CENTER FOR DRUG EVALUATION AND RESEARCH

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OTHER REVIEW(S)

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Epidemiology: Review of Real-World Evidence on PAXLOVID effectiveness

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Subject:	Review of Real-World Evidence on PAXLOVID effectiveness
Drug Name:	PAXLOVID (nirmatrelvir tablets; ritonavir tablets)
Application Type/Number:	NDA 217188
Applicant/sponsor:	Pfizer
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EXECUTIVE SUMMARY

Pfizer, the applicant, submitted the New Drug Application (NDA) for PAXLOVID **(nirmatrelvir tablets; ritonavir tablets)** in June 2022. The applicant is seeking an indication for COVID-19 treatment among high-risk patient regardless of their vaccination status, similar to the PAXLOVID indication for its Emergency Use Authorization (EUA). The clinical review team considers the clinical trial data submitted for the NDA sufficient to support the benefit of PAXLOVID as COVID-19 treatment in the Omicron era, regardless of vaccination status. The Division of Antivirals requested an assessment of the publicly available literature on observational real-world evidence (RWE) studies to determine whether the RWE contradicts the trial conclusions.

The literature search conducted by Division of Epidemiology II (DEPI II) on January 30, 2023, identified 22 RWE studies that evaluated PAXLOVID effectiveness in outpatient COVID-19 populations. Seventeen of the 22 published studies were excluded from in-depth DEPI II review as they included overlapping study populations with the reviewed RWE studies, were based on insufficient longitudinal data in the data sources and/or were unable to account for potential bias introduced by index time selection. The five remaining studies included in our in-depth review were cohort studies conducted in non-hospitalized COVID-19 patients during the Omicron era. Two studies were based on nation-wide or territory-wide electronic health records (EHR) of hospitals and outpatient clinics in Israel and China (Hong Kong); one study used province-wide integrated health care data from Quebec, Canada; two studies used EHR and administrative claims data from the U.S. Veterans Health Administration and an integrated healthcare system in a single U.S. state. All studies evaluated the risk of COVID-19-related hospitalization, or all-cause hospitalization between PAXLOVID-treated COVID-19 patients and those who were not treated with PAXLOVID.

The reviewed RWE studies consistently reported that PAXLOVID use is associated with a reduction in the risk of worsening COVID-19 outcomes in broader populations than those included in the pivotal trials - with respect to age, underlying “high-risk” comorbidities and COVID-19 vaccination status in Omicron era. However, the information available for the reviewed RWE studies is insufficient to determine their quality.

DEPI II determined that the results of the five reviewed studies did not contradict the findings of those trials. Given the lack of information to determine quality, DEPI II recommended against using the results of the available RWE studies to support or refute effectiveness of PAXLOVID treatment in non-hospitalized COVID-19 patients, especially among specific patient subgroups.

1 INTRODUCTION

This review document Division of Epidemiology II's (DEPI II) assessment of the available real-world evidence (RWE) on the effectiveness of PAXLOVID (nirmatrelvir tablets; ritonavir tablets) to address a specific regulatory question from the Division of Antivirals (DAV), as part of the review of the PAXLOVID application for marketing approval.

1.1 BACKGROUND AND REGULATORY HISTORY

PAXLOVID is co-packaged oral tablets that includes nirmatrelvir, a SARS-CoV-2 main protease (M^{pro}: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. On December 22, 2021, FDA authorized PAXLOVID for emergency use for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients with positive results of direct severe acute respiratory syndrome SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[a]

On June 29, 2022, Pfizer, the applicant, submitted the New Drug Application for PAXLOVID. The applicant sought an indication for COVID-19 treatment among high-risk patient regardless of their vaccination status, similar to the indication for the PAXLOVID Emergency Use Authorization.

The applicant submitted two phase 2/3 placebo-controlled clinical trials-Study C4671005 (EPIC-HR) and study C4671002 (EPIC-SR) to support efficacy of PAXLOVID as COVID-19 treatment. These trials were conducted before the dominant circulating SARS-CoV-2 variant was Omicron.

- Although the completed EPIC-HR pivotal trial on efficacy in high-risk patients excluded vaccinated individuals, the relative risk reduction on COVID-19 related hospitalization or all cause death through Day 28 were similar between seropositive patients[b] versus seronegative patients in EPIC-HR trial (88%, p=0.02 vs. 86%, p=<0.0001).
- Fully vaccinated high-risk patients were eligible to enroll into the ongoing supportive EPIC-SR trial until December 19, 2021, since they are considered at low-risk for severe disease.[c] The submitted interim analyses data (with data cut on December 19, 2021) showed non-significant trend towards reduction in of COVID-19 related hospitalization or all cause death through Day 28 in the vaccinated patients (relative risk reduction= 57%, p=0.2).

[a] EUA Factsheet: https://www fda.gov/media/155050/download

[b] "Seropositive" means that the trial participants had antibodies against SARS-CoV-2 antigens detected in their blood at baseline. Given that EPIC-HR excluded vaccinated patients, and patient with prior infection detected by a molecular test (antigen or nucleic acid), the seropositive patients were those with prior asymptomatic/undetected SARS-CoV-2 infection

[c] EPIC-SR stopped enrolling fully vaccinated "high-risk" patients for ethical reasons after PAXLOVID EUA was authorized in December 2021, since high-risk patient regardless of vaccination status could obtain PAXLOVID under EUA.

The clinical review team considers that together the data submitted from EPIC-HR and EPIC-SR support the benefit of PAXLOVID as COVID-19 treatment in high-risk patients for hospitalization or death, regardless of vaccination status and whether in the Omicron era.

1.2 REGULATORY QUESTION

DAV consulted DEPI II to assess the publicly available literature on observational RWE studies of the use of PAXLOVID in vaccinated patients and/or in the Omicron era to answer the following question:

- Does the evidence from published observational RWE studies **contradict** the conclusion of benefit of PAXLOVID for the treatment of mild to moderate COVID-19 in patients who are at high risk for progression to severe COVID-19, including hospitalization or death, regardless of vaccination status and in the Omicron era?

2 REVIEW METHODS AND MATERIALS

We searched the WHO COVID-19-research database[d] and PubMed, using the search terms "PAXLOVID" and "epidemiology/RWE study" (Details in Appendix). We excluded articles that did not:

- report a study that evaluated PAXLOVID effectiveness.
- report observational studies (e.g., articles reported clinical trials, case reports, case series).
- report findings of analyses on PAXLOVID effectiveness, compared to non-PAXLOVID-treated COVID-19 patients.
- evaluate PAXLOVID effectiveness in an outpatient COVID-19 population.

We further applied the following criteria for selecting studies for in-depth review:

- Studies that fulfilled the following key data sources and design features:
    - **Longitudinal data**: used data source(s) that allows longitudinal capture of the key covariates across different healthcare settings:
        - Diagnosis/test of COVID-19 in an ambulatory setting.
        - Exposure to PAXLOVID as outpatient treatment.
        - Vaccination status prior to COVID-19 diagnosis/PAXLOVID exposure.
        - Clinical outcome (hospitalization or death) after COVID-19 diagnosis/PAXLOVID exposure.
        - Comorbid conditions and concurrent medication use at time of COVID-19 diagnosis/PAXLOVID use.
    - **"Nonuser" reference group**: Included "nonuser" as a reference group, since we do not have trial data to support effectiveness of PAXLOVID against an "active control" (i.e., other potential COVID-19 treatments).
    - **Index time selection**: Applied design feature that can account for the potential bias introduced by "index time" selection for the treated and

[d] https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/

untreated patients, given that PAXLOVID users were COVID-19 patients who remained hospitalization-free and survived from diagnosis to treatment, which can lead to bias in favor of finding PAXLOVID effectiveness.

3 REVIEW RESULTS

Our last literature search was conducted on January 30, 2023. Among the 297 English-language articles identified by our search terms, 22 were observational studies that evaluated PAXLOVID effectiveness in outpatient COVID-19 populations (see Appendix). Of those 22 studies, we excluded,

- three publications[1-3] of shorter study duration that used the same data source as another publication.[e]
- one publication[4] that only evaluated "post-acute sequelae of COVID-19"[f] occurring from 30 to 90 days after SARS-CoV-2 infection. This study was excluded due to the following study design concerns:
    - The validity of code-based algorithms to capture the individual post-acute COVID-19 sequelae were not reported.
    - Important confounders were neither reported nor accounted for in the analyses (e.g., use of medications that could influence the risk of clinical conditions classified as "post-acute COVID-19 sequelae").

We screened the remaining publications and further excluded 13 studies that did not meet all the key data source and design features criteria for "in-depth" review (Table 1)

Table 1 Screening of the identified observational RWE studies on outpatient PAXLOVID effectiveness

		Fulfilled key data source and design features for in-depth review		
	Study screened	**Longitudinal data source**	**"Non-user" reference group**	**Design to handle bias due to "index time selection"**
Excluded	Hedvat et al.[5]	No	Yes	No
	Dryden-Peterson et al.[6]	No	Yes	Yes
	Ganatra et al.[7]	No	Yes	No
	Zhou et al.[8]	No	Yes	Yes
	Aggarwal et al.[9]	No	Yes	No
	Bruno et al.(a)[10]	unclear	No	N/A
	Bruno et al.(b)[11]	unclear	No	N/A
	Gentile et al.[12]	unclear	No	N/A
	Park H et al.[13]	Yes	Yes	No
	Park J et al.[14]	Yes	Yes	No

[e] The publication by Najjar-Debbiny et al. was excluded due to an overlapping Israeli data source with Arbel et al. The publications by Yip et al. and Wai et al. were based on the same territory-wide population in Hong Kong as that by Wong et al.

[f] Post-acute death or hospitalization and individual sequela including ischemic heart disease, dysrhythmia, deep vein thrombosis, pulmonary embolism, fatigue, liver disease, acute kidney injury, muscle pain, diabetes, neurocognitive impairment, shortness of breath and cough.

		Fulfilled key data source and design features for in-depth review		
	Study screened	**Longitudinal data source**	**"Non-user" reference group**	**Design to handle bias due to "index time selection"**
	Qian[15]	No	Yes	No
	Shah et al. [16]	No	Yes	unclear
	Tiseo et al.[17]	unclear	No	N/A
Included	Arbel et al.[18]	Yes	Yes	Yes
	Wong et al.[19]	Yes	Yes	Yes
	Bejama et al.[20]	Yes	Yes	Yes
	Schwartz et al.[21]	Yes	Yes	Yes
	Lewnard et al.[22]	Yes	Yes	Yes

Five studies were reviewed in-depth (Arbel, Wong Bejama, Schwartz and Lewnard). Of note, the publications by Bejama, Schwartz and Lewnard are non-peer-reviewed preprints.[g] We summarized the study designs, data sources and methods in Appendix Table 1.

Briefly, the five reviewed studies were cohort studies involving non-hospitalized patients with positive SARS-CoV-2 RT-PCR or antigen test results during the period of Omicron-variant dominance. One study in Israel and one study in China (Hong Kong) used nation-wide or territory-wide electronic health records of hospitals and outpatient clinics. One study in Quebec, Canada used a province-wide integrated health-care data. The final two studies used electronic health records and administrative claims data; one was based on the U.S. Veterans Health Administration and the other based on an integrated healthcare system of a single U.S. state. These five studies also included broader study populations than those included in the pivotal trials—with respect to age, underlying high-risk comorbidities, and COVID-19 vaccination status.

The five studies evaluated the risk of COVID-19-related hospitalization or all-cause hospitalization in PAXLOVID-treated COVID-19 patients compared to those not treated with PAXLOVID (nonusers). They also evaluated other clinical outcomes, such as mortality or in-hospital COVID-19 progression. The reviewed studies in general reported that PAXLOVID was effective or trended towards effectiveness regardless of COVID-19 vaccination status. (Appendix Table 2 and 3).

4 DISCUSSION

Compared to the studies excluded from in-depth review, the five reviewed RWE studies used more appropriate data sources, study design, or analytical approaches to account for the potential bias introduced by inappropriate handling of index time selection.

However, unlike applicant-sponsored efficacy trials that provide more information to assess study quality, none of the reviewed RWE studies published their protocol and analytical plan prior to the final study report. In at least one study (Lewnard), the analyses and results differed notably between two versions of the preprints. So, it was

[g] The manuscripts have not been peer-reviewed. Non-peer-reviewed preprints might not be accepted for publication by a peer-reviewed journal. If they are formally published in a peer-reviewed journal, there might be revisions of the methods or analyses to address the editor's or reviewers' comments.

difficult to track whether these studies were conducted according to a prespecified protocol and analytical plan. Additionally, patient-level data in the observational studies were unavailable to verify the correct implementation of study design and statistical methods, which is a standard review process for trial data used to support treatment efficacy.

Despite insufficient information on reviewed studies due to what is reported in the public domain, we still identified methodological or analytical issues in the reviewed studies. Some of these issues had reasonably predictable impact on the study findings, while there were other review issues for which we would need more information than was provided to determine the potential impact on the study results. We discuss the review issues in Section 4.1 and 4.2.

4.1 REVIEW ISSUES WITH A REASONABLY PREDICTABLE IMPACT ON STUDY FINDINGS

Residual confounding by COVID-19 severity (All studies)

Three of the reviewed studies did not capture or adjust for baseline COVID-19 severity (Arbel, Wong, and Schwartz). The studies by Bajema and Lewnard accounted for the presence of COVID-19 symptoms at baseline; however, the validity of the operational definitions for COVID-19 symptoms was not reported. Residual confounding due to COVID-19 severity would likely to underestimate of PAXLOVID effectiveness, given that PAXLOVID was more likely to be given to symptomatic patients or patients with severe symptoms.

Residual confounding by "high-risk comorbidities" (Arbel and Wong studies)

Although the Arbel study captured information on medical conditions that increase a patient's risk for COVID-19 progression (high-risk comorbidities), not all were adjusted for in the analyses. The Wong study matched the treated and non-treated patients on a summary comorbidity risk score (i.e., Charlson Comorbidity Index), which did not guarantee the component medical conditions of the risk score would be balanced between treatment groups. Furthermore, the component medical conditions of the Charlson Comorbidity Index were not an exact match to the high-risk comorbidities for worse COVID-19 progression. For example, the Charlson Comorbidity Index does not account for all immunosuppressive diseases (e.g., bone marrow or organ transplantation), prolonged use of immune-weakening medications, chronic lung diseases (except for chronic obstructive pulmonary disease), neurodevelopmental disorders, sickle cell disease. Lastly, the Wong study did not report distribution of high-risk comorbidities for COVID-19 progression to inform if these important confounders were balanced between treatment groups.

Residual confounding due to unbalanced high-risk comorbidities would likely underestimate of PAXLOVID effectiveness, given that PAXLOVID treatment for COVID-19 patients with high-risk comorbidities was likely prioritized.

Outcome selection (Bejama and Lewnard studies)

Studies by Bajema and Lewnard used "all-cause hospitalization or death" as the primary outcome, which included events that are unrelated to PAXLOVID effect (i.e.,

hospitalization or death due to causes other than COVID-19). If the proportion of outcome events unrelated to COVID-19 is nondifferential between treated and nontreated groups, it would bias findings toward null (underestimate of PAXLOVID effectiveness). The proportion of events unrelated to COVID-19 can be higher among PAXLOVID users, given that administration of PAXLOVID is prioritized to patients with comorbidities that may lead to a higher risk of hospitalization or death due to non-COVID-19 causes, which will also lead to underestimate of PAXLOVID effectiveness.

Study power to evaluate PAXLOVID effectiveness in subgroups (All studies)

Only one reviewed study reported a priori power analyses (Bajema et al.). All the reviewed studies were not powered to formally test treatment effect modification by patient characteristics, or to evaluate PAXLOVID effectiveness in any patient subgroup. Some studies suggested that PAXLOVID effectiveness may differ by age, for example, Arbel concluded that "no evidence of benefit was found in patients younger than 65 years of age." The study findings did not support a statistically significant reduction in COVID-19 hospitalization risk (hazard ratio=0.74, 95% CI=0.35 to 1.58) or death (hazard ratio=1.32, 95% CI=0.16 to 10.75) associated with PAXLOVID use among a younger population (40 to 65 years of age). However, it is likely that the study did not have sufficient power to evaluate PAXLOVID effectiveness in the younger population, evidenced by the wide 95% CIs of the effect estimates.

4.2 REVIEW ISSUES THAT REQUIRE MORE INFORMATION TO EVALUATE THE IMPACT ON STUDY RESULTS

Unvalidated outcome measures

COVID-19-Related Hospitalization (Arbel, Wong, and Schwartz Studies)

Three reviewed studies included "hospitalization due to COVID-19" as the endpoint, or part of the endpoints (Arbel, Wong, and Schwartz). However, none of the studies provided data to support the validity of the measure for "COVID-related hospitalization." Without a better understanding of how information on COVID-19 related hospitalization was recorded or derived, it is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

Post-COVID-19 Conditions (Bajema Study)

The Bajema study also evaluated PAXLOVID's effectiveness on multiple potential post-COVID-19 conditions; however, they did not provide data to support the International Classification of Diseases, 10th Edition diagnosis codes that were used to capture these conditions. It is difficult to predict if the outcome misclassification would be differential and how it might influence the study findings.

Residual confounding by other potential confounders

Information on the frequencies and the distribution of the potential confounders (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

Detailed Information on COVID-19 Vaccination (Arbel, Wong, and Lewnard Studies)

Total dose, timing of last dose, type or manufacturer of the COVID-19 vaccine could impact PAXLOVID effectiveness for COVID-19 outcomes. Not all reviewed studies captured or accounted for detailed information on COVID-19 vaccination in their analyses. The Arbel and Wong studies only reported and accounted for vaccination status as dichotomous variables ("presence of prior immunity or not" in Arbel study, "fully vaccinated or not" in the Wong study). The Lewnard study only adjusted for the number of total vaccine doses received in their analyses.

