvir at standard doses, both given for 5 days, and no study drug. The primary endpoint was the oropharyngeal SARS-CoV-2 viral clearance rate assessed between day 0 and day 5 in the modified intention-to-treat population (defined as patients with at least 2 days of follow-up). Patients had four oropharyngeal swabs taken on day 0 and two swabs taken daily from days 1 to 7, then on days 10 and 14. Viral clearance rates were derived under a Bayesian hierarchical linear model fitted to $\log_{10}$ viral densities in standardised paired oropharyngeal swab eluates taken daily over the 5 days (14 samples). An individual patient data meta-analysis of all small molecule drugs evaluated in this platform trial using published results was also performed, adjusting for temporal trends in viral clearance. This trial is registered at ClinicalTrials.gov, NCT05041907.

Findings Between March 17, 2023, and April 21, 2024, 604 of 903 patients enrolled were concurrently assigned to the three treatment groups (ensitrelvir n=202; ritonavir-boosted nirmatrelvir n=207; no study drug n=195). Median estimated SARS-CoV-2 clearance half-lives were 5·9 h (IQR 4·0–8·6) with ensitrelvir, 5·2 h (3·8–6·6) with nirmatrelvir, and 11·6 h (8·1–14·5) with no study drug. Viral clearance following ensitrelvir was 82% faster (95% credible interval 61–104) than no study drug and 16% slower (5–25) than ritonavir-boosted nirmatrelvir. In the meta-analysis of all unblinded small molecule drugs evaluated in the platform trial, nirmatrelvir and ensitrelvir had the largest antiviral effects (1157 patients). Viral rebound occurred in 15 (7%) of 207 patients in the nirmatrelvir group and 10 (5%) of 202 in the ensitrelvir group (p=0·45).

Interpretation Both ensitrelvir and nirmatrelvir accelerate oropharyngeal SARS-CoV-2 viral clearance. Ensitrelvir is an effective alternative to currently available antivirals in treating COVID-19. Although COVID-19 is now generally a mild disease, it still causes substantial morbidity, particularly in vulnerable groups, and new variants or other coronaviruses could still emerge with pandemic potential. Safe effective and affordable antivirals are needed, and these are best assessed initially in pharmacometric platform trials assessing viral clearance.

Funding Wellcome Trust through the COVID-19 Therapeutics Accelerator.

Introduction

COVID-19 remains prevalent throughout the world. Although it has become an increasingly mild illness for most people as population immunity has increased and viral virulence has decreased, COVID-19 still causes substantial morbidity in immunocompromised and older patients. Two effective oral antiviral drugs (ritonavir-boosted nirmatrelvir and molnupiravir) are currently available. Ritonavir-boosted nirmatrelvir is the more potent, but it is expensive, commonly causes troubling dysgeusia (bad taste), is associated with a long list of potential drug–drug interactions, and there are concerns over symptomatic viral rebound after stopping the medication. Additionally, there is little availability

Lancet Infect Dis 2026; 26: 139–47

Published Online October 10, 2025 https://doi.org/10.1016/S1473-3099(25)00482-7

This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on December 17, 2025

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for clinical studies published in English between Jan 1, 2020, and April 10, 2025, using the terms "randomised" AND ["nirmatrelvir OR paxlovid"] AND "ensitrelvir". Both ritonavir-boosted nirmatrelvir and ensitrelvir have shown in-vivo antiviral activity and clinical benefit, but we identified no direct randomised head-to-head comparisons. Comparisons between the preregistration studies are confounded by substantial differences in the study populations and timing of the studies.

Added value of this study

Comparison of antiviral drug efficacy in COVID-19 using clinical endpoints is difficult. So-called hard endpoints, such as hospitalisation or death, require prohibitively large sample sizes because of their rarity, and classification of more frequently encountered milder symptoms is imprecise. By contrast, this pharmacometric approach provides a quantitative measure of antiviral effects in patients in clinical trials with tractable sample sizes. This randomised study provides the first direct comparison of the in-vivo antiviral effects of ritonavir-boosted nirmatrelvir and ensitrelvir. Both drugs accelerate SARS-CoV-2 viral clearance. An individual patient data meta-analysis of all drugs included in the study confirms these drugs have the most potent anti-SARS-CoV-2 antiviral effects.

Implications of all the available evidence

Both ritonavir-boosted nirmatrelvir and ensitrelvir have potent in-vivo antiviral activity in patients with early COVID-19. Ensitrelvir can be considered an efficacious and well-tolerated alternative to available antivirals. Candidate antivirals and antiviral combinations for respiratory virus diseases (including COVID-19 and Influenza) should be assessed and compared using this pharmacometric method.

outside high-income settings.[1] Molnupiravir is associated with fewer side-effects but is less potent,[2] so most countries have not adopted it in their guidelines. There are also concerns that molnupiravir might generate more pathogenic or drug-resistant mutant viruses.[2–4] These perceived drawbacks, costs, and a lack of available alternatives have limited the use of oral antiviral drugs in COVID-19.

Ensitrelvir, like nirmatrelvir, is a 3C-like SARS-CoV-2 main protease inhibitor, with the potential advantages of increased stability and slower elimination.[5] It can be given once daily (nirmatrelvir requires twice daily dosing) and does not require ritonavir boosting. Ensitrelvir is registered in Japan and Singapore and has been given to more than 1 million people, but it has not been compared directly with other antiviral drugs. The increasing rarity of hospitalisation and death in COVID-19, in marked contrast to 5 years ago, means that prohibitively large comparative studies in high-risk groups are now needed to detect clinically important differences between antiviral drugs. Given that acceleration in viral clearance reflects clinical benefit in COVID-19,[6–8] we present the results of a head-to-head randomised controlled platform trial comparing the in-vivo antiviral activities of ensitrelvir versus ritonavir-boosted nirmatrelvir on the basis of viral clearance in adults with early symptomatic COVID-19.

