# Nirmatrelvir/Ritonavir PAXLOVID Orally for Treatment of Unvaccinated COVID-19 Patients with 1+ Risk Factors (The EPIC-HR RCT)[1]

## SUMMARY

**n=2246 unvaccinated, higher risk COVID-19 outpatients, not on supplemental $O_2$, presenting ≤5 days of symptoms**

**Nirmatrelvir/Ritonavir {PAXLOVID} 300mg/100mg PO q12h x5 days** (2 drugs given sequentially in trial) **vs Placebo**

**Primary Endpoint Result:**
**COVID-19 hospitalization or all-cause mortality by day 28:**
**↓RR ~89%; NNT ~17** /28d follow-up

**Adverse events (AE) = 22.6% vs 23.9%**
(Dysgeusia, diarrhea, headache, vomiting more common in the PAXLOVID group)
**Serious AEs (SAE) = 1.6% vs 6.6%**
(SAE more common in placebo group)

**Other: Benefit highly related to the patient being at high enough risk to outweigh potential harms (especially DIs (e.g. 3A4). Safety demonstrated. Concerns also re viral resistance.**

**Bottom line**: Oral nirmatrelvir/ritonavir initiated **within 5 days of symptoms** reduced the risk of hospitalization or death in unvaccinated, symptomatic COVID-19 adult outpatients at high risk for COVID-19 progression to severe disease. Assess for/manage drug interactions.

## TRIAL BACKGROUND {See additional information section at end of trial summary for full inclusion/exclusion criteria}

**DESIGN**: randomized, double-blind (participants, clinicians, outcome assessors; however, **sponsor unblinded throughout**), placebo-controlled trial; concealed allocation; various modified ITT (mITT) approaches used for efficacy endpoints. The trial was conducted between July-Dec, 2021 (Delta variant most prominent.)
- In-person or telemed visit at baseline & day 3; in-person visit day 5; various follow-up visits (in-person or telemed) day 10,14,21,34.

**INTERVENTION**: **nirmatrelvir 300mg + ritonavir 100mg PAXLOVID** po q12h vs matching **placebo** q12h, **x5 days** (initiated **≤5** days symptom onset)

**INCLUSION, select:** COVID-19 confirmed, symptomatic ≤5 days, unvaccinated, non-hospitalized adults at high-risk (≥1 characteristic or condition) for progression to severe COVID-19, e.g. age ≥60, BMI >25, smoker, immunosuppressive disease or meds corticosteroids, biologics, chronic lung, hypertension, CVD, diabetes, CKD.

**EXCLUSION, select:** previous COVID-19, anticipated need for hospitalization within 48hrs, prior receipt of convalescent COVID-19 plasma, renal impairment (eGFR <45mL/min/1.73m$^2$), active liver disease, pregnancy/lactation, HIV (VL: >400 copies/mL), $O_2$ <92% on room air obtained at rest within 24 hours prior to randomization; excluded patients with interacting drugs (CYP3A4 substrates/inducers). {See pg 3 for full criteria.}d

**POPULATION** n=2246; median age = 46 (18-88); ♂ ~51%; global representation but white 72% (45% Hispanic/Latinx); ~66% initiated ≤3 days of symptom onset; viral load median ~5.4 $\log_{10}$ copies/mL. (Estimated risk of hospitalization or death in baseline group was **7%**). **Comorbidities: BMI mean 29.2, smoker 39%, hypertension 33%, diabetes 12%. 61% of patients had 2 or more risk factors.** Baseline demographics: well-balanced groups. Under-representation (<1% of enrolled) of: CKD, immunosuppressive disease, neurodevelopmental disorder, sickle cell disease, HIV.