Other Outpatient COVID-19 Medication Use at Baseline (Lewnard Study)

Prior or concurrent use of other outpatient medications for COVID-19 at baseline can be a potential confounder as they can influence COVID-19-related clinical outcomes. The Lewnard study did not exclude patients who used other COVID-19 medications at baseline, while several treatment options were available in the United States during the timeframe of the study. The study also did not report the use of the other outpatient COVID-19 treatment at baseline, nor adjusted for baseline use of these medications in their analyses.

Other Medications Use (Bajema Study)

The Bajema study included analyses of PAXLOVID effectiveness on risk of long-term outcomes (i.e., hospital admission, nursing skilled nursing home facility admission, all-cause death, or post-COVID-19 conditions) that occurred 31 to 180 days after diagnosis. PAXLOVID was prioritized for patients with COVID-19 and certain comorbidities that are also components of the "post-COVID conditions", for example, cardiovascular disease, hypertension, asthma, chronic obstructive pulmonary disease, chronic kidney disease, cerebrovascular disease, diabetes, obesity. The use of other medications, especially those indicated for the components of the post-COVID-19 conditions, are important confounders that were not reported, nor accounted for in the study.

Handling of post-index time COVID-19 treatment

Information on the frequencies and the distribution of post-index time COVID-19 treatment changes (discussed below) by treatment groups is needed to understand the magnitude and direction of potential biases on study findings.

Other Outpatient COVID-19 Medication Use (All Studies)

In the analyses of PAXLOVID's effectiveness on hospitalization, use of other outpatient COVID-19 medications during follow-up could be on the causal pathway between PAXLOVID use and COVID-19 outcome—the need to use another treatment can be an early indication that PAXLOVID did not work well in preventing disease progression. Use of other COVID-19 treatments also have an impact on COVID-19 outcome, independently from PAXLOVID's effectiveness.

Use of other outpatient COVID-19 medications was a censor criterion in the Wong study, but not in the Lewnard or Bajema studies, while the Arbel and Schwartz studies did not clearly state how they handled patients who initiated another outpatient COVID-19 treatment during follow-up. If the use of other outpatient COVID-19 medication is uncommon, these different approaches would likely all be acceptable; however, none of the three reviewed studies reported the extent of other COVID-19 medications used during follow-up.

Inpatient Medical Management (Arbel, Wong, Bajema, and Lewnard Studies)

Four of the reviewed studies (Arbel, Wong, Bajema, and Lewnard) also evaluated outpatient PAXLOVID's impact on in-patient outcomes, such as in-hospital disease progression, invasive mechanical ventilation use, intensive care unit admission and death, or post-acute COVID-19 symptoms. In these analyses, the medical treatment that patients received during hospitalization, such as inpatient COVID-19 treatment, could be in the causal pathway. None of these studies reported information on inpatient medical management during follow-up, nor accounted for its impact in the analyses.

Concern on Statistical Methods

Ambiguous Statistical Methods and Results (Lewnard Study)

The details of the analyses and the results are not clear. Without knowledge of the details, some of the results are difficult to review and interpret. The definition of the discordant pairs in the results tables (Table 2 and Table 3 of the publication) is not clear and the summaries of the discordant pairs do not seem to align with the effectiveness estimates. It is also unclear whether immortal time in treated subjects is handled properly when determining discordant pairs. In addition, about 42% of eligible PAXLOVID-treated patients were not included in the analyses, calling into question the generalizability of the results to that population..

Handling of Immortal Time Bias (Schwartz and Wong Studies)

The Schwartz study assigned random index dates to the unexposed group based on the time-to-dispense distribution from the exposed group. This approach did not consider factors that may impact the dispensing time for each subject (e.g., the presence of symptoms) and may not fully fix the immortal time bias problem.

The primary analyses of the Wong study set the index time at COVID-19 symptom onset or diagnosis, which introduced immortal time in the PAXLOVID-treated group and could overestimate PAXLOVID effectiveness. The investigators conducted post hoc sensitivity analyses that treated exposure status as a "time-varying" variable to account for immortal time bias. The findings of this sensitivity analysis that accounted for immortal time bias consistently support PAXLOVID effectiveness as the primary analyses in the overall study population. It is unclear if the conclusion would be the same for the subgroup analyses stratified by vaccination status, as the author did not report the findings of the sensitivity analyses by patient subgroup.

Handling of Missing Data (All Studies)

All the studies except for the Lewnard study did not report the degree of missing data for important baseline covariates. Most of the studies did not specify a method of handling missing data other than excluding subjects with missing covariates.

4.3 OVERALL ASSESSMENT OF THE AVAILABLE PAXLOVID RWE STUDIES

Seventeen of the twenty-two identified RWE studies reporting effectiveness of outpatient PAXLOVID use were excluded from in-depth review as they included overlapping study populations with the reviewed RWE studies, were based on insufficient longitudinal data in the data sources, and/or were unable to account for potential bias introduced by index time selection. The five remaining studies consistently reported that PAXLOVID use was associated with a reduced risk of worsening COVID-19 outcomes in broader populations than included in the pivotal trials—with respect to age, underlying "high-risk" comorbidities, and COVID-19 vaccination status in the Omicron era.

However, the information available for the reviewed observational studies was insufficient to determine their quality.

5 CONCLUSION

The pivotal trials data showed benefit of PAXLOVID for the treatment of mild to moderate COVID-19 in patients who are at high risk for progression to severe COVID-19, including hospitalization or death, regardless of vaccination status and in the Omicron era. The results of the five published studies reviewed did not contradict the findings of those trials. The findings from these studies alone cannot be used to support or refute effectiveness of PAXLOVID treatment in non-hospitalized COVID-19 patients, especially among specific patient subgroups.

6 RECOMMENDATIONS

Given the lack of information to determine quality, DEPI recommended against using the results of the available RWE studies to support or refute effectiveness of PAXLOVID treatment in non-hospitalized COVID-19 patients, especially among specific patient subgroups.

7 REFERENCES

1. Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients. *Clin infect dis*. 2022/06 2022;doi:10.1093/cid/ciac443 PMC -

2. Wai AK-CCCYCAW-LWKCSC-LLTT-LLLY-FYET-FHJ. Association of Molnupiravir and Nirmatrelvir-Ritonavir with preventable mortality, hospital admissions and related avoidable healthcare system cost among high-risk patients with mild to moderate COVID-19. *The Lancet regional health Western Pacific*. 2022/00 2022;

3. Yip TCF, Lui GCY, Lai MSM, et al. Impact of the use of oral antiviral agents on the risk of hospitalization in community COVID-19 patients. *Clin Infect Dis*. Aug 29 2022;doi:10.1093/cid/ciac687

4. Xie Y, Choi T, Al-Aly Z. Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19 (preprint). 2022.

5. Hedvat J, Lange NW, Salerno DM, et al. COVID-19 therapeutics and outcomes among solid organ transplant recipients during the Omicron BA.1 era. *Am j transplant*. 2022/07 2022;doi:10.1111/ajt.17140 PMC -

6. Dryden-Peterson S, Kim A, Kim AY, et al. Nirmatrelvir plus ritonavir for early COVID-19 and hospitalization in a large US health system. *medRxiv*. Jun 17 2022;doi:10.1101/2022.06.14.22276393

7. Ganatra S, Dani SS, Ahmad J, et al. Oral Nirmatrelvir and Ritonavir in Non-hospitalized Vaccinated Patients with Covid-19. *Clin Infect Dis*. Aug 20 2022;doi:10.1093/cid/ciac673

8. Xiaofeng Z. Real-World Effectiveness of Nirmatrelvir/Ritonavir in Preventing Hospitalization Among Patients With COVID-19 at High Risk for Severe Disease in the United States: A Nationwide Population-Based Cohort Study (preprint). 2022.

9. Aggarwal N, R. , Kyle M, Laurel B, Tellen DB, Nichole C, Adit AG. Real-world Use of Nirmatrelvir-Ritonavir in COVID-19 Outpatients During the Emergence of Omicron Variants BA.2/BA2.12.1. 2022.

10. Bruno G, Giotta M, Perelli S, De Vita G, Bartolomeo N, Buccoliero GB. Early Access to Oral Antivirals in High-Risk Outpatients: Good Weapons to Fight COVID-19. *Viruses*. 2022/11 2022;14(11)doi:10.3390/v14112514

11. Bruno G, Perelli S, Giotta M, Bartolomeo N, De Vita G, Buccoliero GB. Efficacy and safety of oral antivirals in individuals aged 80 years or older with mild-to-moderate COVID-19: preliminary report from an Italian Prescriber Center. *Infezioni in Medicina*. 2022/00 2022;30(4):547-554. doi:10.53854/liim-3004-9

12. Gentile I, Scotto R, Schiano Moriello N, et al. Nirmatrelvir/Ritonavir and Molnupiravir in the Treatment of Mild/Moderate COVID-19: Results of a Real-Life Study. 2022/10 2022;10(10)doi:10.3390/vaccines10101731

13. Park H, Park YJ, Lee HY, et al. The effectiveness of Paxlovid treatment in long-term care facilities in South Korea during the outbreak of the Omicron variant of SARS-CoV-2. *Osong Public Health Res Perspect*. Dec 2022;13(6):443-447. doi:10.24171/j.phrp.2022.0262

14. Park JJ, Lee J, Seo YB, Na SH. Nirmatrelvir/Ritonavir Prescription Rate and Outcomes in Coronavirus Disease 2019: A Single Center Study. *Infect Chemother*. 2022/00 2022;doi:10.3947/ic.2022.0123

15. Qian G, Wang X, Patel NJ, et al. Outcomes with and without outpatient SARS-CoV-2 treatment for patients with COVID-19 and systemic autoimmune rheumatic diseases: A retrospective cohort study. *medRxiv*. Oct 30 2022;doi:10.1101/2022.10.27.22281629

16. Shah MM, Joyce B, Plumb ID, et al. Paxlovid Associated with Decreased Hospitalization Rate Among Adults with COVID-19 - United States, April-September 2022. *MMWR - Morbidity & Mortality Weekly Report*. 2022/00 2022;71(48):1531-1537. doi:10.15585/mmwr.mm7148e2

17. Tiseo G, Barbieri C, Galfo V, et al. Efficacy and Safety of Nirmatrelvir/Ritonavir, Molnupiravir, and Remdesivir in a Real-World Cohort of Outpatients with COVID-19 at High Risk of Progression: The PISA Outpatient Clinic Experience. *Infect Dis Ther*. Jan 2023;12(1):257-271. doi:10.1007/s40121-022-00729-2

18. Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge. *N Engl J Med*. Aug 24 2022;doi:10.1056/NEJMoa2204919

19. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. *The Lancet*. 2022/00 2022;400(10359):1213-1222. doi:10.1016/s0140-6736(22)01586-0

20. Bajema KL, Berry K, Streja E, et al. Effectiveness of COVID-19 treatment with nirmatrelvir-ritonavir or molnupiravir among U.S. Veterans: target trial emulation studies with one-month and six-month outcomes. *medRxiv*. Dec 16 2022;doi:10.1101/2022.12.05.22283134

21. Schwartz K, Wang J, Tadrous M, et al. Real-world effectiveness of nirmatrelvir/ritonavir use for COVID-19: A population-based cohort study in Ontario, Canada (preprint). 2022.

22. Lewnard JA, McLaughlin JM, Malden D, et al. Effectiveness of nirmatrelvir-ritonavir against hospital admission or death: a cohort study in a large US healthcare system. *medRxiv*. Jan 10 2023;doi:10.1101/2022.10.02.22280623

APPENDICES

Search process (Steps and number of articles left)

1. English language article with "PAXLOVID OR nirmatrelvir" AND keywords of "epidemiology or RWE study," excluding animal, cellular, pharmacokinetic/pharmacodynamics, identified 297 articles (search terms are required in Title, Abstract, or Subject)
2. Restrict to studies evaluate PAXLOVID effectiveness 44
3. Exclude duplicate publications 26
4. Exclude study conducted in hospitalized COVID-19 patient 22

Search terms

- Key words for epidemiology or RWE study
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babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR mugil curema OR atlantic cod OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR xenopus laevis OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras OR cell OR "cell line" OR cellular OR tissue OR "in vitro" OR spectroscopic OR spectrometer OR spectrophotometry OR "transformation products" OR synthesized OR "gene variants" OR polymorphism OR plant OR pharmacokinetics OR pharmacokinetic OR pharmacodynamic OR pharmacodynamics

Table 1 Data source, design, and methods of the submitted EPIC HR and EPIC SR trials and reviewed RWE studies

Product, therapeutic area, indication	Paxlovid (nirmatrelvir/ ritonavir), Antiviral, treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death			
Regulatory purpose	Marketing approval			
Existing evidence	The main efficacy evidence submitted for Paxlovid as COVID-19 treatment is based on two phase 2/3 placebo-controlled clinical trials- Study C4671005 (EPIC-HR) and study C4671002 (EPIC-SR).			
Regulatory need and gap	The clinical review team considers that the submitted data from EPIC-HR and EPIC-SR together support the benefit of Paxlovid as COVID-19 treatment in high-risk patients for hospitalization or death, regardless of vaccination status and in the Omicron era. Review of available RWE studies was conducted to evaluate if any RWE study findings contradicts with trial findings.			
Study	**EPIC-HR (Pivotal trial)**	**EPIC-SR (Supportive trial)**	**Arbel (RWE)**	**Wong (RWE)**
Objective	To compare efficacy of Paxlovid to placebo for the treatment of symptomatic COVID-19 in non-hospitalized adult participants with COVID-19 who are at increased risk of progression to severe disease	To compare efficacy of Paxlovid to placebo for the treatment of symptomatic COVID-19 in non-hospitalized adult participants with COVID-19 who are at low risk of progression to severe disease	To assess the effectiveness of Paxlovid in preventing severe Covid-19 outcomes during the omicron surge in a population with widespread SARS-CoV-2 immunity.	To assess the clinical effectiveness of Paxlovid among community-dwelling COVID-19 outpatients in Hong Kong during the Omicron BA.2.2 wave in January to June 2022[1]
Country	Multi-countries (41% US, 30% Europe, 9% India, 20% rest of the World)	Multi-countries (43% US, 28% Europe, 29% rest of the World)	Israel	China (Hong Kong)
Data source	Primary collected data	Primary collected data	EHR of an integrated payor-provider healthcare system covered 52% of Israeli population	Territory-wide EHR (did not provide clear description on the data source)
Design	Randomized (1:1), doble blink, placebo-controlled study	Randomized (1:1), doble blink, placebo-controlled study	Cohort study	Cohort study[2]
Population/setting	Non-hospitalized, symptomatic, adult patients with COVID-19 who were at increased risk of progression to severe illness	Non-hospitalized, symptomatic, adult patients with COVID-19 who were at low risk of progression to severe illness	Non-hospitalized COVID-19 patients (40+ yrs), at high risk for progression to severe disease and deemed eligible to received Paxlovid	Non-hospitalized COVID-19 patients (18+ yrs)

[1] The study also evaluated the effectiveness of molnupiravir as outpatient treatment of COVID-19, which is out of the review scope.
[2] Study included a sensitivity analysis using case-control design. Our evaluation focused on the primary analyses using cohort design.

Time period •Total duration Date of first enrollment, date of last completed	07/16/2021 to 04/26/2022	08/25/2021-12/19/2021	01/09-03/31/22 Patients diagnosed between 01/09 and 02/24/22, with a min of 35 days follow-up	02/26- 07/03/2022 Patients diagnosed between 02/26 and 06/26/22, did not require min follow-up time
Exposure	Paxlovid, PO q12h for 5 days	Paxlovid, PO q12h for 5 days	Paxlovid use in 5 days vs. non-use Paxlovid use was ascertained by medical staff*	Paxlovid use in 5 days vs. non-use Unclear how the study ascertained data on Paxlovid use (the data source was stated to have both prescribing and dispensing records)
Reference group	Placebo (non-users)	Placebo (non-users)	Non-users	Non-users
Primary Outcome	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28	Hospitalization due to COVID-19 Unclear how the reason for hospitalization was determined	1) All-cause mortality, 2) hospitalization due to COVID-19 3) a composite outcome of in-hospital disease progression (in-hospital mortality, invasive mechanical ventilation [IMV], or intensive care unit [ICU] admission), and (4) individual in-hospital outcomes (in-hospital death, IMV initiation, and ICU admission) Unclear how the reason for hospitalization was determined
Secondary	Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Death due to COVID-19 Unclear how cause of death was determined	
Index time	At enrollment	At enrollment	Positive SARs-COV-2 test date, with time-varying exposure status	Symptom onset or diagnosis, whichever is earlier Post-hoc sensitivity analyses of treating oral Paxlovid use as a time-varying covariate in the Cox regression models (did not provide details on this analyses)

Censor	Follow-up up to 24 weeks	Follow-up up to 24 weeks	Follow-up stopped at hospitalization or death from any causes, 35 days after diagnosis, end of study	Follow-up stopped at death, outcome event occurrence, receiving molnupiravir or end of study (07/03/2022) (median follow-up=99 days (IQR=92-104))
Covariates reported	**Demographic:** Age, sex, race/ethnicity, geographic region **Clinical risk factors:** BMI, duration from first COVID-19 diagnosis, duration since first COVID-19 symptom, number of risk factors of interest, comorbidities (cardiovascular disorder, chronic kidney disease, chronic lung disease, cigarette smoker, diabetes, hypotension, immunosuppression, cancer, neurodevelopmental disorder, sickle cell disease, HIV infection, device dependence), mAb treatment, serology status, viral load	**Demographic:** Age, sex, race/ethnicity, geographic region **Clinical risk factors:** BMI, duration from first COVID-19 diagnosis, duration since first COVID-19 symptom, number of risk factors of interest, comorbidities (cardiovascular disorder, chronic kidney disease, chronic lung disease, cigarette smoker, diabetes, hypotension, cancer, neurodevelopmental disorder, sickle cell disease, HIV infection, device dependence), vaccination status, serology status, viral load, baseline severity	**Demographic:** Age, sex, population section (general Jewish, Ultra-Orthodox Jewish, Arab), Score for socioeconomic status **Clinical risk factors:** Obesity, HTN, diabetes, history of smoking, immunosuppression, neurologic disease, current cancer, Asthma, history of stroke, chronic hepatic disease, COPD, chronic heart failure, CKD, recent hospitalization **SARS-CoV-2 Immunity status** No previous immunity vs previous immunity induced by vaccination, infection or both	**Demographic:** Age, sex **Clinical risk factors:** Carlson's comorbidity index (did not report the individual component of the score) **Vaccination status:** Fully vaccinated or not
Key unmeasured covariates of concern	Not applicable (due to randomization)	Not applicable (due to randomization)	Symptoms and severity of COVID-19 at baseline Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized, detailed vaccination information	Symptoms and severity of COVID-19 at baseline Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized, detailed vaccination information