Methods

Study design and participants

PLATCOV is an ongoing phase 2 open label, multicentre, randomised, controlled, adaptive, pharmacometric platform trial running in Thailand, Brazil, Nepal, and Laos.[9] The trial provides a standardised quantitative comparative method for the in-vivo assessment of potential antiviral treatments in low-risk adults with early symptomatic COVID-19. Full details of the trial procedures have been published previously.[2,9,10,12] Potential antiviral treatments enter the trial when they become available and leave when prespecified endpoints are reached. The platform trial began recruitment on Sept 30, 2021. The initial drugs studied were ivermectin, favipiravir, remdesivir and the casivirimab–imdevimab monoclonal antibody cocktail.[9–12] All these groups reached the prespecified endpoints for efficacy or lack of efficacy and have now stopped. Additional groups were subsequently introduced (molnupiravir, ritonavir-boosted nirmatrelvir, fluoxetine, tixagevimab–cilgavimab monoclonal antibody cocktail, the combination treatment of molnupiravir plus ritonavir-boosted nirmatrelvir, and hydroxychloroquine).[2,13] The evaluation of ensitrelvir was conducted in the Hospital for Tropical Diseases (Bangkok, Thailand) and Mahosot Hospital (Vientiane, Laos).

Previously healthy adults aged between 18 years and 60 years were eligible for trial enrolment if they understood the study procedures and requirements and gave fully informed consent for participation, reported symptoms of COVID-19 for less than 4 days (to ensure high viral loads on admission), were SARS-CoV-2 positive (defined as a nasal lateral flow antigen test [STANDARD Q COVID-19 Ag Test; SD Biosensor, Suwon-si, Korea] positive within 2 min or a positive PCR test with a cycle threshold value <25 [all viral gene targets] within the previous 24 h), had oxygen saturation of at least 96% measured by pulse oximetry, were unimpeded in activities of daily living, and agreed to adhere to all procedures, including availability and contact information for follow-up visits. Exclusion criteria included taking any concomitant medications or drugs, chronic illness or condition requiring long-term treatment or other significant comorbidity, laboratory abnormalities discovered at screening (haemoglobin

<8 g/dL, platelet count <50 000 per µL, abnormal liver function tests, eGFR <70 mL/min per 1·73 m², pregnancy (a urinary pregnancy test was performed in women), or actively trying to become pregnant, lactation, or contraindication or known hypersensitivity to any of the proposed therapeutics, currently participating in a COVID-19 therapeutic or vaccine trial or evidence of pneumonia (although imaging was not required). 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, Thailand. The trial was overseen by a trial steering committee and was conducted according to Good Clinical Practice principles. The trial was approved by local and national research ethics boards in Thailand (Faculty of Tropical Medicine Ethics Committee, Mahidol University; reference TMEC 21-058, approval number MUTM 2021-057-03) and the Central Research Ethics Committee (Bangkok, Thailand; reference CREC048/64BP-MED34), in Laos by the National Ethics Committee for Health Research (submission identification 2022.48) and the Federal Drug Administration (13066/FDD_12Dec2022) and by the Oxford University Tropical Research Ethics Committee (Oxford, UK; reference 24-21). Results were reviewed regularly by an independent data and safety monitoring board, comprised of a statistician, clinicians, and a lay member.

This ongoing platform trial is registered with ClinicalTrials.gov, NCT05041907.

Randomisation and masking

Randomisation was generated separately for each site using block sizes of four times the number of interventions available, with additional randomisation (fuzziness) applied to one allocation per block to reduce predictability. For randomisation, we used a centralised web-app designed by MORU software engineers using RShiny and 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 group comprised a minimum proportion of 20% of patients at all times, with uniform randomisation ratios applied across the active treatment groups at each site. The ensitrelvir comparative analysis included only patients from Thailand and Laos enrolled between the March 17, 2023, and April 21, 2024, because the test drugs were unavailable at the other study sites). During this period, patients were also randomly assigned to tixagevimab–cilgavimab, fluoxetine, hydroxychloroquine, ritonavir-boosted nirmatrelvir plus molnupiravir, and nitazoxanide. Apart from the trial statisticians (JAW, PW), the clinical investigators were all blinded to the qPCR results, and the laboratory personnel were blinded to the treatment allocations.

Procedures

Enrolled patients were admitted to the study ward or managed as outpatients, as per patient preference (none of the admissions were for clinical reasons, but for ease of adherence with the study procedures, or for self-isolation). All patients received standard symptomatic treatment (ie, paracetamol). Oral ensitrelvir (Xocova; Shionogi, Osaka, Japan) and ritonavir-boosted nirmatrelvir (Paxlovid; Pfizer, New York, NY, USA) were given in standard doses. A loading dose of 375 mg ensitrelvir (three tablets) was given on the first day and 125 mg (one tablet) was given daily for the next 4 days. Nirmatrelvir 300 mg with 100 mg ritonavir (separate tablets) was given twice daily for 5 days.

All treatments were directly observed or video recorded. After randomisation and baseline procedures (appendix p 8), oropharyngeal swabs (two swabs from each tonsil) were taken as follows. A flocked swab (FLOQSwabs; COPAN, Brescia, Italy) was rotated against the tonsil through 360° four times and placed in COPAN URT viral transport medium (3 mL). Swabs were transferred at 4–8°C, aliquoted, and then frozen at –80°C within 48 h. Separate swabs from each tonsil were taken once daily from day 0 to day 5 (14 samples), then on days 6, 7, 10, and day 14 (total 22 per patient). Each swab was processed and tested separately. Vital signs were recorded three times daily by the patient (initial vital signs on the first day were recorded by the study team), and symptoms and any adverse effects were recorded daily.