## RESULTS

**follow-up: ~28 days after initiating tx regimen**

| Outcome | Nirmatrevir/Ritonavir n=697 @ ≤3days n=1039 @ ≤5days | Placebo n=682 @ ≤3days n=1046 @ ≤5days | Difference %; 95% CI NNT or NNH (if statistically significant) | | Comments |
|---|---|---|---|---|---|
| **1°**: Hospitalization (COVID-19) or death (any cause) in those **where tx initiated within 3 days of symptom onset** | 5<br>0.72% | 44<br>6.4 % | -<br>- 5.81%;<br>-7.78 to -3.84<br>**NNT** ~17; 95% CI 13-26 | | Note "n=…" numbers represent number of subjects analyzed who presented within ≤3 or ≤5 days of symptom onset.<br>1°Outcome: ↓RR ~ 89%; p<0.001<br>Individual component h s (both hospitalization and death) were significant as well.<br>All deaths were COVID-19 related (e.g. pneumonia 5, hypoxia 1, ARDS 1, acute resp failure 1)Supp Appx: Table S4. Note: a 13th death occurred in the Placebo group - day 34Ad.<br>Applicability to current context (Omicron strain & vaccinated population), uncertain. |
| - COVID-19 Hospitalization (tx initiated within 3 days … | 5<br>0.72% | 44<br>6.45% | -5.81%<br>**NNT** =17 | | |
| - Death, any cause (tx initiated within 3 days …) | 0<br>0 % | 9<br>1.32% | -1.32%<br>**NNT**=76 | | |
| Hospitalization (COVID-19) or death **in those tx initiated within 5 days symptom onset** | 8<br>0.77% | 66<br>6.31 % | - 5.54%;<br>-7.21 to -4.03<br>**NNT** ~18; 95% CI 14-25 | | |
| - COVID-19 Hosp (tx initiated within 5 days …) | 8<br>0.77% | 65<br>6.21% | -5.44%<br>**NNT**=19 | | |
| - Death, any cause (tx initiated within 5 days …) | 0<br>0% | 12<br>1.15 % | -1.15 %<br>**NNT**=87 | | |
| **Harms – Safety Analysis** | n=1109 | n=1115 | | | |
| Patients with Adverse Events (AE), Tx Emergent | 251<br>22.6% | 266<br>23.9% | - 0.7% | - | Most AE non-serious. AE leading to discontinuation was more common with placebo (2.1% vs 4.2%). {Reports of dysgeusia are common post-RCT.}<br>SAE: more common with placebo. Primarily pneumonia related (none deemed due to treatment) |
| AE – any, related to treatment | 7.8% | 3.8% | 3.9% | **NNH**=26 | |
| - dysgeusia taste disturbance | 5.6% | 0.3% | 5.3% | **NNH**=18 | |
| - diarrhea | 3.1% | 1.6% | 1.5% | **NNH**=66 | |
| Serious Adverse Events (SAE) | 18<br>1.6% | 74<br>6.6% | - 5% | **NNT**=20<br>95% CI 15-30 | |

**Planned interim analysis**: mITT of patients treated ≤3 days since symptom onset: COVID-19 hospitalization or death was reduced 0.77% vs 7.01%. ARR=6.24; RRR=89%.

**Subgroup results of interest**: a) all primary outcome points on the side of benefit;
b) most absolute benefit seen in age ≥ 65yrs though underrepresented, & those with CV disease due to higher baseline risk.

## STRENGTHS, LIMITATIONS, & UNCERTAINTIES

**STRENGTHS:**

- Strong primary outcome that matters; efficacy shown for both components, a) hospitalization and b) all-cause death
- A major concern around COVID-19 is death, and this trial showed a reassuring benefit on all-cause mortality for high-risk patients. It is somewhat unusual to show such an impact on mortality without a large sample size.
- Good size trial, well-designed, adequate follow-up, solid safety analysis
- Day 3 and day 5 data provide insight on impact of treatment timing "window of opportunity"
- Indigenous individuals were included and this subgroup appear to have had similar benefit; global participation; broad applicability

**LIMITATIONS:**

- Trial data represent a window of time where the Delta variant was most prevalent. Are trial findings relevant to current and evolving COVID-19 waves?
  Note: there is some study evidence that nirmatrelvir/ritonavir retains activity against Omicron variant in vitro (it targets an essential protein in all coronaviruses).
- Trial includes and pools patients with various degrees of risk; additional study/analysis helpful to identify who benefits most
- Antivirals are susceptible to resistance and this trial window may not offer a true picture of potential resistance over time, with overuse, or with variant strains (changing rates of severe illness may reduce absolute improvements and possible virus mutations may change with time and impact efficacy)
- Exclusion of patients on interacting drugs is a limitation as many of the 'high risk' patients we want to treat are on an interacting drug. Is the modification/holding of drugs of proven benefit (e.g. an anticoagulant) to start a a drug of unproven benefit in a vaccinated population increasing their risk of an adverse outcome?
- Some populations under-represented (e.g. African-Ancestry who are at higher risk; older patients who would be at higher COVID-19 risk, risk of AEs, and DIs)
- Sponsor had unblinded access to the data during the study
  The sponsor was blinded except for a small, separate, unblinded team interacting with an external data monitoring committee evaluating safety throughout the study. Select sponsor personnel were unblinded following premature study termination due to overwhelming efficacy (see Statistical Analyses section), with the remainder blinded until all patients completed, or discontinued prior to, the Day 34 visit, at which point the study was to continue in an unblinded fashion.