Statistical Analysis	Randomization was stratified by geographic region, by whether participants had received mAb treatment Analyses were conducted in all participants who take at least 1 dose of study intervention, who at baseline did not receive mAb and were treated within 3 days of symptom onset. Participants will be analyzed according to the study intervention they were randomized (ITT approach). The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method.	Randomization was stratified by geographic region, by vaccination status and by COVID-19 symptom onset (≤3 or >3-5 days) Analyses were conducted in all participants who take at least 1 dose of study intervention, Participants will be analyzed according to the study intervention they were randomized (ITT approach). Time to sustained alleviation of all targeted COVID-19 signs/symptoms were summarized with Kaplan-Meier curves. Log-rank test will be used to compare the difference in outcome between treatment groups	Hazard ratios (HR) with 95% confidence intervals (CI) of outcome was estimated with the multivariate Cox proportional-hazards regression model with time-dependent exposure status. The analyses were conducted in subgroups defined by age (40-64 yrs vs 65+) and immune status (**patients with or without previous immunity, acquired by vaccination, prior infection, or both**) The stratified analyses for each subgroup adjusted for different covariates, selected based on a two-step testing criteria[3]	HR with 95% CI of each outcome between Paxlovid users and their propensity score matched non-users were estimated using Cox regression models. The propensity score model included age, sex, date of confirmed SARS-CoV-2 infection, Charlson Comorbidity Index, and vaccination status
Methods to evaluate effectiveness by vaccination status	Not applicable	Not applicable	Primary analyses were stratified by age and immune status	Stratified analyses evaluated impact of vaccination status (**fully vaccinated vs not fully vaccinated**)
Sample Size and power	3,000 participants for 90% power to show a difference of 3.5% in the proportion of participants hospitalized/dying that did not receive mAb and were treated within 3 days after symptom onset.	1980 participants for 90% power to detect 2 days difference in the median days to sustained alleviation of all targeted COVID-19-associated symptoms	Did not report a priori sample size/power calculation	Did not report a priori sample size/power calculation

[3] First, a univariate Kaplan–Meier analysis with a log-rank test was applied to evaluate the associations between each independent candidate variable and the time-dependent primary outcome. Then, a comparison of the survival curves and Schoenfeld's global test was used to test the proportional-hazards assumption for those variables. Variates that met these two testing criteria served as the inputs for the multivariate regression analysis

Table 1 Data source, design, and methods of the submitted EPIC HR and EPIC SR trials and reviewed RWE studies (cont.)

Product, therapeutic area, indication	Paxlovid (nirmatrelvir/ ritonavir), Antiviral, treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death				
Regulatory purpose	Marketing approval				
Existing evidence	The main efficacy evidence submitted for Paxlovid as COVID-19 treatment is based on two phase 2/3 placebo-controlled clinical trials-Study C4671005 (EPIC-HR) and study C4671002 (EPIC-SR).				
Regulatory need and gap	The clinical review team considers that the submitted data from EPIC-HR and EPIC-SR together support the benefit of Paxlovid as COVID-19 treatment in high-risk patients for hospitalization or death, regardless of vaccination status and in the Omicron era. Review of available RWE studies was conducted to evaluate if any RWE study findings contradicts with trial findings.				
Study	**EPIC-HR (Pivotal trial)**	**EPIC-SR (Supportive trial)**	**Bejama (RWE)**	**Shwartz (RWE)**	**Lewnard (RWE)**
Objective	To compare efficacy of Paxlovid to placebo for the treatment of symptomatic COVID-19 in non-hospitalized adult participants with COVID-19 who are at increased risk of progression to severe disease	To compare efficacy of Paxlovid to placebo for the treatment of symptomatic COVID-19 in non-hospitalized adult participants with COVID-19 who are at low risk of progression to severe disease	To determine the effectiveness of nirmatrelvir-ritonavir and molnupiravir for the outpatient treatment of COVID-19[4]	To evaluate the real-world effectiveness of nirmatrelvir/ritonavir on health outcomes including hospitalization and death from COVID-19 while Omicron and its subvariants predominate.	To measure the effectiveness of nirmatrelvir-ritonavir in preventing severe outcomes of SARS-CoV-2 infection among cases ascertained via outpatient testing within a large, integrated US healthcare system
Country	Multi-countries (41% US, 30% Europe, 9% India, 20% rest of the World)	Multi-countries (43% US, 28% Europe, 29% rest of the World)	US	Canada (Ontario)	US
Data source	Primary collected data	Primary collected data	Administrative claims data and EHR from the Veterans Health Administration	Province-wide prescription dispensing data, SARS-CoV-2 PCR test data, COVID-19 vaccination data, insurance plan data, disease specific databases	Kaiser Permanente Southern California, and comprehensive healthcare system providing integrated care. Vaccination capture through California Immunization Registry
Design	Randomized (1:1), doble blink, placebo-controlled study	Randomized (1:1), doble blink, placebo-controlled study	Cohort study	Cohort study	Cohort study
Population/setting	Non-hospitalized, symptomatic, adult patients with COVID-19 who were at increased risk of progression to severe illness	Non-hospitalized, symptomatic, adult patients with COVID-19 who were at low risk of progression to severe illness	Non-hospitalized patients (18+ yr) who newly tested positive for COVID-19 and had at least one risk factor for progression to severe COVID-19	Non-hospitalized patients tested positive for COVID-19 (18+ yrs)	Non-hospitalized patients (12+ yr) who newly tested positive for COVID-19

[4] The study also evaluated the effectiveness of molnupiravir as outpatient treatment of COVID-19, which is out of the review scope.

Time period •Total duration Date of first enrollment, date of last completed	07/16/2021 to 04/26/2022	08/25/2021-12/19/2021	01/01/2022-08/31/2022 Patients with positive test between 01/01/2022 and 02/28/22, with up to 6 months follow-up	04/04- 9/30/2022 Patients with positive PCR test between 04/04 and 08/31/22	04/08/2022-10/20/2022 Patients with positive test between 04/08 and 10/07/2022, up to 60 days follow-up
Exposure	Paxlovid, PO q12h for 5 days	Paxlovid, PO q12h for 5 days	Paxlovid use in 10 days vs. non-use Paxlovid use was identified from dispensing records	Paxlovid use vs. non-use Paxlovid use was identified from dispensing records	Paxlovid use (in 5 days, or at any time) vs. non-use Paxlovid use was identified from dispensing records
Reference group	Placebo (non-users)	Placebo (non-users)	Non-users	Non-users	Non-users
Primary Outcome	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28	All cause hospitalization or death in 30 days.	Hospitalization for COVID or death in 1-30 days COVID-19 hospitalization was determined by local public health units, unclear about the criteria	All-cause hospitalization or death in 30 days
Secondary	Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Intensive care unit (ICU) admission and mechanical ventilation occurring during hospitalizations through day 30. Acute or long-term care admission, death, post-COVID condition from day 31-180	Death in 1-30 days	ICU admission, mechanical ventilation, or death within 60 days
Index time	At enrollment	At enrollment	**Paxlovid users:** Treatment initiation **Non-users:** Assigned an index date with the same duration between test date and treatment initiation date of their matched treated patients	**Paxlovid users**: Treatment initiation **Non-users:** Assigned index date that matched the distribution of the time from positive test-to-dispensing in Paxlovid users	**Positive SARS-CoV-2 test date** with time-varying exposure status
Censor	Follow-up up to 24 weeks	Follow-up up to 24 weeks	Follow-up stopped at outcome events, 30 days after index for short-term outcomes, or 31-180 days after index for post-COVID conditions	Did not specified follow-up/censor criteria	Follow-up stopped at outcome events, loss of insurance coverage, end of follow-up (30 days or 60 days) or end of study (10/20/2022)

Covariates captured	**Demographic:** Age, sex, race/ethnicity, geographic region **Clinical risk factors:** BMI, duration from first COVID-19 diagnosis, duration since first COVID-19 symptom, number of risk factors of interest, comorbidities (cardiovascular disorder, chronic kidney disease, chronic lung disease, cigarette smoker, diabetes, hypotension, immunosuppression, cancer, neurodevelopmental disorder, sickle cell disease, HIV infection, device dependence), mAb treatment, serology status, viral load	**Demographic:** Age, sex, race/ethnicity, geographic region **Clinical risk factors:** BMI, duration from first COVID-19 diagnosis, duration since first COVID-19 symptom, number of risk factors of interest, comorbidities (cardiovascular disorder, chronic kidney disease, chronic lung disease, cigarette smoker, diabetes, hypotension, cancer, neurodevelopmental disorder, sickle cell disease, HIV infection, device dependence), vaccination status, serology status, viral load, baseline severity	**Demographic:** Age, sex, race/ethnicity, rurality, VA integrated Service Network (VISN), area deprivation index **Clinical risk factors:** Calendar week of positive test, presence of symptom in preceding 30 days, NIH risk tier of prioritization for anti-SARS-CoV-2 therapies, smoking, alcohol dependence, substance dependence, number of comorbidities, care assessment need (CAN) score for mortality, obesity (BMI 30+), chronic kidney disease, diabetes, immunosuppressive medications or cancer therapies, cancer, cardiovascular diseases, chronic lung disease, dementia, cerebrovascular disease, chronic liver disease, mental health conditions, number of prior healthcare encounters, days from test to treatment **SARS-CoV-2 Immunity status** Vaccination status and time since last dose	**Demographic:** Age, sex **Clinical risk factors:** Previous COVID-19 infection, Ontario Science Table (OST) risk group (standard or high risk), comorbidities (chronic respiratory disease, chronic heart disease, diabetes, immune compromised conditions, hypertension, dementia, autoimmune disease, chronic kidney disease, advanced liver disease), long-term care resident, **Vaccination status:** Number of dose (0,1,2,3+), time from last vaccine dose (14-89 days, 90-179 days, 180-269 days, 270+ days)	**Demographics:** Age, sex, race/ ethnicity, neighborhood deprivation index **Clinical risk factors:** Time from COVID-19 symptoms onset[5] to testing, Outpatient care received within 1 day prior to COVID-19 testing, prior SARS-CoV-2 infection, Charlson comorbidity index, BMI, cigarette smoking, prior year health care use, receipt of other respiratory vaccines[6] **Vaccination status:** Number of doses (0,1,2,3,4) received

[5] The date of SARS-CoV-2 symptom onset was defined as the earliest date that cases reported acute fever, cough, headache, fatigue, dyspnea, chills, sore throat, myalgia, anosmia, diarrhea, vomiting/nausea, or abdominal pain within 14 days before or after their index test date. If new-onset symptoms were not recorded within this period, we categorized cases as "not experiencing acute COVID-19 symptoms" in association with their infection

[6] Other vaccine including: 2021-22 season influenza vaccination, pneumococcal polysaccharide vaccine, and pneumococcal conjugate vaccine.

Key unmeasured covariates of concern	Not applicable (due to randomization)	Not applicable (due to randomization)	Severity of COVID-19 at baseline Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized	Symptoms and severity of COVID-19 at baseline Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized	Use of other COVID-19 treatment at follow-up, in-patient COVID-19 management when hospitalized

Statistical Analysis	Randomization was stratified by geographic region, by whether participants had received mAb treatment Analyses were conducted in all participants who take at least 1 dose of study intervention, who at baseline did not receive mAb and were treated within 3 days of symptom onset. Participants will be analyzed according to the study intervention they were randomized (ITT approach). The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method.	Randomization was stratified by geographic region, by vaccination status and by COVID-19 symptom onset (≤3 or >3-5 days) Analyses were conducted in all participants who take at least 1 dose of study intervention, Participants will be analyzed according to the study intervention they were randomized (ITT approach). Time to sustained alleviation of all targeted COVID-19 signs/symptoms were summarized with Kaplan-Meier curves. Log-rank test will be used to compare the difference in outcome between treatment groups	Users and non-users were first exact-matched as of their assigned index date on: NIH tier, VISN, and calendar time (±7 days of positive test). Then matched on propensity score (PS) calculated based on demographic, geographic, healthcare utilization, and clinical factors. Up to 4 non-users with the closest PS within 0.2 standard deviations of the mean were matched to each user. For 30-day outcomes of hospitalization or death, risk rates, risk differences, risk ratios (and 95% CIs) were calculated. Time-to-event analyses treating death as a competing risk was used for incidence of long-term outcomes extending from 31-180 days. Subgroup analyses by age, vaccination status and presence of symptoms was conducted. All analyses were importance-weighted to account for variable-ratio matching. A robust sandwich-type variance estimator was used to account for clustering within the matched group due to ties in the PS, clustering within subjects due to matching with replacement, and clustering	Weighted odds ratios with 95% CI of each outcome between IPTW weighted Paxlovid users and non-users were estimated using logistics regression models. The IPTW was calculated from propensity score model included age, sex, number of SARS-CoV-2 vaccine dose, previous infection, time from last vaccine dose, individual comorbidities, long-term care residence and OST risk group Pre-specified stratified analyses were conducted based on age, vaccination status, potential DDIS for those over 70 years of age, comorbidities, long-term care residents, OST risk group and time period (April-June 2022 vs July to August 2022)	For each endpoint, treatment effectiveness was calculated as (1 − adjusted hazards ratio [aHR]) × 100%, for the aHR comparing outcomes among users and non-users. aHR and 95% (CI) was estimated by Cox proportional hazards models, using the Andersen-Gill extension update time-varying exposures. Cluster-robust standard errors were used to account for multiple observations from cases whose treatment status changed during follow-up. We verified the proportional hazards assumption by Schoenfeld residuals. Regression strata (matches) among cases were defined based on week of testing, age, sex, receipt of any clinical care in association with testing (across ED, urgent care, outpatient, or telehealth settings), days from symptom onset, or absence of acute symptoms, healthcare utilization, COVID-19 vaccine doses received; Charlson comorbidity index, and body mass index category. Analyses further controlled for race/ethnicity, smoking status, neighborhood deprivation index quintile,

			in the cross-classification of the matched and within subject clusters. We verified that the proportional hazards assumption was met using log-log plots and Schoenfeld residuals.		and receipt of other vaccines. Analyses were repeated in subgroups who received ≥2 or ≥3 COVID-19 vaccine doses. Multiple imputations were used to handle missing value on smoking status, BMI and census-tract neighborhood deprivation index measures
Methods to evaluate effectiveness by vaccination status	Not applicable	Not applicable	Stratified analyses evaluated impact of vaccination status (**unvaccinated versus any primary or booster vaccination**)	Stratified analyses evaluated impact of vaccination status (**0, 1-2, 3+ doses**)	Conduct sensitivity analyses restricted to patients who received **2+ or 3+ doses of COVID-19 vaccine**
Sample Size and power	3,000 participants for 90% power to show a difference of 3.5% in the proportion of participants hospitalized/dying that did not receive mAb and were treated within 3 days after symptom onset.	1980 participants for 90% power to detect 2 days difference in the median days to sustained alleviation of all targeted COVID-19-associated symptoms	A sample size of 2,650 persons (530 Paxlovid users, 2,120 non-users) was determined to have 80% power to detect a 2% difference in 30-day hospitalization or death, given a 1:4 match and assuming a 3% incidence of 30-day hospitalization or death among non-users	Did not report a priori sample size/power calculation	Did not report a priori sample size/power calculation

Table 1-1 Inclusion and exclusion criteria for the submitted EPIC HR and EPIC SR trials and reviewed RWE studies

EPIC HR	EPIC SR	Arbel	Wong
Inclusion criteria			
Age 18+		40+	18+
Confirmed SARS-CoV-2 infection (RT-PCR) within 5 days prior to randomization (non PCR test are allowed as long as test results can be available)		Confirmed SARS-CoV-2 infection (RT-PCR or antigen test), received outpatient COVID-19 diagnosis Excluded use more than 5 days	Confirmed outpatient COVID-19 diagnosis
Initial onset of COVID-19 signs/symptoms within 5 days prior to the day of randomization and at least 1 of the specified COVID-19 signs/symptoms present on the day of randomization		Not required	Not required
Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19	Did not required	Assessed as being at "high risk" for progression to severe disease, based on a risk score	Not required
Agreement to use contraceptives	Same	Not required	Not required
Exclusion			
History of hospitalization for the medical treatment of COVID-19		Hospitalized before the positive SARS-CoV-2 test or Paxlovid use	History of hospitalizations
Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator		Hospitalized on the same day of the positive SARS-CoV-2 test	Diagnosed at the time of hospitalization, death on the same day of diagnosis, and Paxlovid users who initiated the treatment during hospitalization
Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collected		Did not exclude	Did not exclude
Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hep B or C, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure		Hepatic disease is a component of risk score	Did not exclude
Receiving dialysis or have known moderate to severe renal impairment (eGFR <45 within 6 months of screening, using the serum creatinine-based CKD-EPI formula)	Receiving dialysis or have known renal impairment	eGFR <60	Did not exclude