The TaqCheck SARS-CoV-2 Fast PCR Assay (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA) quantitated viral loads (expressed as RNA copies per mL). This multiplexed real-time PCR method detects the SARS-CoV-2 N and S genes, and human RNase P gene in a single reaction. RNase P was used in the linear model to adjust for variation in sample human cell content (see statistical analysis plan; appendix p 11). Viral loads were quantified against heat-inactivated SARS-CoV-2 standards (VR-1986HK strain 2019-nCoV/USA-WA1/2020; ATCC, Manassas, VA, USA). The laboratory team was blinded to treatment allocation and the clinical investigators were blinded to the virology results until the comparative study was terminated. Whole-genome sequencing was done to identify viral variants and allocate genotypes (appendix p 14). Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0. Summaries were generated if the adverse event was grade 3 or more and was new or had increased in intensity. Serious adverse events were defined as adverse events that resulted in death, were life threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or consisted of a congenital anomaly or birth defect, and were recorded separately and reported to the data and safety monitoring board.

Outcomes

The primary outcome was the oropharyngeal viral clearance rate measured between day 0 and day 5. Originally, the trial evaluated viral clearance over 7 days, but the marked shortening of natural viral clearance in recent years has meant that evaluation over a shorter period now has greater discriminative value.[14] The change from 7 days to 5 days of evaluation occurred on March 5, 2024, on the basis of unblinded data from other treatment groups not including the blinded ensitrelvir group.[14] Viral clearance was expressed as a slope coefficient and estimated under a Bayesian hierarchical linear model with random effect terms for the individual patient slope and intercept.[9] The model was fitted to the daily $\log_{10}$ viral load measurements between days 0 and 5 (14 measurements per patient), using weakly informative priors and treating non-detectable viral loads (cycle threshold value ≥40) as left-censored (appendix p 11).[15] The treatment effect was defined as the multiplicative change (%) in the viral clearance rate, relative to the no study drug arm or to the positive control arm.[15] The viral clearance rate (ie, slope coefficient from the model fit) can also be expressed as a clearance half-life ($t_{1/2}=\log_{10} 0{\cdot}5 \div$ slope). Thus, a 50% increase in viral clearance rate was equal to a 33% reduction in clearance half-life.

Secondary outcomes were all cause hospitalisation for clinical deterioration (until day 28), time to fever clearance up to day 7, time to symptom resolution up to day 7, and viral rebound. Patients were defined as febrile at baseline if at least one axillary temperature measurement within 24 h of randomisation was 37·5°C or more. Resolution of fever was defined as an axillary temperature of 37·0°C or less for at least 24 h. Resolution of symptoms was defined as no reported symptoms. Viral rebound was defined as a mean daily oropharyngeal eluate viral load of less than 100 genomes per mL for at least 2 consecutive days that then rose to more than 1000 genomes per mL at any time thereafter.

Statistical analysis

All analyses were done in a modified intention-to-treat population, comprising patients who had >2 days follow-up data. A sensitivity analysis was performed using a non-linear model fitted to the serial viral densities, which allows for an initial increase in densities followed by a log-linear decrease (exact specification is given in the appendix pages 11). All models included site and calendar time as a covariate for the slope and intercept.

Times to resolution of fever and symptoms were assessed using survival methods, using the R survival package (version 3.5–7), because the data were right-censored at the last visit, and described using restricted mean survival time over 7 days. The restricted mean survival time of a treatment group was calculated as the area under the survival curve from randomisation to 7 days, representing the average duration that patients in the treatment group remained febrile or symptomatic (95% CIs were calculated as ±1·96-times the standard error). Comparisons between different treatment groups used the log-rank test, while the relative change in the rate of time to fever or symptom resolution was estimated from the Cox proportional hazards model. Proportions were compared using Pearson's χ^2 test. For each studied intervention in the PLATCOV trial the sample size was adaptive based on prespecified futility and success stopping rules (appendix p 13).

The comparison with the positive control (ritonavir-boosted nirmatrelvir) terminated when the intervention was shown to be inferior, non-inferior, or superior to the positive control group using a 10% non-inferiority margin (appendix p 13). If a stopping rule was not met after 200 patients had been enrolled and evaluated, the group was stopped anyway. All stopping decisions were prespecified and made using data from contemporaneously randomised patients only.

To compare the antiviral effects of all the unblinded small molecule drugs tested in the PLATCOV platform trial, we did an individual patient data meta-analysis using patients recruited in Thailand and Laos. The meta-analysis comprised recipients of ivermectin,[2] remdesivir,[10] favipiravir,[12] fluoxetine,[16] molnupiravir,[2] nirmatrelvir,[2] ensitrelvir, or no study drug (hydroxychloroquine, nitazoxanide, molnupiravir plus ritonavir-boosted nirmatrelvir remained blinded). Because the interventions were not randomised concurrently, and temporal confounding is expected, the analysis was adjusted for calendar time (appendix p 26).[14] The no study drug group spanned the entire study period. For the meta-analysis of all small molecule antiviral interventions in the study we included random effects on the slope term by time period, breaking the whole study period into 10 bins with approximately equal numbers of patients in each time period. Adjustment for calendar time allowed adjustment for temporal trends confounding the comparison of interventions which were not assessed concurrently.