**UNCERTAINTIES**

- Would there be potential for benefit if initiated >5 days post symptom onset?
- Does Paxlovid speed the time of recovery or reduce the odds of long COVID (or other COVID complications)?
- Based on the current context of a milder strain and high levels of vaccination, does the weighing of benefits/risks remain the same?
- Would there be relative benefit over harm in lower risk (e.g. vaccinated, previously infected) patients? (e.g. Should it be given a role in lower-risk patients?)[2]
  {More recent data – **EPIC-SR** – suggests lack of role/benefit in lower/standard risk patients. Pfizer press release: "Due to a very low rate of hospitalization or death observed in the standard-risk patient population, Pfizer has decided to cease enrollment into EPIC-SR. (1° outcome favourable but not stat. significant}"[6]
- How does this treatment option compare to other treatment/antiviral options?
- What is the benefit/safety in those with renal impairment (eGFR <45mL/min) who were excluded from the trial? Would a lower dose be safe/effective?
- Trial studied non-vaccinated. Would it be effective in those who are partially vaccinated, or fully vaccinated but with multiple COVID-19 risk factors?
- In the real world, will safety be compromised given the strong potential for drug-interactions that aren't well managed (especially with CYP3A4 related DIs)?
- How to best assess risk/benefit potential and/or navigate drug interactions for commonly interacting drugs? (e.g. in patients on apixaban where switching to an alternative anticoagulant (dabigatran) might be recommended, but also opens the door for mistakes, and drug related problems)
- FDA data shows relapses can happen; how does the frequency compare to no treatment?[3] Is relapse due to preventing the immune system's full response?

**OBSERVATIONAL STUDY OF INTEREST**[5]

- Observational data from Israel found PAXLOVID to be effective in reducing severe COVID-19 and mortality in real-world, high-risk patients in the era of Omicron. Value was especially seen in older patients. Of note, the study included patients who were vaccinated and excluded patients who had medications that were contraindicated for use with PAXLOVID. The study also noted that vaccine remains the most effective treatment intervention.[5]

**SHARED DECISION MAKING**

- Patients who stand the most to benefit from nirmatrelvir/ritonavir (older, cardiovascular history) will also be more likely to have complicating risk factors (e.g. renal impairment) and multiple medications on their profile (e.g. significant drug interactions). Thus, patients who are reasonable candidates to offer nirmatrelvir/ritonavir may warrant a shared decision making assessment/discussion to identify their values, individual COVID-19 risk, potential for benefit, potential for drug interactions and/or related harms/inconvenience. The value of COVID-19 vaccination in preventing hospitalization and mortality should also be considered. Navigating concomitant drug therapy and potential interactions well will be key to optimizing drug therapy, as will striving for good communication between team members for patient follow-up.

**RXFILES & RELATED LINKS:**

- **Drug Interaction Checker – Resources:**
  1) Liverpool COVID-19 Drug Interactions Checker: https://www.covid19-druginteractions.org/checker
  2) BC COVID Practice Tool 3: HTTP://WWW.BCCDC.CA/HEALTH-PROFESSIONALS-SITE/DOCUMENTS/COVID-TREATMENT/PRACTICETOOL3_DRUGINTERACTIONSCONTRAINDICATIONS.PDF
  3) *LEXICOMP*® DRUG *INTERACTION* DATABASE. LEXI-INTERACT – Available by subscription through Lexi.com, and Up-to-Date. (provides suggestions for management)
- **SK: medSask** Resources for nirmatrelvir/ritonavir (**PAXLOVID**) available at: **A) Health Professional Tools,** and **B) Patient Info**
- **What pharmacists need to know (U of Waterloo)**

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**Abbreviations, select**: DI=drug interaction CI=confidence interval NNH=number needed to harm NNT=number needed to treat RCT=randomized controlled trial RR=relative risk, SAE=serious adverse events. **Ongoing EPIC RCTs**: 1) EPIC-SR (standard risk adults) & 2) EPIC-PREP (Pre-exposure prophylaxis of SARS-CoV-2)

**References**:

[1] Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with COVID-19. *N Engl J Med*. 2022;386(15):1397-1408. doi:10.1056/NEJMoa2118542. Supplementary Appendix available online.

[2] NEJM Journal Watch. https://blogs.jwatch.org/hiv-id-observations/index.php/should-we-prescribe-nirmatrelvir-r-paxlovid-to-low-risk-covid-19-patients/2022/04/12/

[3] NEJM Journal Watch. https://blogs.jwatch.org/hiv-id-observations/index.php/yes-relapses-after-paxlovid-happen-now-what/2022/04/25/

[4] Vangeel L, Chiu W, De Jonghe S, Maes P, Slechten B, Raymenants J, André E, Leyssen P, Neyts J, Jochmans D. Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. Antiviral Res. 2022 Feb;198:105252.