EPIC HR	EPIC SR	Arbel	Wong
Known human immunodeficiency virus (HIV) infection with a viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (within past 6 months of screening)		HIV carrier is a component of risk score despite viral load. Study excluded all patients taking contraindicated medication to Paxlovid	Did not exclude
Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere evaluation of response to the treatment		Did not exclude	Did not exclude
History of hypersensitivity or other contraindication to any of the components of the study intervention as determined by the investigator		Did not exclude	Did not exclude
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 or for 4 days after the last dose		Patients treated with contraindicated medication with Paxlovid (referenced FDA Fact Sheet)	Did not exclude
Concomitant use of any medications of substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose and during study treatment		Patients treated with contraindicated medication with Paxlovid (referenced FDA Fact Sheet)	Did not exclude
Has received or is expected to receive convalescent COVID-19 plasma	Has received or is expected to receive mAb, convalescent COVID-19 plasma	Has received molnupiravir or Evusheld	Has received molnupiravir
Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit	Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit ***Did not exclude fully vaccinated patients prior to December 19, 2021** (Fully vaccinated participants with underlying med conditions associated with an increased risk of COVID-19 must not receive a booster before Day 34 visit.)	Did not exclude unvaccinated patients. Vaccinated status is a component of risk score	Did not exclude patient based on vaccination status
Participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 through the long-term follow-up visit		Did not exclude	Did not exclude
Previous administration with any investigational drug or vaccine within 30 days or 5 half-lives preceding the first dose of study innervation		Did not exclude	Did not exclude
Known prior participation in this trial or other trial involving Paxlovid		Did not exclude	Did not exclude

EPIC HR	EPIC SR	Arbel	Wong
Oxygen saturation of <92% on room air within 24 hours prior to randomization, or on their standard home oxygen supplementation for those who regularly receive chronic supplementary oxygen for an underlying lung condition		Did not exclude	Did not exclude
Abnormal tests in past 6 months AST or ALT level 2.5+X ULN Total bilirubin 2+X ULN eGFR <45, **using serum creatinine-based CKD-EPI** Absolute neutrophil count < 1000	Abnormal tests in past 6 months AST or ALT level 2.5+X ULN Total bilirubin 2+X ULN eGFR <45 Absolute neutrophil count < 1000	Did not exclude	Did not exclude
Females who are pregnant or breastfeeding		Did not exclude	Did not exclude
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		Did not exclude	Did not exclude
Other medical or psychiatric condition including recent (in the past year) or active suicidal ideation or lab abnormality that may increase the risk of study participation, or in the investigator's judgement, make the participant inappropriate for the study		Did not exclude	Did not exclude
	Having criteria for high-risk **Participants with high-risk condition who are fully vaccinated against SARS-CoV-2 are eligible until December 19, 2021** (since they are considered at low risk for severe disease)		
		Patients who were residents in long-term care facilities	Patients who were residents in long-term care facilities

Table 1-1 Inclusion and exclusion criteria for the submitted EPIC HR and EPIC SR trials and reviewed RWE studies (cont.)

EPIC HR	EPIC SR	Bejama	Schewartz	Lewnard
Inclusion criteria				
Age 18+		18+	18+	12+
Confirmed SARS-CoV-2 infection (RT-PCR) within 5 days prior to randomization (non PCR test are allowed as long as test results can be available)		Confirmed SARS-CoV-2 infection (NAAT or antigen test)	Confirmed SARS-CoV-2 infection (PCR test)	Confirmed SARS-CoV-2 infection, diagnosed in outpatient setting
Initial onset of COVID-19 signs/symptoms within 5 days prior to the day of randomization and at least 1 of the specified COVID-19 signs/symptoms present on the day of randomization		Not required	Not required	Not required
Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19	Did not required	**Required**	Not required	Not required
Agreement to use contraceptives	Same	Not required	Not required	Not required
Exclusion				
History of hospitalization for the medical treatment of COVID-19		Hospitalized within 7 days before the test-positive date or Paxlovid treatment date	Hospitalized prior to positive test	Hospitalized within 0-7 days before COVID-19 test
Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator		Hospitalized on the same day of the positive SARS-CoV-2 test or Paxlovid treatment	Hospitalized on the same day of positive test	COVID-19 diagnosis during hospitalization
Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collected		Excluded	Did not exclude	Prior COVID-19 diagnosis 1-90 days prior to COVID-19 test
Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hep B or C, primary biliary cirrhosis, Child-Pugh Class B or C or acute liver failure		Patients with advanced hepatic disease	Did not exclude	Did not exclude
Receiving dialysis or have known moderate to severe renal impairment (eGFR <45 within 6 months of screening, using the serum creatinine-based CKD-EPI formula)	Receiving dialysis or have known renal impairment	Patients with advanced renal disease	Did not exclude	Did not exclude
Known human immunodeficiency virus (HIV) infection with a viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (within past 6 months of screening)		Did not exclude	Did not exclude	Did not exclude

EPIC HR	EPIC SR	Bejama	Schewartz	Lewnard
Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere evaluation of response to the treatment		Did not exclude	Did not exclude	Did not exclude
History of hypersensitivity or other contraindication to any of the components of the study intervention as determined by the investigator		Did not exclude	Did not exclude	Did not exclude
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 or for 4 days after the last dose		Patients treated with contraindicated medication with Paxlovid	Did not exclude	Did not exclude
Concomitant use of any medications of substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose and during study treatment		Patients treated with contraindicated medication with Paxlovid	Did not exclude	Did not exclude
Has received or is expected to receive convalescent COVID-19 plasma	Has received or is expected to receive mAb, convalescent COVID-19 plasma	Has received any outpatient COVID-19 treatment	Has received molnupiravir	Did not exclude
Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit	Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit ***Did not exclude fully vaccinated patients prior to December 19, 2021** (Fully vaccinated participants with underlying med conditions associated with an increased risk of COVID-19 must not receive a booster before Day 34 visit.)	Did not exclude unvaccinated patients.	Did not exclude patient based on vaccination status	Did not exclude patient based on vaccination status
Participating in another interventional clinical study with an investigational compound or device, including those for COVID-19 through the long-term follow-up visit		Did not exclude	Did not exclude	Did not exclude
Previous administration with any investigational drug or vaccine within 30 days or 5 half-lives preceding the first dose of study innervation		Did not exclude	Did not exclude	Did not exclude
Known prior participation in this trial or other trial involving Paxlovid		Did not exclude	Did not exclude	Did not exclude

EPIC HR	EPIC SR	Bejama	Schewartz	Lewnard
Oxygen saturation of <92% on room air within 24 hours prior to randomization, or on their standard home oxygen supplementation for those who regularly receive chronic supplementary oxygen for an underlying lung condition		Did not exclude	Did not exclude	Did not exclude
Abnormal tests in past 6 months AST or ALT level 2.5+X ULN Total bilirubin 2+X ULN eGFR <45, **using serum creatinine-based CKD-EPI** Absolute neutrophil count < 1000	Abnormal tests in past 6 months AST or ALT level 2.5+X ULN Total bilirubin 2+X ULN eGFR <45 Absolute neutrophil count < 1000	Did not exclude	Did not exclude	
Females who are pregnant or breastfeeding		Did not exclude	Did not exclude	Did not exclude
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		Did not exclude	Did not exclude	Did not exclude
Other medical or psychiatric condition including recent (in the past year) or active suicidal ideation or lab abnormality that may increase the risk of study participation, or in the investigator's judgement, make the participant inappropriate for the study		Did not exclude	Did not exclude	Did not exclude
	Having criteria for high-risk **Participants with high-risk condition who are fully vaccinated against SARS-CoV-2 are eligible until December 19, 2021** (since they are considered at low risk for severe disease)			
		Patients who were residents in long-term care facilities No VA primary care encounters in the 18 months prior to positive test	Patients who were residents of Ontario or have invalid date of birth, patient tested from centers that dispense Paxlovid as exposure status cannot be verified in dispensing records. Patients whose dispensing date is prior to test date	

Table 1-2 High risk definition in the submitted EPIC HR and EPIC SR trials and RWE study

EPIC HR	EPIC SR	Arbel (Components for COVID-19 risk score)
≥60 years of age	≥65 years of age	Deduct points if < 60yrs, add 2 points if 70+yrs

EPIC HR	EPIC SR	Arbel (Components for COVID-19 risk score)
BMI >25	BMI >30	Add 1 point if BMI>30
Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes		Adds 1 point if >10 packs cigarette/day
Chronic Kidney Disease **(exclude those who on dialysis or moderate to severe renal impairment)**	Chronic Kidney Disease	Adds 1 point for renal disease
Diabetes		Adds 1 point for diabetes
Immunosuppressive disease (e.g. bone marrow or organ transplantation or primary immune delicacies) OR prolonged use of immune-weakening meds (has received CS equivalate to prednisone 20+mg daily for at least 14 consecutive days within 30 days prior, treatment with biologics (infliximab, ustekinumab, etc) immunomodulators (methotrexate, 6MP, azathioprine, etc) or cancer chemotherapy within 90days prior to study entry, HIV infection with CD4+ cell count <200 **and viral load <400**	Immunosuppressive disease (e.g. bone marrow or organ transplantation or primary immune delicacies) OR prolonged use of immune-weakening meds (has received CS equivalate to prednisone 20+mg daily for at least 14 consecutive days within 30 days prior, treatment with biologics (infliximab, ustekinumab, etc) immunomodulators (methotrexate, 6MP, azathioprine, etc) or cancer chemotherapy within 90days prior to study entry, HIV infection with CD4+ cell count <200	Adds 7 points for immunosuppression Adds 1 point for organ transplant, bone marrow transplant or previous splenectomy or AIDS patient/HIV carrier, treatment at least twice with immunosuppressants in the last year or steroid treatment at least twice in the last year
CVD, defined as history of MI, stroke ,TIA, HF, angina with prescribed NO, CABG, PCI, carotid endarterectomy and aortic bypass. Known diagnosis of HTN		Adds 1 point for heart disease, vascular disease or cerebrovascular disease
Chronic lung disease (if asthma, required daily prescribed therapy)		Adds 1 points for COPD
Sickle cell disease		Not included
Neurodevelopmental disorders (eg, cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies)		Adds 1 point for neurological disease
Active cancer other than localized skin cancer, including those requiring treatment (including palliative treatment), as long as the treatment is not among the prohibited meds		Adds 1 point for active malignancy
Medical-related technological dependence not related to COVID-19 (eg, tracheostomy, gastrostomy, or positive pressure ventilation)		Not included
Did not include hepatic disease as "high-risk" criteria		Adds 1 point for hepatic disease

Table 1-2 High risk definition in the submitted EPIC HR and EPIC SR trials and RWE study (cont.)

EPIC HR	EPIC SR	Bejama
≥60 years of age	≥65 years of age	≥65 years of age
BMI >25	BMI >30	BMI > 25
Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes		Current or formal Tobacco use

EPIC HR	EPIC SR	Bejama
Chronic Kidney Disease **(exclude those who on dialysis or moderate to severe renal impairment)**	Chronic Kidney Disease	Chronic kidney disease including dialysis
Diabetes		Diabetes
Immunosuppressive disease (e.g. bone marrow or organ transplantation or primary immune delicacies) OR prolonged use of immune-weakening meds (has received CS equivalate to prednisone 20+mg daily for at least 14 consecutive days within 30 days prior, treatment with biologics (infliximab, ustekinumab, etc) immunomodulators (methotrexate, 6MP, azathioprine, etc) or cancer chemotherapy within 90days prior to study entry, HIV infection with CD4+ cell count <200 **and viral load <400**	Immunosuppressive disease (e.g. bone marrow or organ transplantation or primary immune delicacies) OR prolonged use of immune-weakening meds (has received CS equivalate to prednisone 20+mg daily for at least 14 consecutive days within 30 days prior, treatment with biologics (infliximab, ustekinumab, etc) immunomodulators (methotrexate, 6MP, azathioprine, etc) or cancer chemotherapy within 90days prior to study entry, HIV infection with CD4+ cell count <200	Immunosuppressive meds or cancer therapies HIV
CVD, defined as history of MI, stroke ,TIA, HF, angina with prescribed NO, CABG, PCI, carotid endarterectomy and aortic bypass. Known diagnosis of HTN		CVD including cardiomyopathy, chronic rheumatic heart disease, congestive heart failure, coronary artery disease, hypertension, myocardial infarction, peripheral artery disease, pulmonary heart disease Stroke or cerebrovascular disease
Chronic lung disease (if asthma, required daily prescribed therapy)		Chronic lung disease including asthma, chronic obstructive pulmonary disease, emphysema, pulmonary fibrosis
Sickle cell disease		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 (including palliative treatment), as long as the treatment is not among the prohibited meds		-
Medical-related technological dependence not related to COVID-19 (eg, tracheostomy, gastrostomy, or positive pressure ventilation)		-
-		Chronic liver disease including chronic hepatitis and cirrhosis
-		Chronic neurologic conditions including epilepsy, multiple sclerosis and Parkinson's disease
-		Dementia
-		Mental health conditions including bipolar disorder, major depressive disorder, PTSD and schizophrenia
-		Pregnancy
-		Substance use, alcohol dependence, non-alcohol substance dependence
-		Thalassemia

Table 2 Main findings on hospitalization in reviewed RWE studies

	Outcome	Paxlovid user			Non-users			Effect estimates (95% Confidence interval)
		N	Event N	Event rate*	N	Event N	Event rate*	
Arbel age 40-64	Hospitalization due to COVID-19	1,418	7	15.2 0.5%	65,015	327	15.8 0.5%	0.74 (0.35 to 1.58)
With previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	1.13 (0.50 to 2.58)
Without previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	0.23 (0.03 to 1.67)
Arbel age ≥ 65	Hospitalization due to COVID-19	2,484	11	14.7 0.4%	40,337	766	58.9 1.9%	0.27 (0.15 to 0.49)
With previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	0.32 (0.17 to 0.63)
Without previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	0.15 (0.04 to 0.60)
Wong (**86% >60**)	COVID-19 Hospitalization	5,542	n/a	48.5	54,672	n/a	61	0.76 (0.67 to 0.86) *0.85 (0.75 to 0.97)-post-hoc sensitivity analyses*
Fully Vaccinated		1,850	n/a	20.4	18,138	n/a	28.3	0.71 (0.51 to 1.01)
Not fully-vaccinated		3,692	n/a	60.6	36,534	n/a	76	0.76 (0.66 to 0.87)
Age 18- 60		784	n/a	25.4	8071	n/a	46.9	0.5 (0.31 to 0.81)
Age >60		4758	n/a	51.5	46601	n/a	63.8	0.8 (0.69 to 0.91)

	Outcome	Paxlovid user			Non-users			Effect estimates (95% Confidence interval)
		N	Event N	%	N	Event N	%	
Lewnard (54% age 60+)	Hospital admission or death in 30 days	7,274	51	0.7	126,152	695	0.5	HR=0.46 (0.23-0.93)
≥3 COVID-19 vaccine doses		5,866	n/a	n/a	75,837	n/a	n/a	0.34 (0.15-0.76)
≥2 COVID-19 vaccine doses		6,831	n/a	n/a	107,377	n/a	n/a	0.45 (0.21-0.93)
							0-5 days	HR=0.20 (0.06-0.66)
								0.08 (0.01-0.48)
								0.17 (0.04-0.70)
	Hospital admission		46	0.6		641	0.5	
Bejama (median age 65)	Hospitalization or death in 30 days	1,587	45	2.8	1,587	84.8	5.3%	RR=0.53 (0.39-0.72)
Primary/booster vaccination		1,126	25	2.2	1,108	50.8	4.6%	0.48 (0.32-0.73)
Unvaccinated		461	20	4.3	479	34	7.1%	0.61 (0.38-0.97)
18-64		743	15	2	733	18.3	2.5%	0.81 (0.46-1.42)
≥65		844	30	3.6	853	66.4	7.8%	0.46 (0.31-0.66)
	Hospitalization in 30 days	1,587	43	2.7	1,587	65.2	4.1	0.66 (0.48-0.91)
Shewartz (73.5% age 70+)	Hospitalization or death in 30 days	8,876	n/a	2.1	168,669	n/a	3.7%	OR=0.56 (0.47- 0.67)
Vaccine doses 3+		7,524	n/a	2.2	127,906	n/a	3.5%	0.62 (0.51-0.75)
Vaccine doses 1-2		885	n/a	1.1	30,329	n/a	4.4%	0.25 (0.12-0.50)

unvaccinated		467	n/a	3	10,434	n/a	6.6%	0.44 (0.23-0.84)
<70		2,443	n/a	0.3	129,647	n/a	0.8%	0.34 (0.15-0.79)
≥70		6,433	n/a	2.8	39,022	n/a	5%	0.55 (0.45-0.66)

*per 100,000 person-days, HR=Hazard ratio, RR=risk ratio, OR=odds ratio;

Table 3 Main findings on all-cause mortality in reviewed RWE studies

	Outcome	Paxlovid user			Non-users			Hazard ratio (95% Confidence interval)
		N	Event N	Event rate*	N	Event N	Event rate*	
Arbel 40-64 yr	Death	1,418	1	n/a	65,015	16	n/a	1.32 (0.16-10.75)
With previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	n/a
Without previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	n/a
Arbel ≥65 yr	Death	2,484	2	n/a	40,337	158	n/a	0.21 (0.05-0.82)
With previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	n/a
Without previous immunity		n/a	n/a	n/a	n/a	n/a	n/a	n/a
Wong (86% >60 yr)	Death	5,542	n/a	4.2	54,672	n/a	11.6	0.34 (0.22 to 0.52) *0.35 (0.23 to 0.54)*
Fully Vaccinated		1,850	n/a	0.6	18,138	n/a	2.3	n/a
Not fully-vaccinated		3,692	n/a	7.1	36,534	n/a	15.1	0.44 (0.30 to 0.66)
Age 18- 60		784	n/a	0.0	8071	n/a	1.2	n/a
Age >60		4758	n/a	5.2	46601	n/a	10.5	0.48 (0.32 to 0.74)
Bejama	Death	1,875	5	0.3%	1,875	23.6	1.5%	0.21 (0.09-0.52)
Schwartz	Death	8,876	n/a	1.6%	168,669	n/a	3.3%	0.49 (0.40-0.60)
3 doses		7,524	n/a	1.7%	127,906	n/a	3.1%	0.54 (0.42-0.67)
1-2 doses		885	n/a	0.9%	30,329	n/a	3.8%	0.23 (0.11-0.51)
No vaccine		467	n/a	1.9%	10,434	n/a	5.5%	0.34 (0.16-0.74)
Age <70		2,443	n/a	0.1%	129,647	n/a	0.6%	0.13 (0.03-0.57)
Age >=70		6,433	n/a	2.2%	39,022	n/a	4.5%	0.48 (0.39-0.59)

*per 100,000 person-days

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 8, 2023

To: Myong-Joo Patricia Hong, Regulatory Project Manager
Division of Antivirals (DAV)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Sam Skariah, Team Leader, OPDP
CC: Andrew Haffer, Director, DAPR1, OPDP

Subject: OPDP Labeling Comments for PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use

NDA: 217188

Background:

In response to DAV's consult request dated June 30, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for Paxlovid.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on May 2, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on May 8, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on May 5, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

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WENDY R LUBARSKY
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 8, 2023
To:	Myung-Joo Patricia Hong, M.S. Senior Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	PAXLOVID (nirmatrelvir tablets; ritonavir tablets)
Dosage Form and Route:	co-packaged for oral use
Application Type/Number:	NDA 217188
Applicant:	Pfizer, Inc.