Posterior distributions were approximated using Hamiltonian Monte Carlo in stan through the rstan interface. 4000 iterations were run over four independent chains with 2000 iterations for burn-in. Convergence was assessed visually from the trace plots (appendix p 21) using the R-hat statistic (a value <1·1 was considered acceptable convergence). Goodness of fit was assessed by plotting the residuals over time and comparing the daily median model predictions with the observed values (appendix p 20). Model fits were compared using approximate leave-one-out comparison as implemented in the loo package. All point estimates are given with 95% credible intervals (CrIs), defined by the 2·5% and the 97·5% quantiles of the posterior distribution. All data analysis was done in R version 4.3.2. All code and data are openly accessible through a GitHub repository.

For the **GitHub repository** see https://github.com/jwatowatson/PLATCOV-Ensitrelvir

Role of the funding source
The funder of the study and the pharmaceutical companies had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The ensitrelvir group started enrolment on March 17, 2023. By that time ritonavir-boosted nirmatrelvir had become the positive control and no study drug remained the negative control of the PLATCOV trial. Initially, the prespecified interim analyses compared ensitrelvir to the concurrent no study drug group to assess antiviral efficacy. The first interim analysis, using data from 27 of 56 patients assigned to ensitrelvir and 29 concurrent negative controls, showed that ensitrelvir had met the criteria for efficacy (probability >0·9 of >20% increase in viral clearance). Therefore, without interruption, ensitrelvir then entered a non-inferiority assessment with the positive control ritonavir-boosted nirmatrelvir. On April 21, 2024, the prespecified maximum number of participants had been recruited and evaluated, although inferiority and non-inferiority thresholds had not been met. By then 202 of 604 patients had been assigned concurrently to ensitrelvir, 207 to ritonavir-boosted nirmatrelvir, and 195 to no study drug. 15 of 604 patients were excluded from the analyses because of non-adherence to study procedures before day 2 (6 of 15) or undetectable viral loads at all timepoints (9 of 15), resulting in a modified intention-to-treat population of 589 being included into the non-inferiority assessment and subsequent analyses (figure 1). 577 (98%) of these 589 patients were from Thailand, and 12 (2%) were from Laos (table). 545 (93%) had received at least one COVID-19 vaccine dose. The mean interval from symptom onset to randomisation was 1·8 days (SD 0·8) and the geometric mean baseline viral density in oropharyngeal eluates was 5·1 $\log_{10}$ genomes per mL (SD 1·4). The baseline viral loads in the ensitrelvir arm were slightly lower (0·3 $\log_{10}$ genomes per mL) than in the ritonavir-boosted nirmatrelvir and no study drug groups. There were no major protocol deviations. Minor protocol non-compliances included one drug administration error, issues relating to the redistribution of signed consent forms, missing questions in the day 120 long-COVID questionnaire and an incomplete delegation log (appendix p 28).

Both ensitrelvir and ritonavir-boosted nirmatrelvir accelerated viral clearance. By day 3 the median viral densities were 2·9-fold lower in the ensitrelvir group and 2·4-fold lower in the ritonavir-boosted nirmatrelvir group compared with patients receiving no study drug (figure 2). Under a linear model fitted to all viral load data up to day 5, the rates of viral clearance relative to the no study drug group were 82% faster (95% CrI 61–104) with ensitrelvir and 116% faster (91–142) with nirmatrelvir (appendix p 23). The median estimated viral clearance half-lives under the linear model were

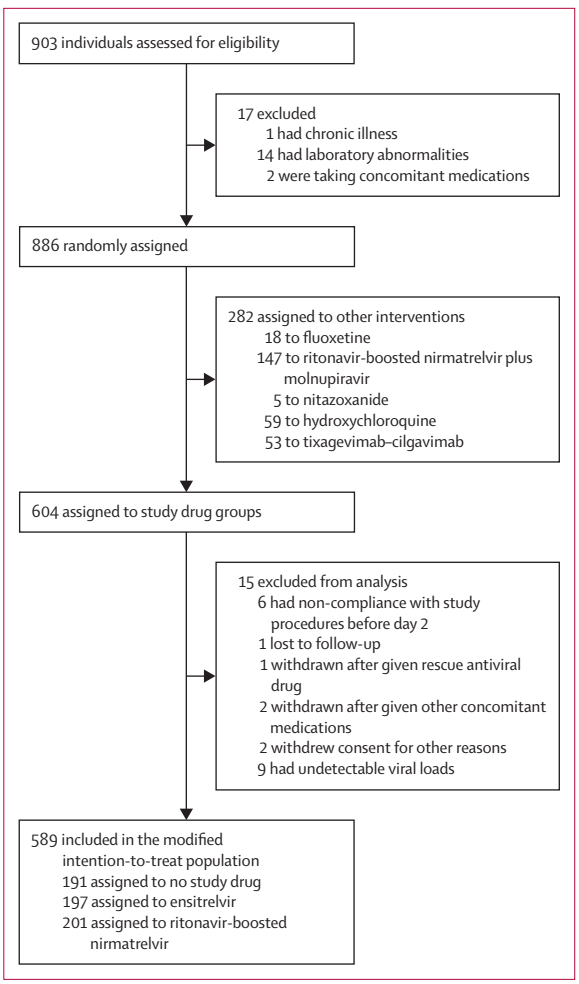


Figure 1: **Study profile**

	Ritonavir-boosted nirmatrelvir group (n=201)	Ensitrelvir group (n=197)	No study drug group (n=191)
Study site			
Laos	4 (2%)	4 (2%)	4 (2%)
Thailand	197 (98%)	193 (98%)	187 (98%)
Sex			
Male	53 (26%)	61 (31%)	58 (30%)
Female	148 (74%)	136 (69%)	133 (70%)
Median age, years (IQR)	31 (26–39)	31 (26–39)	33 (27–42)
BMI, kg/m²	23·3 (4·7)	23·3 (4·7)	24·0 (4·2)
Weight, kg	61·8 (14·5)	62·5 (15·8)	63·9 (13·1)
Symptom duration, days	1·8 (0·8)	1·8 (0·9)	1·8 (0·9)
Baseline viral densities, $\log_{10}$ genomes per mL	5·2 (1·4)	4·9 (1·4)	5·2 (1·4)
Vaccinated	188 (94%)	177 (90%)	180 (94%)

Data are n (%) or mean (SD), unless otherwise specified.