[5] Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients [published online ahead of print, 2022 Jun 2]. Clin Infect Dis. 2022;ciac443. doi:10.1093/cid/ciac443. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciac443/6599020?login=true (Exclusion criteria - contraindicated drugs: ALFUZOSIN, AMIODARONE, APALUTAMIDE, CARBAMAZEPINE, CLOZAPINE, COLCHICINE, DIHYDROERGOTAMINE, DRONEDARONE, ERGOTAMINE, FELCAINIDE, LOVASTATIN, MEPIRIDINE, MIDAZOLAM, PHENOBARBITAL, PHENYTOIN, PIMOZIDE, PIROXICAM, PROPAFENONE, PROPOXYPHENE, QUINIDINE, RIFAMPIN, SILDENAFIL (FOR PAH),SIMVASTATIN,DISOPYRAMIDE, PRIMIDONE ,IVACAFTOR ,EPLERENONE, BOSENTAN, IVABRADINE)

[6] Pfizer Reports Additional Data on PAXLOVID™ Supporting Upcoming New Drug Application Submission to U.S. FDA. Tuesday, June 14, 2022 - 04:30pm. Accessed 30Aug 2022 at HTTPS://WWW.PFIZER.COM/NEWS/PRESS-RELEASE/PRESS-RELEASE-DETAIL/PFIZER-REPORTS-ADDITIONAL-DATA-PAXLOVIDTM-SUPPORTING

**Additional info:**

**Full inclusion criteria (from Protocol):**

Participants are eligible to be included in the study only if all of the following criteria apply:

**Age and Sex:**

1. Participants ≥18 years of age (or the minimum country-specific age of consent if >18) at the time of the Screening Visit.
   - WOCBP may be enrolled.
   - All fertile participants must agree to use a highly effective method of contraception. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.



**Type of Participant and Disease Characteristics:**

2. Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization.

Note: RT-PCR is the preferred method; however, with evolving approaches to confirmation of SARS-CoV-2 infection, other molecular or antigen tests that detect viral RNA or protein are allowed. The test result must be available to confirm eligibility. Participants may be enrolled based on positive results of a rapid SARSCoV-2 antigen test performed at screening.

3. Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization (see Appendix 9 for criteria).
4. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:
   - ≥60 years of age;
   - BMI >25;
   - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes;
   - Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
     - Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry.
     - Has received treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study entry.
     - HIV infection with CD4 cell count <200 mm3 and a viral load less than 400 copies/mL
   - Chronic lung disease (if asthma, requires daily prescribed therapy);
   - Known diagnosis of hypertension;
   - CVD, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass;
   - Type 1 or Type 2 diabetes mellitus;
   - CKD provided the participant does not meet Exclusion Criterion 5;
   - Sickle cell disease;



   - Neurodevelopmental disorders (eg, cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies);
   - Active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period;
   - Medical-related technological dependence (eg, CPAP [not related to COVID-19]).
5. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

**Informed Consent:**

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

**Full exclusion criteria (from Protocol):**

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions:**

1. History of hospitalization for the medical treatment of COVID-19.
2. Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator (see Section 8.1.2.)
3. Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection.
4. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C, or acute liver failure.
5. Receiving dialysis or have known moderate to severe renal impairment [ie, eGFR <45 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula].30
6. Known HIV infection with a viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit) (Appendix 8).



7. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention.
8. Any comorbidity requiring hospitalization and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator.
9. History of hypersensitivity or other contraindication to any of the components of the study intervention, as determined by the investigator.
10. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

**Prior/Concomitant Therapy:**

11. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir (See Appendix 8).
12. Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment (see Appendix 8).
13. Has received or is expected to receive convalescent COVID-19 plasma.
14. Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit.
15. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 therapeutics, through the long-term follow-up visit.

**Prior/Concurrent Clinical Study Experience:**

16. Previous administration with any investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).
17. Known prior participation in this trial or other trial involving PF-07321332.



**Diagnostic Assessments:**

18. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5 X ULN;
    - Total bilirubin ≥2 X ULN (≥3 X ULN for Gilbert's syndrome);
    - Absolute neutrophil count <1000/mm3.
    - GFR <45 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula30

    Note: If the investigator suspects the participant may have any of the above laboratory values, confirmatory tests should be performed at screening to confirm eligibility before the first dose of study intervention. See Appendix 2 for more details.
19. Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomization.

    Note: for a potential participant who regularly receives chronic supplementary oxygen for an underlying lung condition, oxygen saturation should be measured while on their standard home oxygen supplementation.

**Other Exclusions:**

20. Females who are pregnant or breastfeeding.
21. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.