1 INTRODUCTION

On June 29, 2022, Pfizer, Inc., submitted for the Agency's review an original New Drug Application (NDA) 217188 for PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use indicated for the treatment of mild-to-moderate COVID-19 in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on June 30, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use.

2 MATERIAL REVIEWED

- Draft PAXLOVID (nirmatrelvir tablets; ritonavir tablets) co-packaged for oral use PPI received on June 29, 2022, and received by DMPP and OPDP on May 2, 2023.
- Draft PAXLOVID (nirmatrelvir tablets; ritonavir tablets) co-packaged for oral use Prescribing Information (PI) received on June 29, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 2, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 2, 2023
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 217188
Product Name and Strength:	Paxlovid (Nirmatrelvir 300 mg[a]; Ritonavir 100 mg) and (Nirmatrelvir 150 mg; Ritonavir 100 mg) dose packs
Applicant/Sponsor Name:	Pfizer Inc.
OSE RCM #:	2022-33-3
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph.
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on April 28, 2023 for Paxlovid. The previously reviewed container labels were also included in the submission.[b] The Division of Antivirals (DAV) requested that we review the revised carton labeling for Paxlovid (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The carton labeling was revised to include the following alert to patients:

"Find out about medicines that should not be taken with Paxlovid."

Our evaluation of the proposed changes did not identify any areas of vulnerability to medication error. We have no additional recommendations at this time.

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[a] packaged as two 150 mg Nirmatrelvir tables.
[b] Fanari, Melina. Label and Labeling Review for Paxlovid (NDA 217188). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Dec 12. RCM No.: 2022-33-1.

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/s/

MELINA N FANARI
05/02/2023 12:21:35 PM

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Clinical Inspection Summary

Date	31 Jan 2023
From	Elena Boley, M.D., M.B.A. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Myung-Joo Patricia Hong, M.S., SRPM Glen Huang, M.D., Clinical Reviewer Stephanie Troy, M.D., Clinical Team Leader Sarah Connelly, M.D., Cross-Discipline Team Leader
NDA #	NDA 217188
Applicant	Pfizer, Inc.
Drug	PAXLOVID (nirmatrelvir [PF-07321332] 150 mg co-packaged with ritonavir 100 mg)
NME	Yes
Proposed Indication	Treatment of mild-to-moderate COVID-19 in adults (b) (4) [redacted] who are at high risk for progression to severe COVID-19, including hospitalization or death.
Consultation Request Date	16 Aug 2022
Summary Goal Date	8 Feb 2023
Action Goal Date	20 Apr 2023
PDUFA Date	28 May 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Igbinadolor, Hernandez, Martinez, Mitreva, Simova, Medzhidiev, Haytova as well as the sponsor, Pfizer, Inc., were inspected in support of NDA 217188. With the exception of the inspection of Dr. Medzhidiev, which covered only Protocol C4671002 (EPIC-SR), all of these inspections covered the pivotal study, Protocol C4671005 (EPIC-HR).

(b) (7)(A) [redacted]

Dr. Hernandez (site #1470 in Florida for EPIC-HR) was inspected due to a complaint. For this site, we recommend a sensitivity analysis not based primarily on the results of inspection, which were not able to confirm a whistleblower's complaint, but instead on the sponsor's report of Good Clinical Practice non-compliance following their own investigation. The sponsor subsequently decided, per the NDA submission, to perform sensitivity analyses without the data for the subjects (n=2) enrolled at site #1470 who withdrew consent. Because the 36 subjects who were transferred to site #1276 at the time of site termination had already reached the primary efficacy analysis timepoint, it seemed appropriate to perform a sensitivity analysis without the data from all 38 subjects.

At the sites of Drs. Martinez, Medzhidiev, and Haytova, use of birthyear or commonly used e-diary PIN code(s) was found. For these three inspections, instructions or suggestions for subjects to create PIN codes using specific numbers or easily identifiable numbers (birthyear) were provided by the site. Nevertheless, the inspections found no evidence that anyone other than the subject entered data into the e-diaries.

Overall, the inspections found that the primary efficacy endpoint data for EPIC-HR were verifiable. Except for significant protocol deviations at the Martinez and Hernandez sites, the study appears to have been conducted adequately, and the data generated from the other sites appear reliable in support of the proposed indication. As mentioned above, we recommend sensitivity analyses for the data from the Martinez and Hernandez sites.

II. BACKGROUND

NDA 217188 was submitted in support of the use of PAXLOVID (nitmatrelvir/ritonavir) tablets for oral administration for the treatment of treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) ho are at high risk for progression to severe COVID-19, including hospitalization or death. The pivotal study supporting the application was the following:

- Protocol C4671005: "An interventional efficacy, safety, Phase 2/3, double-blind study to investigate oral nirmatrelvir/ritonavir compared with placebo in nonhospitalized symptomatic high risk adults with COVID-19 (EPIC-HR)"

This study was a Phase 2/3, multinational, multicenter, randomized, double-blind, placebo-controlled trial in nonhospitalized symptomatic adult participants with COVID-19 who were at increased risk of progressing to severe illness. The primary efficacy objective was to compare the efficacy of nirmatrelvir/ritonavir to placebo for the treatment of COVID-19 in this population. The secondary efficacy objective was to compare nirmatrelvir/ritonavir to placebo for the duration and severity of signs and symptoms in this population.

Eligible subjects were males or females, aged 18 to 80 years of age, who had laboratory confirmed (see protocol for more details) SARS-CoV-2 infection from a specimen collected

within five days prior to randomization and whose initial onset of signs/symptoms attributable to COVID-19 occurred within five days prior to the day of randomization with at least one of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. Enrolled participants had at least one characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (age 60 years, body mass index >25, smoker, immunocompromised, history of chronic lung disease, hypertension, cardiovascular disease, diabetes mellitus, chronic kidney disease, sickle cell disease, neurodevelopmental disorders, active cancer, medical-related technological dependence). Participants were excluded if they received or were expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit.

The study was comprised of three periods: a screening and randomization period, a study intervention period, and a follow-up period. The total duration of the study was 24 weeks.

After screening, subjects were randomized in a 1:1 fashion (stratified by geographic region and whether participants had received/were expected to receive COVID-19 therapeutic mAb treatment [yes/no])). Subjects then began the study intervention period, during which they received either nirmatrelvir 300 mg (i.e., two tablets of 150 mg or three tablets of 100 mg for participants in the sentinel cohort) and ritonavir 100 mg (i.e., one capsule of 100 mg) q12h by mouth for five days, or a matching placebo for nirmatrelvir (two tablets [three tablets for the sentinel cohort]) and placebo for ritonavir (one capsule) q12h by mouth for five days.

The ***primary efficacy endpoint*** was the proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.

The review division was also particularly interested in the ***secondary efficacy endpoint*** of viral titers measured via RT-PCR in nasal swabs over time.

Details relevant to Study C4671005

Study C4671005 was conducted at 343 centers that screened subjects in 19 countries/regions worldwide (Argentina, Brazil, Bulgaria, Colombia, Czech Republic, Hungary, India, Japan, Republic of Korea, Malaysia, Mexico, Poland, Russian Federation, South Africa, Spain, Thailand, Turkey, Ukraine, and US); 191 of the centers randomized at least one subject. The first subject was enrolled on July 16, 2021, and the last subject completed final visit on April 26, 2022. Of the 2246 subjects that were randomized, 2092 subjects (93.1%) completed the study. The original protocol was dated June 18, 2021, there were four protocol amendments, and the final protocol was dated November 20, 2021.

Protocol C4671002

The supportive study is entitled:

- Protocol C4671002: "An interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered PF-07321332/Ritonavir compared with placebo in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness (EPIC-SR)"

This Phase 2/3, multinational, multicenter, randomized, double-blind, placebo-controlled study in nonhospitalized symptomatic adult participants with COVID-19 who were at low risk of progressing to severe illness. The primary efficacy objective was to compare the efficacy of nirmatrelvir/ritonavir to placebo for the treatment of symptomatic COVID-19 in this population. The secondary efficacy objective was to compare nirmatrelvir/ritonavir versus placebo for COVID-19 related hospitalization and all-cause mortality in this population.

Eligible participants were male or females, aged ≥18 years of age (or the minimum country-specific age of consent if >18) with a laboratory confirmed diagnosis (see protocol for more details) of SARS-CoV-2 infection from a specimen collected within five days prior to randomization and whose initial onset of signs/symptoms attributable to COVID-19 occurred within five days prior to the day of randomization with at least one of the specified signs/symptoms attributable to COVID-19 present on the day of randomization. Participants were excluded if they had at least one of the following characteristics indicating an underlying medical condition associated with an increased risk of developing severe illness from COVID-19: ≥65 years of age; body mass index ≥30 kg/m^2; smoker; chronic lung disease; hypertension; cardiovascular disease; diabetes mellitus; chronic kidney disease; sickle cell disease; neurodevelopmental disorders; active cancer; and immunosuppressive disease (see protocol for full list with details).

The study was comprised of three periods: a screening and randomization period, a study intervention period, and a follow-up period. The total duration of the study was 24 weeks.

After screening, subjects were randomized in a 1:1 fashion (stratified by geographic region, by vaccination status, and by COVID-19 symptom onset [≤3 days vs >3 to 5 days]). Subjects then began the study intervention period, during which they received either nirmatrelvir 300 mg (i.e., two tablets of 150 mg) and ritonavir 100 mg (i.e., one capsule of 100 mg) q12h by mouth for five days., or a matching placebo for nirmatrelvir (two tablets) and placebo for ritonavir (one capsule) q12h by mouth for five days.

The ***primary efficacy endpoint*** was the time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.

Details relevant to Study C4671002

Study C4671002 was conducted at 343 centers that screened subjects in 18 countries/regions worldwide (Argentina, Brazil, Bulgaria, Colombia, Czech Republic, Hungary, Japan, Republic of Korea, Malaysia, Mexico, Poland, Russian Federation, South Africa, Spain, Thailand, Turkey, Ukraine, and US); 173 of the centers randomized at least one subject. The first subject was enrolled on August 25, 2021. The data cutoff point for the interim analysis was December 19, 2021. At that time, 1153 (92%) of the 1251 randomized subjects had completed the study. Enrollment restarted on March 16, 2022, and the last subject completed their final visit on July 25, 2022. The original protocol was dated June 18, 2021, there were six protocol amendments, and the final protocol was dated June 9, 2022.

Rationale for Site Selection

Initially, five clinical investigator (CI) sites were selected for inspection. Of the 5 sites, 4 sites (#1274, #1108, #1158, and #1097, all sites in Study C4671005) were chosen for routine inspection primarily based on the regional distribution of subjects, the numbers of enrolled subjects, and site-specific efficacy results (based on a composite of endpoints). Two (2) of these 4 clinical sites (sites #1158 and #1097 in Bulgaria) were selected for inspection because there were insufficient domestic data (i.e., subjects from the US comprised only 40% of the safety population in Study C4671005), and 30% of subjects were at sites in Eastern Europe. The fifth site, site 1470 (Study C4671005) in Florida, was chosen to be inspected due to a complaint.

The Division of Antivirals' (DAV's) review detected data anomalies (viral load and e-diary symptom data) at site 1274 in Study C4671005 (previously selected for routine inspection) as well as three additional sites: sites #1281, #1157, and #1197 (all in Study C4671002). These three sites were added to the inspections. In addition, because the clinical investigator Nezabravka Petrova Haytova in Bulgaria participated in both Study C4671002 (site #1197) and Study C4671005 (site #1193), Study C4671005 was added to the inspection of Dr. Haytova.

III. RESULTS (by site):

1. **Awawu Igbinadolor, M.D.**
   Site #1108
   Protocol: C4671005 (EPIC-HR)
   343 Venus Street
   Monroe, NC 28112
   PDUFA Inspection Dates: September 19-22, 2022

At this site for Protocol EPIC-HR, 25 subjects were screened, 24 were randomized, and 18 subjects completed the study. One subject (subject # (b) (6)) was randomized but never treated because it was learned that he had met exclusion criterion #14 (he had received the SARS-CoV-2 vaccine). Of the 5 subjects who did not complete the study, 3 subjects withdrew consent (subjects # (b) (6) and # (b) (6) were assigned to the placebo group and subject (b) (6) was assigned to the Paxlovid group). The two remaining subjects, both assigned to the placebo group, died prior to study completion.

The inspection evaluated the study records for the 24 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

There was no evidence of under-reporting of adverse events, with the exception of two instances of low potassium (K= 3.0 mEq/L for subject (b) (6) and K= 3.3 mEq/L for subject # (b) (6)) identified during routine clinical laboratory testing. In both cases, the CI had noted the low potassium on the lab results and had recommended that the subject be treated with potassium supplementation.

Reviewer's comment: These two protocol deviations are minor and isolated. Although these clinical laboratory test abnormalities should have been reported as AEs, the NDA submission contained this data in the clinical laboratory datasets and so they were included in the safety analyses for this application.

During the inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 24 randomized subjects. No discrepancies were noted. Viral RNA level measurements for this site were verified at the sponsor inspection.

2. **Humberto Hernandez, M.D.**
   Site #1470
   Protocol: C4671005 (EPIC-HR)
   14001 NW 4th Street, Suite C
   Sunrise, FL 33325
   PDUFA Inspection Dates: September 22, 23, 26, 27, and 30, 2022 and October 3-7 and 11-13, 2022

At this site for Protocol EPIC-HR, 39 subjects were screened, 38 were randomized, and zero subjects completed the study. Thirty-six (36) subjects were transferred to another site (site #1276) to complete the study after the study was terminated by the IRB (1/13/2022) for serious noncompliance and the site was closed by the sponsor (2/19/2022). Of the 4 subjects who did not complete the study, 2 subjects (subjects (b) (6) and # (b) (6) discontinued after experiencing a serious adverse event (SAE), and 2 subjects (subjects (b) (6) and (b) (6)) withdrew consent.

Reviewer's comment: At the time of their transfer to site #1276, the transferred subjects had already reached the primary efficacy analysis timepoint. For this reason, we determined that verification of the primary efficacy endpoint data for the transferred subjects could be conducted during the inspection of Dr. Hernandez.

The inspection evaluated the study records for 38 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

Adverse events were reviewed for 23 randomized subjects. One (1) adverse event for each of 9

subjects was not recorded in the EDC. These included 2 events of metallic taste, 5 events of abnormal lab results (elevated ALT [n=2]; increased PTT, increased D-dimer, and increased CPK [n=1 each]), and a single event each of hypertension and elevated TSH/low T3 (hypothyroidism). The occurrence of COVID-19 related hospitalizations and death from any cause were verified against the data line listings provided by the sponsor for 23 of 38 randomized subjects. Viral RNA level measurements for this site were verified at the sponsor inspection.

Reviewer's comment: Although these clinical laboratory test abnormalities should have been reported as AEs, all but one (metallic taste, a known side effect of Paxlovid) were contained in the NDA submission in the clinical laboratory datasets and vital sign datasets and so these data were included in the safety analyses.

An FDA Form 483 was issued stating that 5 of 23 subjects did not meet an inclusion criterion, or met an exclusion criterion, but were screened, enrolled, randomized, and received investigational product. Specifically, subject (b) (6) had a chronic lung disease but was not taking daily prescription therapy as required (a protocol deviation was recorded and submitted to the IRB); subjects # (b) (6) and (b) (6) were enrolled >5 days after the onset of their COVID-19 signs/symptoms; and subjects # (b) (6) and (b) (6) both had received or were expected to receive a dose of SARS-CoV-2 vaccine before the Day 34 visit.

Reviewer's comment: At the time the protocol deviations for subjects (b) (6) were noted by the study monitors, the subjects had completed the study treatment. No notation regarding vaccination-related protocol deviations for subjects (b) (6) and (b) (6) appears in the monitoring records. With the exception of subject (b) (6) each of these subjects was appropriately not included in the per protocol analysis set. Subject (b) (6) 's data should have been removed by the sponsor from the per-protocol analysis set, a single extra subject is very unlikely to make a difference for the per-protocol analysis.

3. **Carlos Martinez, M.D.**
   Site #1274
   Protocol: C4671005 (EPIC-HR)
   Site #1281
   Protocol: C4671005 (EPIC-SR)
   10912 Southwest 184th Street
   Cutler Bay, FL 33157
   PDUFA Inspection Dates: October 17, 2022, to November 1, 2022

At this site for Protocol EPIC-HR, 101 subjects were screened, 95 were randomized, and 94 subjects completed the study. At this site for Protocol EPIC-SR, 50 subjects were screened, 46 were randomized, and 46 subjects completed the study.