Table: **Baseline patient characteristics**

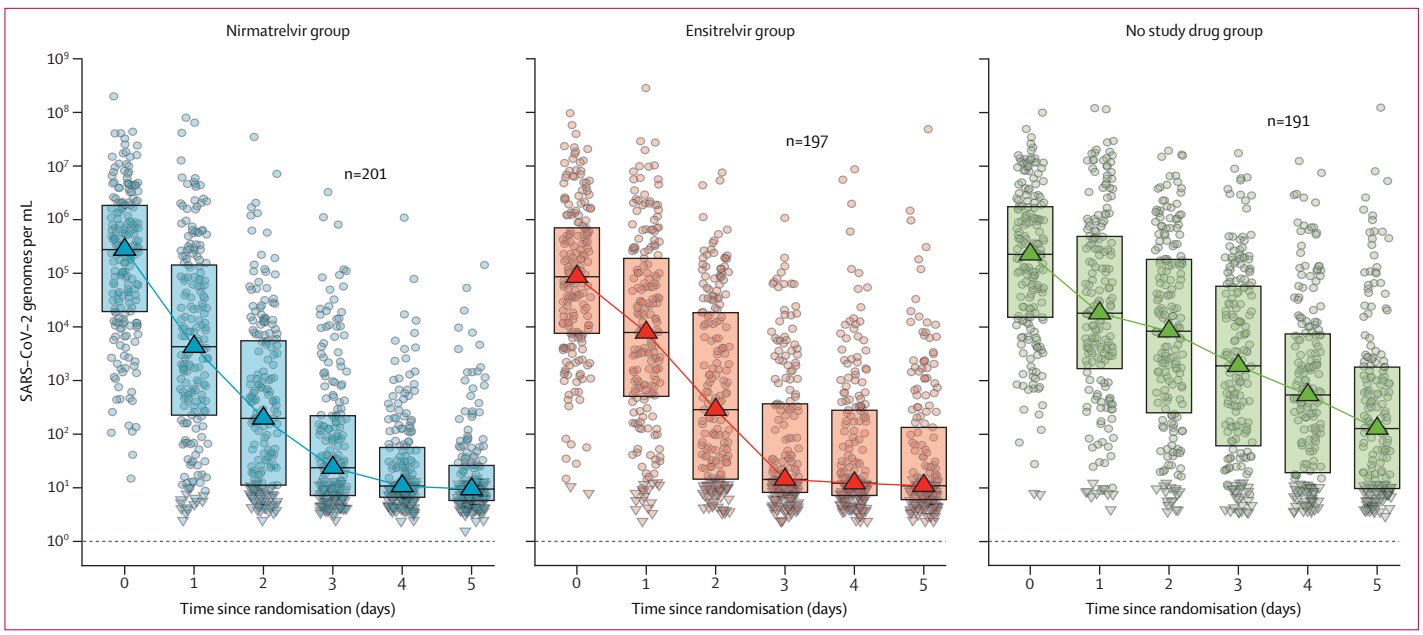


Figure 2: **Viral density dynamics**
SARS-CoV-2 oropharyngeal median viral loads over time in the three contemporaneous randomised groups. Observed individual data points shown as circles and censored individual data points as inverted triangles. Boxplots indicate median and IQR.