The inspection evaluated the study records for the 95 randomized subjects for Protocol EPIC-HR and all 46 subjects for Protocol EPIC-SR. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review

board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

Adverse events were reviewed for both studies. There was no evidence of under-reporting of adverse events, with the exception of a single AE of headache (subject # (b) (6) in Study EPIC-HR).

Reviewer's comment: This single AE should have been reported to the sponsor. However, headache is proposed to be included in the label for Paxlovid.

Regarding adverse events, the inspection found that an SAE (subject (b) (6) in Study EPIC-HR) was reported more than 24 hours after the site became aware of their occurrence. The protocol required that any subject with an eGFR <45 ml/min/1.73m^2 be discontinued from the study intervention dosing. The eGFR measured on Day 1 (b) (6) was 32 ml/min/1.73m^2. The CI signed the result as reviewed on (b) (6), but the initial SAE report was not submitted to the sponsor until six days later (b) (6). The subject was not discontinued from the study intervention dosing and completed all five days of the study treatment.

Reviewer's comment: In general, the failure to report SAEs within the 24-hour time frame as required by the protocol puts subjects at increased risk. In this case, Dr. Martinez did not discontinue the study drug for this subject. As a result, subject (b) (6) was unnecessarily exposed to potential increased risk.

During the EPIC-HR inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 95 randomized subjects. No discrepancies were noted. Viral RNA level measurements for this site were verified at the sponsor inspection.

A comparison of the PIN codes used by each subject to the PIN codes used by other subjects was performed for all randomized subjects in both studies. An FDA Form 483 was issued stating that during the conduct of EPIC-HR and EPIC-SR, multiple subjects were instructed to change their e-diary PIN code (used for recording their daily dosing and symptoms data) to one provided by the study staff.

Reviewer's comment: The inspection found no information to suggest that anyone other than the subjects entered e-diary data into their e-diaries. However, we recommend sensitivity analyses with regard to this site.

(b) (7)(A)

(b) (7)(A)

4. Roza Mitreva, M.D.
Site #1158
Protocol: C4671005 (EPIC-HR)
49 Macedonia St.
Samokov 2000 BULGARIA
PDUFA Inspection Dates: October 24-28, 2022

At this site for Protocol EPIC-HR, 56 subjects were screened, 56 were randomized, and 50 subjects completed the study. Of the 6 subjects who did not complete the study, 5 subjects discontinued due to personal reasons, and one subject died. Of the 5, 3 were assigned to the Paxlovid group and 2 were assigned to the placebo group.

The inspection evaluated the study records for the 56 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation.

Serious adverse events were reviewed for all subjects and nonserious adverse events were reviewed for over half of the subjects. There was no evidence of under-reporting of adverse events. During the inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 56 randomized subjects. No discrepancies were noted. Viral RNA level measurements for this site were verified at the sponsor inspection.

A notable number of laboratory reports indicated that samples sent for clinical laboratory testing were “unable to process” or “out of stability.” The site staff was not aware of these issues until well after samples were received by the laboratory. Pfizer became aware of this issue and arranged for high-enrolling sites to have daily sample pickup for shipment to the central laboratory.

Reviewer’s comment: Although a number of laboratory tests were not completed, because this lab data did not contribute to the primary efficacy endpoint, this did not impact the efficacy results of the study. However, missing lab results did limit the robustness of the safety data for subjects at this site.

5. Iana Simova, M.D.
Site #1097
Protocol: C4671005 (EPIC-HR)
2, Pier Curie Str.
Pleven 5800 BULGARIA
PDUFA Inspection Dates: October 31, 2022, to November 4, 2022

At this site for Protocol EPIC-HR, 41 subjects were screened, 41 were randomized, and 36 subjects completed the study. Of the 5 subjects who did not complete the study, 2 subjects discontinued for personal reasons, 1 subject was randomized but did not receive treatment due to enrollment closure, and 2 subjects died. Both of the subjects who discontinued were assigned to the Paxlovid group.

The inspection evaluated the study records for the 41 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation.

Serious adverse events were reviewed for all subjects and nonserious adverse events were reviewed for over half of the subjects. There was no evidence of under-reporting of adverse events. During the inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 41 randomized subjects. No discrepancies were noted.

A modest number of laboratory reports indicated that samples sent for clinical laboratory testing were “unable to process” or “out of stability.” The site was not aware of these issues until well after samples were received by the laboratory. Pfizer became aware of this issue and arranged for high-enrolling sites to have daily sample pickup for shipment to the central laboratory.

Reviewer’s comment: Although a modest number of laboratory tests were not completed, because this lab data did not contribute to the primary efficacy endpoint, this did not impact the efficacy results of the study. However, missing lab results did limit the robustness of the safety data for subjects at this site.

6. **Asen G. Medzhidiev**
   Site #1157
   Protocol: C4671002 (EPIC-SR)
   UMHATEM N. I. Pirogov EAD, Department of Ear & Throat Diseases
   Bulevard Gen Totleben 21, Sofiya, Oblast Sofiya Grad,
   1606 Bulgaria
   PDUFA Inspection Dates: December 12-16, 2022

At this site for Protocol EPIC-SR, 49 subjects were screened, 48 were randomized, and 46 subjects completed the study. Two subjects did not complete the study. Of the 2 subjects who did not complete the study, 1 (subject # (b) (6)) never started treatment due to "insufficient medication" and the other withdrew consent (subject # (b) (6)). Both were assigned to the placebo group.

The inspection evaluated the study records for 16 of the 49 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug administration records; monitor logs and follow-up letters; and other regulatory documentation.

Adverse events were reviewed for 16 randomized subjects. There was no evidence of under-reporting of adverse events. During the inspection, the paper medical and other source records were reviewed, and, although not a primary efficacy endpoint, the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for 16 of randomized subjects. No discrepancies were noted.

PIN code comparisons to subject birth years and to other subject's PIN codes were performed for all randomized subjects. An FDA Form 483, Inspectional Observations, was issued stating that during the conduct of EPIC-SR, the clinical investigator did not ensure that each participant created a new device PIN code that remained confidential to the participant only. Instead, participants were instructed to use PIN codes that were easy to remember, such as their birth dates, which were readily available to the site. Records revealed that 46 of 49 enrolled participants used their birth year as their new PIN code.

Reviewer's comment: The inspection found no information to suggest that anyone other than the subjects entered e-diary data into their e-diaries.

7. **Nezabravka Petrova Haytova**
   Site #1193
   Protocol: C4671005 (EPIC-HR)
   Site #1197
   Protocol: C4671002 (EPIC-SR)
   Specialized Hospital for Active Treatment of
   Pneumo-Phthisiatric Diseases Vratsa EOOD,
   Department of Pneumology

93 General Leonov str. Vratsa,
VRATSA, 3000 BULGARIA
PDUFA Inspection Dates: December 12-16, 2022

At this site for Protocol EPIC-HR, 59 subjects were screened and randomized, and 58 subjects completed the study. A single subject who decided to drop out, subject (b) (6) was assigned to the placebo group.

At this site for Protocol EPIC-SR, 33 subjects were screened, 33 were randomized, and 32 subjects completed the study. Subject (b) (6), assigned to the Paxlovid group, withdrew consent. The inspection evaluated the study records for all 59 randomized subjects for Protocol EPIC-HR and all 33 randomized subjects for Protocol EPIC-SR. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting, protocol deviations; drug administration records; monitor logs and follow-up letters; and other regulatory documentation.

During the EPIC-HR inspection, the paper medical and other source records were reviewed, and the occurrence of COVID-19 related hospitalizations and death from any cause was verified against the data line listings provided by the sponsor for all 59 of randomized subjects. No discrepancies were noted.

After study EPIC-SR closure, the sponsor provided the site with a USB flash drive with copies of the final versions of the e-diary source data. During the inspection, the e-diary data was reviewed, and the time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28 was verified against the data line listings provided by the sponsor for all 33 randomized subjects. No discrepancies were noted.

Adverse events were reviewed for both studies. There was no evidence of under-reporting of adverse events.

PIN code comparisons to subject birth years and to other subject's PIN codes were performed for all randomized subjects from both protocols. An FDA Form 483 was issued stating that during the conduct of EPIC-HR and EPIC-SR, the clinical investigator did not follow the Site User Guide. Specifically, the Site User Guide for the electronic patient reported outcome (ePRO) application used in the study to collect electronic diaries states "The participant should not share their PIN code with anyone, not even with study staff. The new PIN code must remain confidential, with only the participant knowing the PIN code." However, when assisting subjects to download and activate the application, the investigator's site staff provided suggestions in a manner that caused the subjects in the studies to create nonconfidential PIN codes. The investigator's site staff gave examples of easily memorable numbers to use for a PIN code, including birth year and specific numbers such as "2323."

Reviewer's comment: The inspection found no information to suggest that anyone other than the subjects entered e-diary data into their e-diaries.

8. Pfizer, Inc.
Protocol: C4671005 (EPIC-HR)
Protocol: C4671002 (EPIC-SR) – limited coverage of this protocol
445 Eastern Point Road,
Groton, CT 06340
PDUFA Inspection Dates: October 12-28, 2022

This inspection covered the sponsor practices primarily related to Protocol EPIC-HR with limited coverage of Protocol EPIC-SR and focused on the five clinical investigator sites from Study EPIC-HR (sites #1274, #1108, #1470, #1158, and #1097) that had been selected for inspection.

The inspection reviewed the following activities and found them to be adequate:

- Clinical investigator selection (identification and monitoring was provided by (b) (4), who contracted (b) (4) to supplement the site visits and clinical monitoring)
- Site monitoring, as per the monitoring plan, and the sponsor's procedure
- Contractual agreements with (b) (4)
- Vendor data transfer methods to the sponsor
- Monitoring of the vendors to ensure the study was being conducted in accordance with the study protocol, contractual agreement, and sponsor's procedures
- Communication methods and frequency between the sponsor, vendor, and clinical sites
- Completion of monitoring reports and management of findings
- Quality assurance audits
- Custody and retention of records
- Maintenance of financial disclosure forms
- Maintenance of adequate records showing receipt and shipment of the investigational product
- Confirmation of receipt condition and storage conditions of the investigational product

Due to limited time, safety and adverse event reporting was reviewed only briefly. The inspection found that the following related to the data monitoring committee were sufficient: the charter, written procedure, membership qualification, board composition, meeting minutes, blinding, and the process of collection, evaluation, analyses, and reporting of adverse events.

General discussion with management included the following issues: inadequate supply of e-diary devices, inadequate supply of nasal swabs, and concerns about attributing data to specific subjects because a majority of the subjects at Martinez's site for both studies were found to be using the PIN code "1274" for their e-diaries. Of note, the sponsor performed an audit related to the PIN code issue at Dr. Martinez's site. They concluded that (b) (4), which was responsible for the e-diaries, did not have systems in place to prevent and detect the use of common PIN codes among participants.

Reviewer comment: Please see the summary of Dr. Martinez's site above for more detail regarding this issue.

Regarding the inadequate supply of e-diary devices: the sponsor did not track the supply of e-diaries at clinical sites to ensure each site had adequate supplies, and the clinical sites were not required to confirm adequate supply of e-diaries. Therefore, it was concluded that the sponsor oversight of e-diary supplies was inadequate.

Regarding the inadequate supply of nasal swabs, sponsor oversight was similarly not sufficient. As with the e-diary supply problem, the sponsor did not track the supply of nasal swabs at the clinical sites to ensure each site had adequate supplies. Furthermore, the response to the inadequate supply of I SWAB PLUS swabs ultimately led to the approval of locally sourced swabs for use and, ultimately, to the exclusion of this data from the data set because viral RNA data obtained using locally sourced swabs were not permitted per the statistical analysis plan.

{See appended electronic signature page}

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OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Elena Boley
OSI/GCPAB/Program Analyst/Yolanda Patague

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/s/

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PHILLIP D KRONSTEIN
01/31/2023 04:45:42 PM

JENN W SELLERS
01/31/2023 05:36:17 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 9, 2023
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 217188
Product Name and Strength:	Paxlovid (Nirmatrelvir 300 mg[a]; Ritonavir 100 mg) and (Nirmatrelvir 150 mg; Ritonavir 100 mg) dose packs
Applicant/Sponsor Name:	Pfizer Inc.
OSE RCM #:	2022-33-2
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph.
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 20, 2022 for Paxlovid. The Division of Antivirals (DAV) requested that we review the revised container labels and carton labeling for Paxlovid (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] packaged as two 150 mg Nirmatrelvir tables.
[b] Fanari, Melina. Label and Labeling Review for Paxlovid (NDA 217188). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Dec 12. RCM No.: 2022-33-1.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MELINA N FANARI
01/09/2023 03:34:46 PM

MADHURI R PATEL
01/09/2023 05:57:55 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 12, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 217188
Product Name, Dosage Form, and Strength:	Paxlovid (Nirmatrelvir 300 mg[a]; Ritonavir 100 mg) and (Nirmatrelvir 150 mg; Ritonavir 100 mg) dose packs
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	June 29, 2022 and November 9, 2022
TTT ID #:	2022-33-1
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph.
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

[a] packaged as two 150 mg Nirmatrelvir tables.

1 REASON FOR REVIEW

As part of the approval process for Paxlovid (Nirmatrelvir; Ritonavir) tablets (NDA 217188), the Division of Antivirals (DAV) requested that we review the proposed Paxlovid prescribing information, patient prescribing information, container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Paxlovid is currently authorized for use under EUA 105 for the treatment of symptomatic COVID-19 in pediatric and adult patients who are at high risk for progression to severe COVID-19. Under EUA 105, there have been multiple revisions to product labeling to address ongoing wrong dose medication errors occurring during patient self-administration.[b] As a result, FDA requested for Pfizer to revise the product design and/or packaging configuration (e.g., single dose blister cards) under NDA 217188[c] to address the ongoing wrong dose medication errors and support all dosing regimens in the product labeling. Pfizer proposed a new packaging presentation in their November 9, 2022 submission. Our review of the revised packaging presentation of Paxlovid, the prescribing information (PI), patient prescribing information (PPI),

[b] Fanari, M. Label and Labeling Review for Paxlovid (NDA 217188). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Aug 3. RCM No.: 2021-2174-4

[c] Fanari, M. Label and Labeling Review for Paxlovid (NDA 217188). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Aug 29 RCM No.: 2022-33

container labels and carton labeling identified areas that may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error. We collaborated with DAV to update the PI (section 2, 3, 16 and 17) and PPI to reflect the revised single dose blister packaging presentation and administration instructions and provide comments in Section 5 for Pfizer.

4 RECOMMENDATIONS FOR PFIZER

Table 1. Identified Issues and Recommendations for Pfizer (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels (150 mg;100 mg and 300 mg;100 mg)			
1.	Arrows needed to identify tablets needed.	Clearly define the location of tablets.	Insert arrows from the dose statements (Take these 2 tablets together, Take these 3 tablets together) to clearly indicate which tablets to take on the blister card.
2.	Redundancy in use of established name (in 2 locations, (b) (4)	Remove clutter and redundancy of information, which may lead to confusion.	Revise the strength presentation as follows (b) (4) **PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets),** co-packaged for oral use 150 mg;100 mg or **PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets),** co-packaged for oral use 300 mg;100 mg

Table 1. Identified Issues and Recommendations for Pfizer (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Carton Labeling (150 mg;100 mg and 300 mg;100 mg)			
1.	Dose statement is unclear and lacks prominence.	Mitigate wrong dose errors.	Revise the dose statements as follows: <u>150 mg;100 mg Dose Pack</u> Take both tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days. Or <u>300 mg;100 mg Dose Pack</u> Take all 3 tablets from one blister card together, twice daily (in morning and at bedtime) for 5 days. In addition, increase the prominence of the dose statement with the use of different colors, boxing, or some other means and ensure the dose statement follows the product strength throughout the carton labeling.
2.	"Each carton contains" statements (with bullets) are too prominent.	Relocate to a less prominent area to increase prominence for dosing information.	Relocate the "Each carton contains" statements to the bottom of the principal display panel, after the strength statements and dose statements.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Paxlovid received on June 29, 2022 and November 9, 2022 from Pfizer Inc.

Table 2. Relevant Product Information for Paxlovid	
Initial Approval Date	N/A; EUA authorized 12/2022
Active Ingredient	nirmatrelvir copackaged with ritonavir
Indication	Treatment of adult (b) (4) who are at high risk for progression to severe COVID-19.
Route of Administration	oral
Dosage Form	tablet
Strength	150 mg nirmatrelvir and 100 mg ritonavir 300 mg nirmatrelvir and 100 mg ritonavir
Dose and Frequency	300 mg nirmatrelvir (2 tablets of 150 mg) and 100 mg ritonavir (one 100 mg tablet) or 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) twice daily for 5 days
How Supplied	150 mg;100 mg-Cartons of 20 tablets in 10 blister cards. Each blister card contains 2 tablets 300 mg;100 mg-Cartons of 30 tablets in 10 blister cards. Each blister card contains 3 tablets
Storage	Store at room temperature 20°C to 25°C (68°F to 77°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 17, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Paxlovid and EUA 105. Our search did not identify any previous relevant reviews and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Paxlovid labels and labeling submitted by Pfizer Inc..

- Container label received on November 9, 2022
- Carton labeling received on November 9, 2022
- Prescribing Information (Image not shown) received on June 29, 2022, available from \\CDSESUB1\evsprod\NDA217188\0001\m1\us

G.2 Label and Labeling Images

Container Labels

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217188
Submission Number	6
Submission Date	7/29/2022
Date Consult Received	8/1/2022
Drug Name	Paxlovid (nirmatrelvir and ritonavir)
Indication	Treatment of mild to moderate COVID-19
Therapeutic Dose	Nirmatrelvir/ritonavir 300/100 mg BID for 5 days
Clinical Division	DAP
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 8/1/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review for IND-153517 dated 01/27/2022 (link), 11/18/2021 (link), and 10/14/2021 (link) in DARRTS;
- Sponsor's QT evaluation report (SN0005; link);
- Sponsor's CQT analysis report for study #C4671001 (SN0005; link);
- Appendices to CQT analysis report for study #C4671001 (SN005; link);
- Sponsor's protocol #C4671001 (SN0001; link);
- Sponsor's clinical study report for #C4671001 (SN0001; link);
- Sponsor's clinical pharmacology summary (SN0001; link);
- Sponsor's proposed label (SN0001; link);
- Investigator's brochure Version 5.0 (SN0005; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0005; link).

1 SUMMARY

Nirmatrelvir/ritonavir did not prolong the QTcF interval which is based on both the concentration-QTc analysis of study #C4671001 and negative findings in the nonclinical studies (hERG and in vivo QT). This clinical and nonclinical integrated risk assessment can be used as a substitute for a thorough QTc study under ICH E14 Q&A 5.1.

The clinical study #C4671001 included a cross-over study with placebo and nirmatrelvir 2250 mg (divided into three doses) and ritonavir 100 mg (Part 5). The dose provided 1.5-fold high clinical exposure (severe renal impairment with 150 / 100 mg, see section 3.1.2). The high clinical exposure scenario considers severe renal impairment as the proposed label did not include contraindication and assumes that the dose administered would be the same as patients with moderate renal impairment. Because the study did not

provide sufficiently high exposures to support waiving the requirement for a separate positive control, a negative integrated nonclinical risk assessment (hERG and in vivo QT) was therefore used to support study interpretation.

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☒ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings[1]</td><td>• Clinical exposure (with food): 7.5 µg/mL
• High clinical exposure (severe renal impairment with 150/100 mg nirmatrelvir/ritonavir plus food): 10.8 µg/mL
• Exposure coverage in QT assessment: 1.47
<table>
<tr><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>Nirmatrelvir 2250 mg and ritonavir 100 mg</td><td>15943.7</td><td>0.5</td><td>(-2.4 to 3.4)</td></tr>
</table></td></tr>
<tr><td>In vitro findings[2]</td><td>
<table>
<tr><td></td><td>Safety Margin</td><td>Reference Drugs</td><td>Best Practice Deviations</td></tr>
<tr><td>Nirmatrelvir</td><td>>44x (12% inhibition). Extrapolation using h (ranging from 0.5 to 1.5) yield a minimum IC50 of 1158 uM (173x)</td><td>3 - 60x</td><td>Unable to determine IC50, which is addressed by assuming a range of hill slopes (0.5 – 1.5).</td></tr>
</table></td></tr>
<tr><td>In vivo findings</td><td>• No QTc prolongation was observed in the vivo monkey study at exposures expected to exceed the high clinical exposure scenario.</td></tr>
</table>

[1]The findings of the exposure-response analysis are further supported by the lack of QTc prolongation in the by-time analysis (section 4.3) and categorical analysis (section 4.4). [2]Negative integrated nonclinical risk assessment (hERG and in vivo QT) is provided in section 3.1.3).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

(b) (4) in the label submitted to eCTD 0026 (link).

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At [redacted] (b) (4) times the [redacted] (b) (4) recommended dose, nirmatrelvir does not prolong the QT interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance. [redacted] (b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Paxlovid is a combination product of nirmatrelvir (PF-07321332, MW: 499.54) 150 mg and ritonavir 100 mg. Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}: also referred to as $3CL^{pro}$ or nsp5 protease) inhibitor, while ritonavir is a HIV-1 protease inhibitor and a CYP3A inhibitor which was approved previously for treatment of HIV infection in combination with other antiretrovirals. Notably, ritonavir has been observed to prolong PR and QTc in a TQT study (Norvir USPI). The sponsor (Pfizer, Inc) has developed paxlovid for the proposed indication of treatment of mild-to-moderate corona virus disease 2019 (COVID-19) in adults [redacted] (b) (4) The maximum recommended dose of paxlovid for this indication is nirmatrelvir/ritonavir 300/100 mg BID for 5 days.

The sponsor's QT assessment plan for nirmatrelvir was reviewed by IRT previously (see previous IRT reviews). In brief, the sponsor proposed an integrated clinical and nonclinical QT assessments under ICH E14 Q&A 5.1. The sponsor planned to conduct concentration-QTc analysis of time matched PK and ECG data collected from the first in human study, Study C4671001, which was a 5 part study evaluating single ascending doses in Part 1, multiple ascending doses in Part 2, relative bioavailability and food effect in Part 3, metabolism and excretion in Part 4 and safety of supratherapeutic exposures in Part 5.

Part 1 of the study was a randomized, double-blind (open-label, sponsor), placebo-controlled study evaluating safety, tolerability, and pharmacokinetics of single escalating oral doses of nirmatrelvir in healthy subjects. Part 1 included 2 interleaving cohorts with a total of 13 subjects with 3-period cross-over in each cohort (150, 500, 1500, 250 mg with ritonavir, 750 mg with ritonavir, all under fasting conditions; and 250 mg under fed condition with 100 mg ritonavir at -12, 0 and 12 h; n= 4+2/cohort). The peak

concentration (Cmax: ~5 μg/mL) observed with highest dose studied (i.e., 750 mg, with 100 mg ritonavir at -12, 0 and 12 h) only covers the therapeutic Cmax associated with the maximum proposed dose at the steady state (Cmax: ~4.7 μg/mL).

Part 5 of the study was a randomized, double-blind (open-label, sponsor), placebo-controlled, crossover (2-sequnce) study evaluating safety, tolerability, and pharmacokinetics of nirmatrelvir (at supratherapeutic exposures) in healthy subjects (n=10). Subjects received 2250 mg (administered as a split dose 750 mg at 0, 2, and 4 h with 100 mg ritonavir at -12, 0 and 12 h). Study included ECG and PK measurements in fasted state (approximately 4 h after the food) at nominal times of 0, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, 72 and 96 hours after the first dose of nirmatrelvir. The peak concentration (Cmax: ~15.9 μg/mL) observed at studied dose covers ~1.47-fold of the anticipated high clinical exposure in subjects with severe renal impairment taking paxlovid 150 mg/100 mg with food and hence does not meet the requirement for waiving a positive control (i.e., < 2-fold of high clinical Cmax). The findings of this QT study are therefore supported by a negative integrated nonclinical risk assessment (see section 3.1.3).

Part 5 included a shorter dosing regimen of ritonavir (100 mg BID for 1.5 days) than the recommended dosing regimen per label (100 mg BID for 5 days). Based on the observed ritonavir concentrations following 3 days of 100 mg BID (1.4 ug/mL, Study C4671015) clinically significant ECG changes due to ritonavir are not expected for both the recommended dosing per product label and Part 5 dosing regimen based on the reported findings of the TQT study[1].

3.1.2 Clinical Pharmacology

A summary of nirmatrelvir clinical pharmacokinetics is presented in the table of highlights of clinical pharmacology and cardiac safety.

In brief, nirmatrelvir exhibits less than dose proportional increase in exposure between 150 – 1500 mg (alone, and 75 -750 mg, with ritonavir) and reaches steady state of exposures after 2 days of BID dosing with AUC and Cmax accumulation ratio of about ~1.8-fold. The nirmatrelvir/ritonavir 300/100 mg BID dosage, under fasted condition, provides steady state geometric mean Cmax (%CV) of 4.678 (17%) μg/mL (CP summary, table 20, page 66). Based on in vitro assays, nirmatrelvir is mainly metabolized by CYP3A4. However, no metabolites are detected in plasma when nirmatrelvir is co-administered with ritonavir in humans. Except for high fat meal and renal impairment, no other intrinsic and extrinsic factors have impact on nirmatrelvir pharmacokinetics. High fat meal increases nirmatrelvir Cmax and AUC by 1.6- and 1.2-folds respectively (CP summary, table 14, page 135). The anticipated steady-state Cmax therefore includes the effect of food. Increased exposure was observed in patients with severe renal impairment compared to healthy subjects (AUC: ~3-fold; Cmax: ~1.5-fold). In the sponsor's

[1] Per the ritonavir label: The maximum recommended ritonavir dose for treatment of HIV is 600 mg BID (Cmax,ss: 11.2 ug/ml; under fed condition). In a thorough QT study, which evaluated 1.5x Cmax,ss of 600 mg BID, a maximum mean increase of 5.5 msec (95% upper CI: 7.6) and 22 (25 msec) for QTcF and PR, respectively.

proposed label, paxlovid will not be recommended in patient with severe renal impairment, and its dose will be reduced by 50% in patients with moderate renal impairment. Since paxlovid is not contraindicated in subjects with severe renal impairment, physicians may opt to prescribe the drug in this population at a reduced dose. Paxlovid 150 mg/100 mg (nirmatrelvir/ritonavir) is the potential dose in severe renal impairment since the smallest dose unit for nirmatrelvir is 150 mg unscored tablets. The high clinical exposure scenario is therefore 150/100 mg in patients with severe renal impairment under fed conditions. The predicted clinical and high clinical exposure is shown in Table 1 and is based on observed Cmax,ss following 300 / 100 mg in healthy volunteers and predicted Cmax,ss in severe renal impaired patients using superpositioning (QT evaluation report, Table 2).

Table 1: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	Nirmatrelvir/ritonavir 300/100 mg BID for 5 days with food	7.5[1] µg/mL ($C_{max,ss}$)
Sponsor's high clinical exposure scenario	Severe renal impairment taking 150 mg/100 mg with food[2]	10.8 µg/mL
Highest dose in QT assessment	2250 mg nirmatrelvir (split dosing) with 100 mg ritonavir BID	15.9 µg/mL
C_{max} Ratio	1.47	

1: Steady-state Cmax from C4671015 in healthy participants given 300 / 100 mg nirmatrelvir / ritonavir (4.68 µg/mL) x 1.6 (food effect). 2: Predicted steady-state Cmax using superposition for severe renal impaired patients given 100 / 100 mg nirmatrelvir / ritonavir (4.52 µg/mL) x 1.5 (assuming dose proportionality) x 1.6 (food effect).

3.1.3 Nonclinical Safety Pharmacology Assessments

The sponsor assessed the effects of nirmatrelvir and three reference drugs (dofetilide, ondansetron and moxifloxacin) on hERG current (study reports 22LJ022 and 22LJ025). Original electrophysiology records for ion channel studies were provided by the sponsor. We reanalyzed these records of hERG assay to assess data quality and verify study report conclusions (see Appendix 5.2).

The GLP in vivo monkey study (20GR275) assessed pharmacological effects of nirmatrelvir on the cardiovascular system including ECG changes (see Appendix 5.2).

Reviewer's comment: *The hERG assays met most of the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1 (link). The hERG results showed that nirmatrelvir has a hERG safety margin of >44x (12% inhibition at 300 µM, the highest tested concentration). The estimated IC50 of nirmatrelvir on hERG current are from 1158 µM to 18266 µM with the safety margin from 173x to 2726x by fitting data to hill equation with a hill slope from 1.5 to 0.5, respectively. Three reference drugs dofetilide, ondansetron and moxifloxacin have hERG safety margins of 59x, 2.9 x and 21.8x, respectively. The estimated safety margin of nirmatrelvir is larger than the safety margins of dofetilide, ondansetron and moxifloxacin. The results from the hERG assay*

suggest that nirmatrelvir has a low risk for QT prolongation by directly inhibiting the hERG current at high clinical exposure.

No QTc prolongation was observed at exposures exceeding the anticipated high clinical exposure in the in vivo monkey study.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for PF-07321332 was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *The sponsor's by-time analysis used Part 5 data only, and Part 5 with Part 1 pooled data. The reviewer evaluated the ΔΔQTcF effect using descriptive nonparametric statistics for Part 5 and Part 1 separately. Since the treatment group and placebo group are not independent in the crossover study, ΔΔQTcF is used as dependent variable for descriptive nonparametric statistics. The trend shown in by-time analysis from reviewer's analysis is similar to the trend shown in sponsor's by-time analysis. Please see Section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

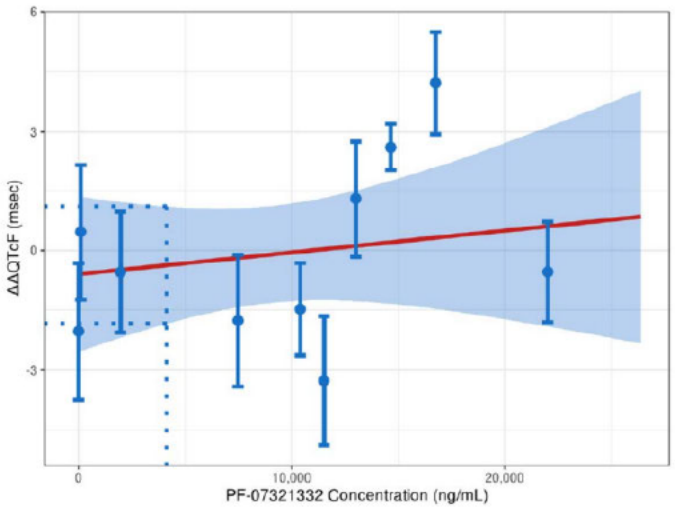
There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (>100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *The reviewer's analysis results are based on subjects from Part 1 and Part 5. The reviewer's analysis results are the same with sponsor's analysis results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

CQTc analysis using the PK and ECG parameters from PART-5:SE were performed as described by Garnett et al.2 Additional sensitivity analysis by pooling with PART-1: SAD was also performed. PART-1 and PART-5 were conducted at the same site. In PART-5, one participant had concentration below limit of quantification at 6h, approximately the time of expected Cmax with split dosing; therefore, that timepoint was removed from the analyses.

The upper bounds of 90% CI for ΔΔQTcF estimates across the entire concentration range were all well below 10 ms, the threshold for potential clinical and regulatory concern. This was also consistent with the pooled analysis (Appendix 2)



The red line is the predicted ΔΔQTcF over the range of observed concentrations and shaded region is the 90% CI. Blue circles and error bars represent the observed ΔΔQTcF (using the model-estimated, time-matched placebo effect subtracted from the ΔQTcF of the active treatment group's observations) across the observed concentration bins (n = 10, with equal number of observations in each bin). The blue dotted lines correspond to the predicted lower and upper 90% CI ΔΔQTcF for the projected mean C_{max} at Phase 2/3 dose.
Source: Appendix 1, Figure 7.

Table 2. Model-derived ΔΔQTcF Prediction for Concentrations of Interest

	Concentration (ng/mL)	Mean ΔΔQTcF (90% CI) (ms)
Therapeutic exposure[a]	4140	-0.37 (-1.84, 1.1)
2x Therapeutic exposure[a]	8280	-0.15 (-1.37, 1.07)
2250 mg mean C_{max} in PART-5:C4671001	15944	0.27 (-1.42, 1.96)

a. Projected steady-state C_{max} at Phase 2/3 dosing regimen i.e. PF-07321332/ritonavir 300/100 q12h

Similar analysis was done for HR, PR, SBP, and DBP. Results from sponsor's analysis are summarized in the table below (Table 2).

Table 2: Summary of sponsor's concentration-response analysis

	Concentration	ΔΔHR (beats/min)	ΔΔPR (ms)	ΔΔSBP (mmHg)	ΔΔDBP (mmHg)
2250mg/RTV 100 mg	15944	-1.9 (-3.8, -0.05)	4.5 (2.5, 6.6)	6 (1.9, 10)	2.8 (0.3, 5.3)
300 / 100 mg nirmatrelvir / ritonavir	4140	-2.2 (-3.1, -1.2)	1.3 (0.1, 2.4)	1.5 (-0.3, 3.2)	1.3 (0.2, 2.5)

Source: Sponsor's CQT analysis of Part 5, Tables 3-6

Reviewer's comment: *The results of the concentration-QTc analysis is similar to the reviewer's independent analysis (see section 4.5.1). Notably, the concentration in the table above was based on a preliminary population PK model. Like the sponsor's analysis, the independent by-time analysis shows a numerical increase in PR (see section 4.3.3). Although, a small increase in blood pressure cannot be excluded based on the sponsor's analysis the intended treatment duration is short (i.e., 3 days) and for drugs with short-term use small increases are generally not considered meaningful.*

3.2.4 Safety Analysis

There were no deaths or serious adverse events. All adverse events were mild in severity except for one moderate adverse event of nasopharyngitis in Part 4. One discontinuation due to adverse event (SARS-CoV-2 test positive in Part 1).

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., unexplained syncope, seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from Part 5 were submitted. Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG for Part 5 and Part 1 separately. By-time analysis was performed using nonparametric statistics and observed ΔΔQTcF.

4.3.1 QTc

Figure 1 and Figure 2 display the time profile of ΔΔQTcF for different treatment groups from Part 5 and Part 1.

Figure 1: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs) – Part 5.