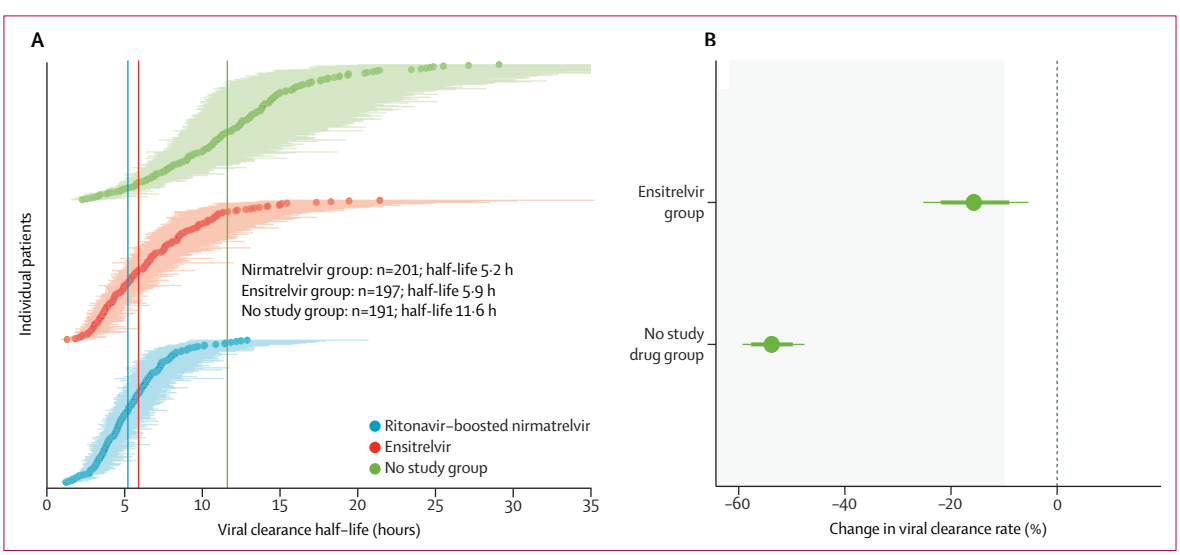
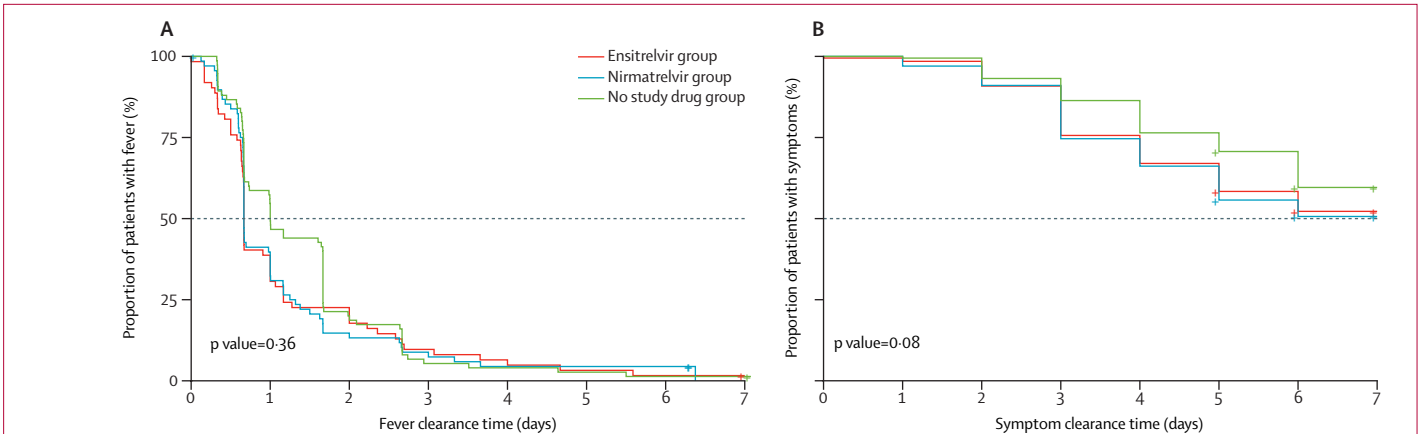


Figure 3: **Viral clearance rates**
(A) Individual patient estimated virus clearance half-lives grouped by treatment group. Point estimates and 80% credible intervals are shown. The vertical lines show the median half-lives in each group. (B) The estimated treatment effects relative to ritonavir-boosted nirmatrelvir under the linear model. The grey zone shows the inferiority zone relative to nirmatrelvir. Thick and thin error bars indicate the 80% and thick error bars the 95% credible intervals.

5·2 h (IQR 3·8–6·6) with nirmatrelvir, 5·9 h (4·0–8·6) with ensitrelvir, and 11·6 h (8·1–14·5) in the contemporaneous no study drug group (figure 3A). In the non-inferiority comparison, viral clearance was 16% slower (95% CrI 5–25) with ensitrelvir relative to nirmatrelvir (0·86 probability less than the non-inferiority margin of 10%; figure 3B). Sensitivity analyses showed that the non-linear model gave slightly smaller treatment effects and that, for both models, incorporation of the prespecified covariates made no difference (appendix p 22).

No patients developed severe disease, although seven patients were admitted to hospital (2 of 197 in the ensitrelvir group, 3 of 201 in the nirmatrelvir group, and 2 of 191 in the no study drug group). Two patients reported fatigue related to COVID-19 (1 in the nirmatrelvir group and 1 in the no study drug group), and one had a likely drug-interaction (nirmatrelvir



Number at risk (censored)																
Ensitrelvir group	62 (0)	24 (0)	14 (0)	6 (0)	4 (0)	2 (0)	1 (0)	1 (1)	197 (0)	196 (0)	194 (0)	179 (0)	149 (0)	132(1)	114 (7)	96 (103)
Nirmatrelvir group	69 (1)	27 (1)	10 (1)	6 (1)	3 (1)	3 (1)	3 (1)	0 (3)	201	201 (0)	195 (0)	183 (0)	150 (0)	133 (2)	110 (6)	96 (102)
No study drug group	75 (0)	41 (0)	15 (0)	4 (0)	3 (0)	2 (0)	1 (0)	1 (0)	191 (0)	191 (0)	190 (0)	178 (0)	165 (0)	146 (1)	134 (3)	111 (114)

Figure 4: **Kaplan-Meier curves for fever and symptom resolution**
(A) Time to fever resolution 7 days after randomisation across three treatment groups. (B) Time to symptom resolution 7 days after randomisation across three treatment groups. p values of the log-rank test are indicated.

group). The other hospitalisations were considered to be unrelated to COVID-19 or the study medications (appendix p 22).

The mean durations of fever were 1·4 days (95% CI 1·2–1·7) in the no study drug group, and 1·2 days (0·9–1·6) in both the ensitrelvir and ritonavir-boosted nirmatrelvir groups and did not significantly differ (p=0·36; figure 4A). The restricted mean duration of symptoms over 1 week was 5·4 days (95% CI 5·2–5·7) in the ensitrelvir group, 5·4 days (5·1–5·6) in the ritonavir-boosted nirmatrelvir group, and 5·9 days (5·6–6·1) in the no study drug group. Relative to the no study drug group, symptom resolution was 32% faster (95% CI −3 to 78) in the ensitrelvir group and 38% faster (3 to 86) in the ritonavir-boosted nirmatrelvir group (figure 4B).

Two patients in the ritonavir-boosted nirmatrelvir group discontinued treatment because of interactions with concomitant drugs (figure 1). 52 (26%) of 201 patients in the ritonavir-boosted nirmatrelvir group, two (1%) of 197 in the ensitrelvir group, and one (1%) of 191 in the no study drug group had dysgeusia (experiencing bitter or metallic taste; appendix p 24).

The proportion of patients with viral rebound was similar between groups (15 [7%] of 201 in the nirmatrelvir group, 10 [5%] of 197 in the ensitrelvir group, and 13 [7%] of 191 in the no study drug group; p=0·61; appendix p 25). The median time to viral rebound (exploratory post-hoc analysis) was 9·9 days (IQR 6·8–13·8) for the nirmatrelvir group, 5·9 days (5·0–6·7) for the ensitrelvir group, and 6·9 days (6·0–9·0) for the no study drug group.

The meta-analysis population comprised 1157 patients randomly assigned between Sept 30, 2021, and April 22, 2024, in Thailand and Laos, with 16 171 qPCR measurements (13 180 [82%] were above the lower limit of quantification). Under the linear model the two interventions reported previously to have no clinical antiviral effect, ivermectin and favipiravir,[9,12] had similar virus clearance rates to the no study drug group (figure 5). Remdesivir, previously reported to have a moderate effect on viral clearance,[10] was estimated to increase viral clearance relative to no study drug by 44% (95% CI 16–77). The increase in viral clearance with molnupiravir was estimated to be 60% (95% CrI 34–92), and the increase with fluoxetine was estimated to be 20% (3–39). In the overall comparison, ensitrelvir accelerated viral clearance relative to no study drug by 87% (95% CrI 68–111) and nirmatrelvir by 126% (105–151).

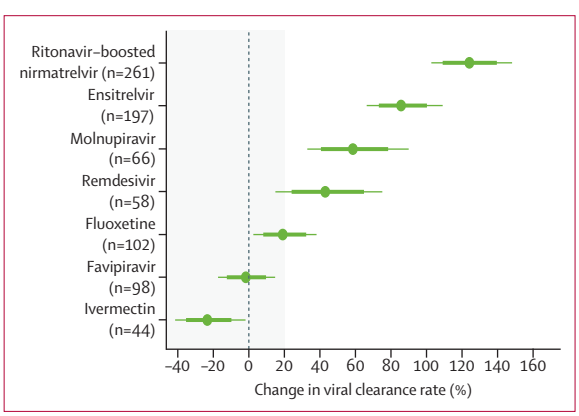


Figure 5: **Estimated treatment effects relative to the no study drug group from the individual patient data meta-analysis under the linear model**
The grey zone shows the futility zone. Thick error bars indicate the 80% and thin error bars the 95% credible intervals.

Discussion

This first comparative in-vivo pharmacodynamic assessment of ensitrelvir and ritonavir-boosted nirmatrelvir confirms that ensitrelvir has potent antiviral activity in treating COVID-19. This effect was slightly less than with ritonavir-boosted nirmatrelvir, although it did not reach the prespecified statistical threshold for non-inferiority. The meta-analysis indicated that ensitrelvir was more potent than all the other antivirals evaluated in this large platform trial, other than ritonavir-boosted nirmatrelvir. Both ritonavir-boosted nirmatrelvir and ensitrelvir resulted in few discontinuations, although more than 25% of the patients who received ritonavir-boosted nirmatrelvir actively complained of dysgeusia. There were no clear differences in clinical responses and, although there were slightly fewer viral rebounds in the ensitrelvir group, the overall number of rebounds under our definition was low.

The main indication for oral antiviral treatment in COVID-19 is to prevent disease progression. Early in the pandemic, when COVID-19 was a major cause of morbidity and mortality in previously healthy people, therapeutic benefit was easily measured by reduction in rates of hospitalisation or death; however, COVID-19 in the general population is now often asymptomatic or results in a self-limiting uncomplicated upper respiratory tract infection. The generally mild nature of the infection makes the comparative evaluation of antiviral drugs difficult using conventional clinical and laboratory measures. Two almost identical studies of ritonavir-boosted nirmatrelvir were conducted 2 years apart (with no appreciable loss of antiviral activity of the drug).[17,18] In the first study,[17] conducted early in the pandemic, there was a clear acceleration in symptom resolution and a life-saving benefit, but the second larger study,[18] conducted when the disease had become milder, struggled to show significant benefit in symptom resolution. Similarly, SCORPIO-SR,[19] a double-blind, randomised, placebo-controlled trial that assigned 1821 patients to ensitrelvir or placebo and was conducted in early 2022 in a predominantly vaccinated population showed a statistically significant reduction in the restricted mean time to sustained resolution of COVID-19, whereas a larger similarly designed study, SCORPIO-HR,[21] which started over a year later did not. As a result, clinical trials assessing disease progression in COVID-19 have all but stopped, because the sample sizes required to show significant differences have become prohibitively large. Although the COVID-19 threat to the general population has receded, this could change if more virulent new SARS-CoV-2 variants or dangerous new coronaviruses emerge and spread. Meanwhile COVID-19 can still be a dangerous illness in frail, older, or immunocompromised patients. These are the patients who may still benefit from effective therapeutics.

Pharmacometric studies assessing rates of viral clearance measure antiviral efficacy in vivo and can be used to compare treatments efficiently with smaller numbers than conventional phase 3 studies.[6–8] They provide a solution to the difficulty in assessing antivirals in COVID-19 clinically and comparing efficacy with those assessed earlier (when the disease was much more severe). Until now, the limited choice of outpatient COVID-19 treatments has been dictated by availability, cost, tolerability, drug interactions, route of administration, and perceived drawbacks and benefits. It is also difficult for new drugs to show comparable benefit to already licensed treatments in clinical trials to satisfy the requirements for regulatory approval. For many governments, health-care workers, and individuals, antivirals for COVID-19 are no longer considered necessary, because the disease is now generally mild and the drawbacks and costs are felt to outweigh the benefits. As a result, symptomatic individuals are often not treated for COVID-19. However, elderly, frail or immuno-compromised patients do sometimes need antiviral treatment and, although the host contribution to viral clearance may be reduced, there is no reason to believe that the antiviral effect of drugs should be lessened in these vulnerable groups. Many of these patients are also receiving other drugs that interact with ritonavir, so they cannot receive nirmatrelvir. Ensitrelvir has potent in-vivo antiviral efficacy, and it has the advantages of a lower pill burden. It does not cause the troubling dysgeusia characteristic of ritonavir-boosted nirmatrelvir. Ensitrelvir does inhibit CYP3A4 (albeit to a lesser extent than ritonavir), which means that many of the same concomitant medications are contraindicated. Because ensitrelvir has the same molecular target and mechanism of action as nirmatrelvir, there is overlap in resistance caused by target mutations, but these are very rare and have not affected treatment efficacy.

Despite the detailed pharmacometric assessment in more than 600 patients, this study has several limitations. We intentionally evaluated the interventions in low-risk adults with high viral burdens to optimise the comparative assessment of the different drugs, and not in high-risk patients or the elderly who are at greatest risk of disease progression or sequelae. Therefore, protection against severe disease could not be assessed in this study, and measures of clinical recovery would require a substantially larger study for confident assessment. Although there is general agreement, on the basis of studies conducted early in the pandemic,[6–8,20] that viral clearance correlates with clinical benefit, there remains a substantial contribution to clinical outcomes of other unrelated factors. Viral rebound was also a relatively rare event in the population studied in this trial. Larger studies would be needed for confident conclusions. We did not assess long-term complications, which are increasingly rare as the disease has become less severe. Therefore, we cannot be confident of the extent to which these potent antiviral effects translate into clinical benefit. This comparison was conducted only in southeast Asia. Population differences in immune status and pharmacokinetics could have affected therapeutic responses, but there is no specific concern and no a-priori reason why these results would not be generalisable.

In summary, ensitrelvir has potent in-vivo antiviral activity and was well tolerated in the treatment of COVID-19. It provides some benefits over other available treatments. Affordable, efficacious, cost-effective, and well tolerated treatments are still needed for COVID-19.

Contributors

WHKS: funding acquisition, investigation, methodology, project administration, supervision, validation, and writing of original draft. PJ: investigation, methodology, project administration, supervision, validation, and writing of original draft. JAW: conceptualisation, data curation, formal analysis, funding acquisition, methodology, visualisation, and writing of original draft. PW: data curation, formal analysis, methodology, visualisation, and writing of original draft. SB, EB, TA, and TS: investigation, methodology, project administration, and writing of original draft. VL, TS, and TN: investigation, methodology, and supervision. EMB: data curation, formal analysis, and visualisation. TJE, KP, SS, VK, NT, and JT: methodology, investigation, and project administration. TN: data curation, software, and supervision. WM, JK, KS, WP, NP, and TP: investigation and methodology. PH, BH, KP, and VC: investigation and supervision. MP, AS, and BL: resources. MYA: methodology and supervision. KC and MI: formal analysis, investigation, resources, and supervision. SP, AMD, MMT, WaP, and WeP: methodology, investigation, resources, and supervision. NPJD: funding acquisition, methodology, investigation, resources, and supervision. NJW: conceptualisation, funding acquisition, methodology, supervision, validation, and writing of original draft. All authors: review of draft, editing, and decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. JAW, PW, WHKS, EMB, TN, MI, and NJW directly accessed and verified the underlying data reported in the manuscript.

Data sharing

All code and de-identified participant data required for replication of the study's endpoints are openly accessible through GitHub, as well as the study protocol and statistical analysis plan, from publication date onwards. Individual patient data can be requested and may be shared with other researchers to use in the future from the date of publication according to the terms defined in the MORU data sharing policy. Further information on how to apply can be found on the MORU website.

Declaration of Interests

We declare no competing interests.

Acknowledgements

We thank all the patients with COVID-19 who volunteered to be part of the study. We thank the data safety and monitoring board (Tim Peto, André Siqueira, and Panisadee Avirutnan); the trial steering committee (Nathalie Strub-Wourgaft, Martin Llewelyn, Deborah Waller, and Attavit Asavisanu); Sompob Saralamba and Tanaphum Wichaita (MORU) for developing the RShiny randomisation app; and Mavuto Mukaka (MORU) for invaluable statistical support. We also thank all the staff of the Clinical Trials Unit at MORU, Thermo Fisher for their excellent support with this project, and all the hospital staff at the Hospital for Tropical Diseases, as well as those involved in sample processing in MORU and the processing and analysis at the Faculty of Tropical Medicine, Mahidol University, molecular genetics laboratory, and the malaria laboratory. We thank Shionogi & Co for the donation of ensitrelvir. We thank the Department of Medical Services, Ministry of Public Health, Thailand for the donation of the ritonavir-boosted nirmatrelvir. We thank the MORU Clinical Trials Support Group for data management, monitoring, and logistics, and the purchasing, administration, and support staff at MORU. This trial was supported by the Wellcome Trust (grant 223195/Z/21/Z) through the COVID-19 Therapeutics Accelerator.

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For the **GitHub repository** see https://github.com/jwatowatson/PLATCOV-Ensitrelvir

For more **details on applying for individual patient data** see https://www.tropmedres.ac/units/moru-bangkok/bioethics-engagement/data-sharing