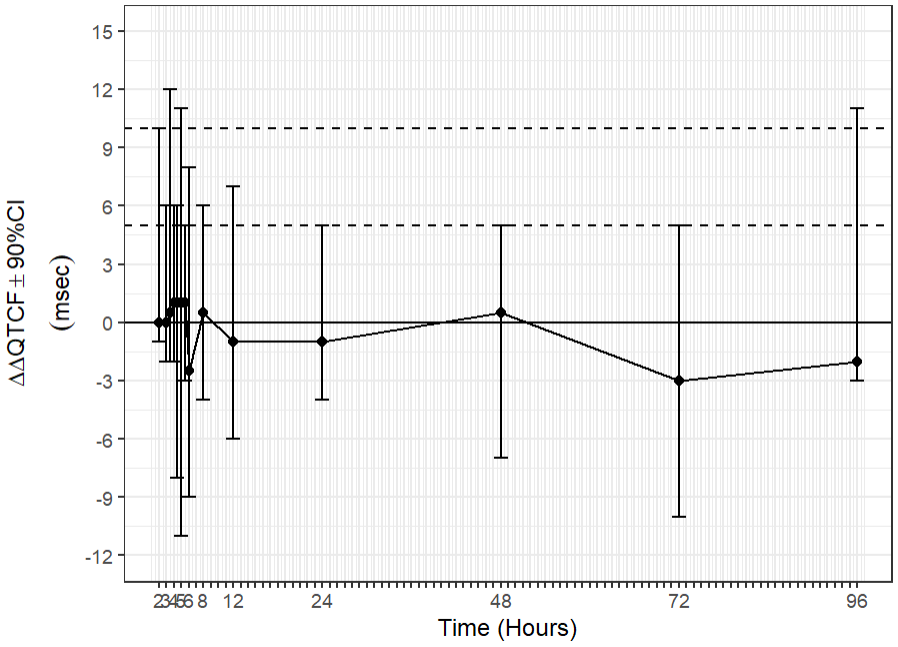
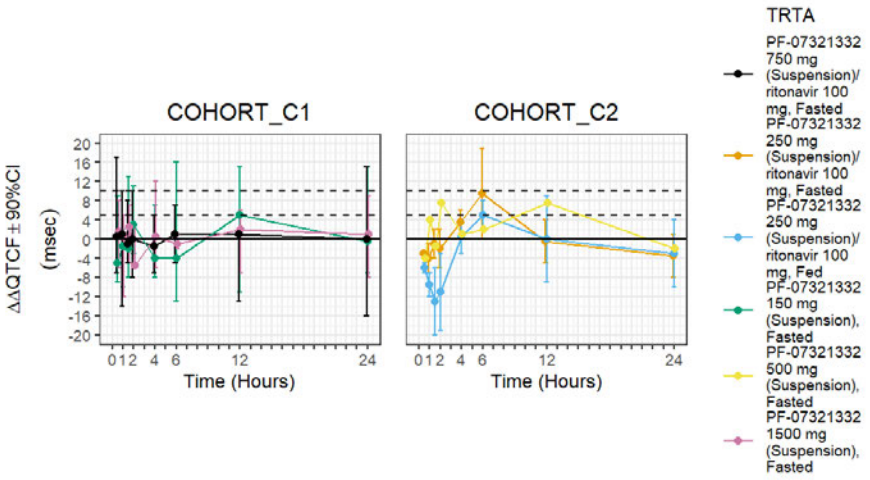


Figure 2: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs) – Part 1.



4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 3 and Figure 4 display the time profile of ΔΔHR for different treatment groups for Part 5 and Part 1.

Figure 3: Median and 90% CI of ΔΔHR Time-course – Part 5

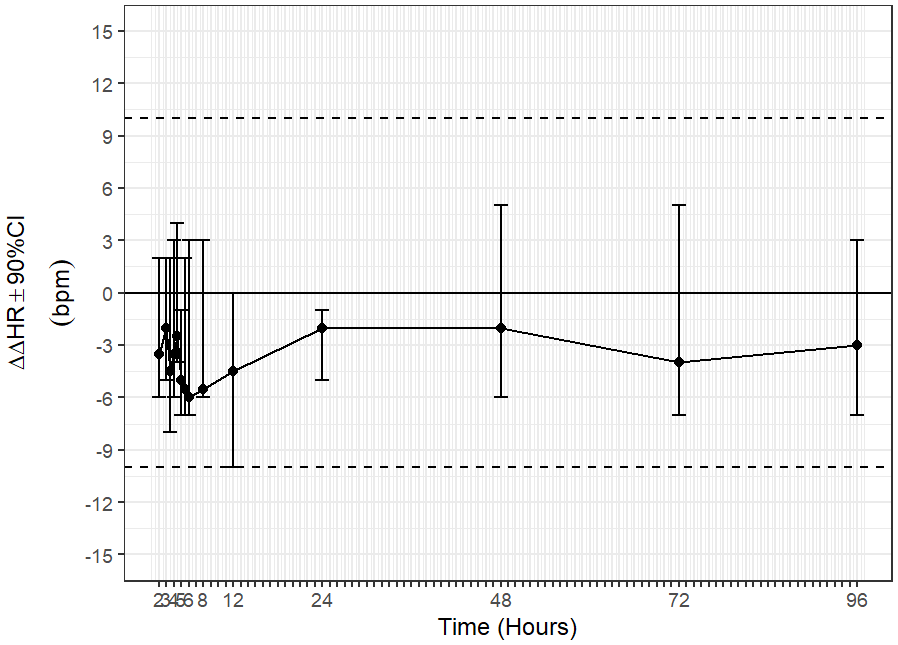
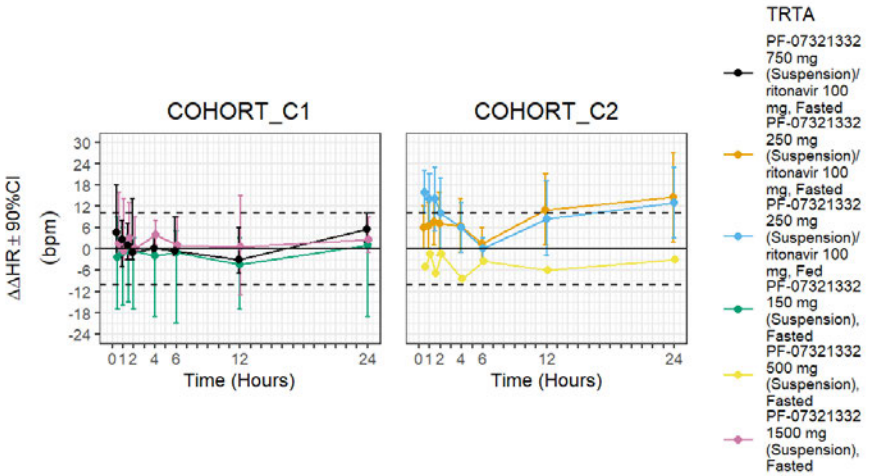


Figure 4: Median and 90% CI of ΔΔHR Time-course – Part 1



4.3.3 PR

Figure 5 and Figure 6 display the time profile of ΔΔPR for different treatment groups for Part 5 and Part 1. Numerical increase in ΔΔPR was observed in both Parts 1 and 5.

While, nirmatrelvir is administered with ritonavir (which has observed to prolong the PR interval) ritonavir is unlikely to have contributed to the observed PR prolongation based on dosing regimen in this study (see section 3.1.1). The findings of the by-time analysis are consistent with the sponsor's concentration-PR analysis (see section 3.2.3). There were no PR > 220 msec in the study (see section 4.4.3) and the numerical increase was observed at exposures exceeding high clinical (see section 3.1.2).

Figure 5: Median and 90% CI of ΔΔPR Time-course – Part 5

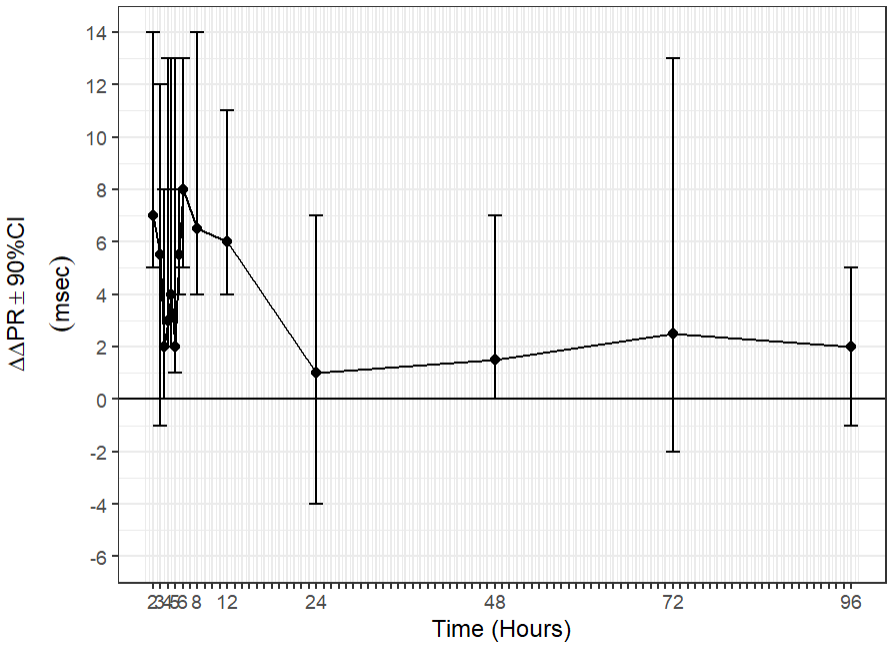
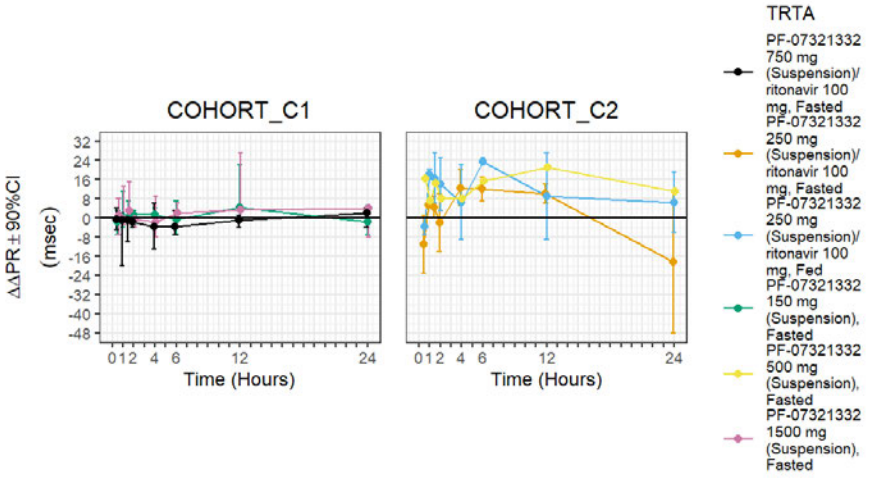


Figure 6: Median and 90% CI of ΔΔPR Time-course – Part 1



4.3.4 QRS

Figure 7 and Figure 8 display the time profile of ΔΔQRS for different treatment groups for Part 5 and Part 1. Numerical increase in QRS was observed following nirmatrelvir 500 mg. The time-course of the increase does not appear to follow nirmatrelvir concentration and QRS prolongation was not observed in Part 5, which evaluated higher exposures of nirmatrelvir. Furthermore, no QRS outliers were observed across Parts 1 and 5 (see section 4.4.4).

Figure 7: Median and 90% CI of ΔΔQRS Time-course – Part 5

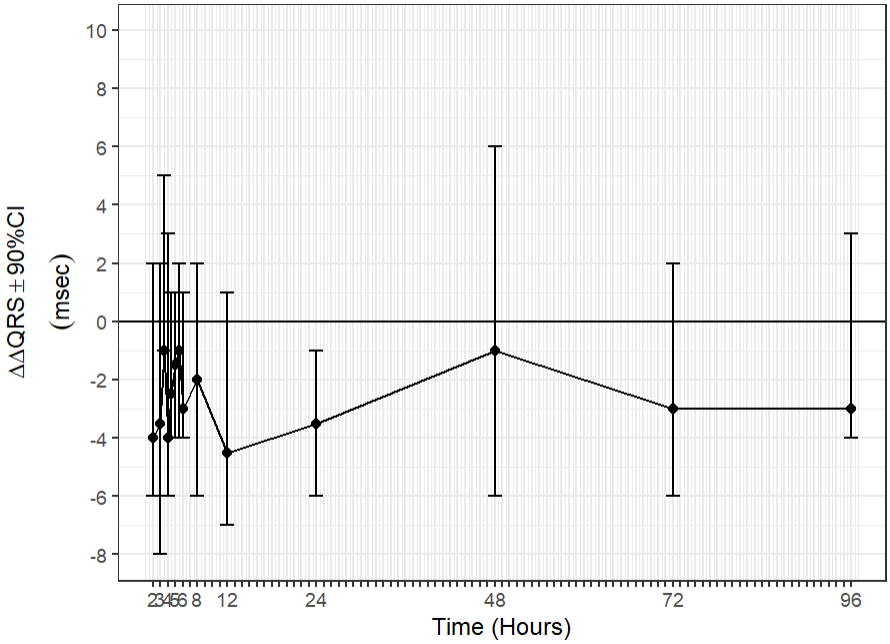
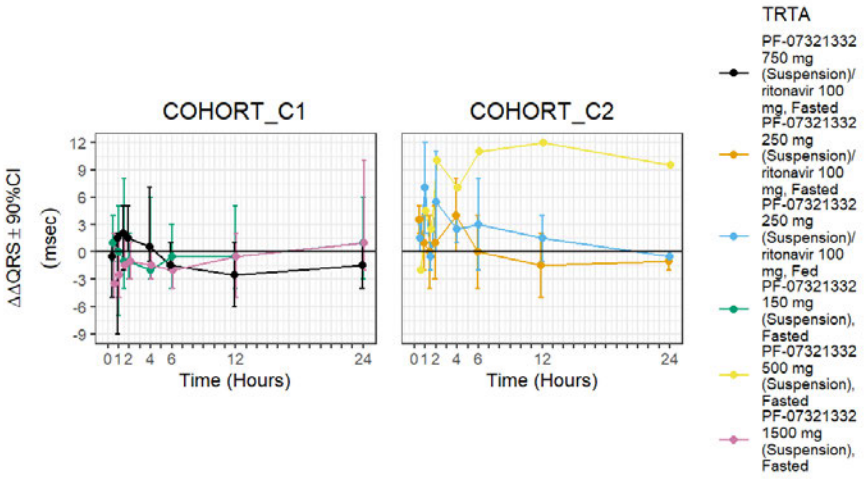


Figure 8: Median and 90% CI of ΔΔQRS Time-course – Part 1



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs for Part 5 and Part 1.

4.4.1 QTc

There were no subjects having observed QTcF above 450 msec or change from baseline above 30 msec.

4.4.2 HR

There were no subjects having observed maximum HR above 100 beats/min.

4.4.3 PR

None of the subjects experienced PR >220 msec in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec and 25% increase over baseline in any of the treatment groups.

4.5 EXPOSURE-RESPONSE ANALYSIS

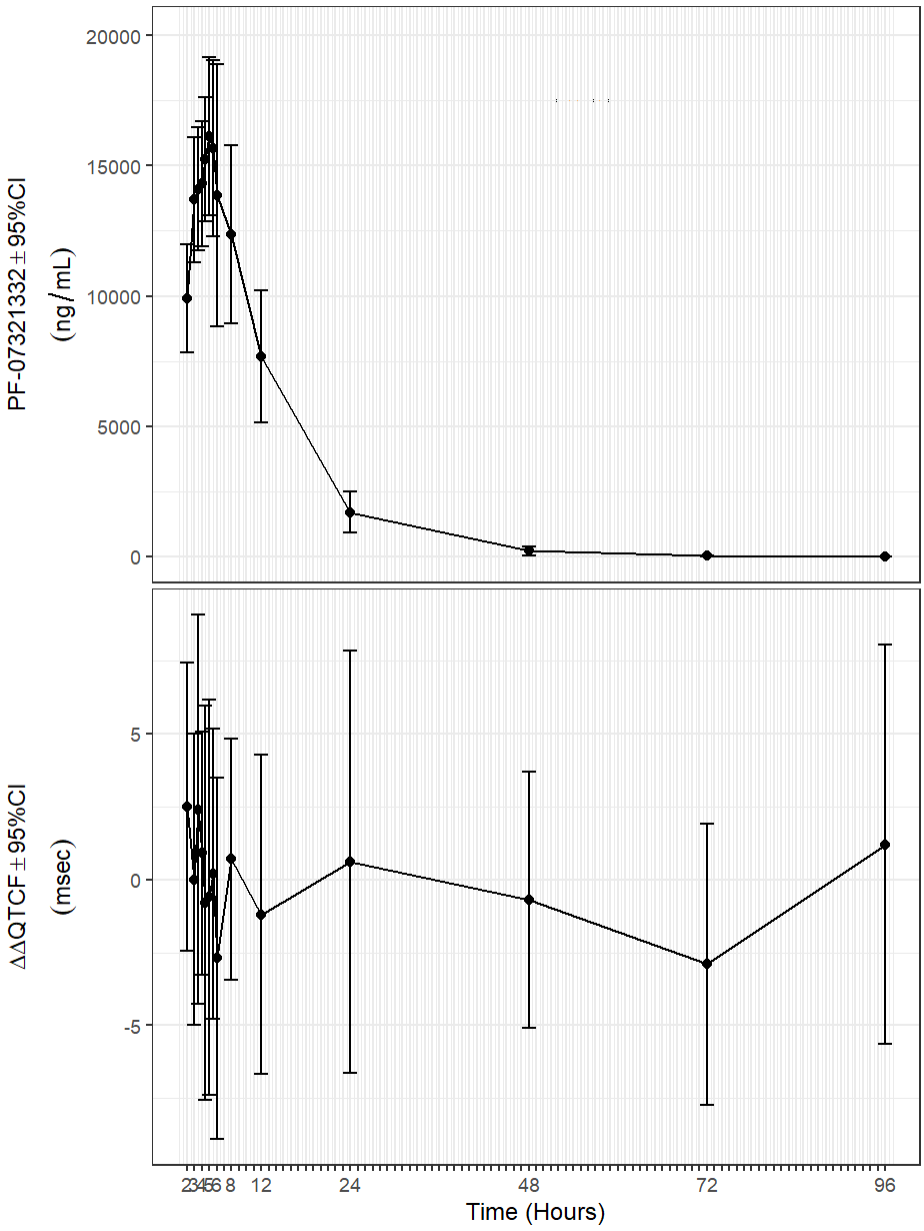
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK for Part 5 only, which achieved the highest exposures. The participant who had concentration below limit of quantification at 6 h is included in the reviewer's analyses. Consistency with by-time analysis, ΔΔQTcF is used as the dependent variable in the model. The model includes nirmatrelvir concentration and baseline as covariates. Subject is included as a random effect on both intercept and slope terms.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model need to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

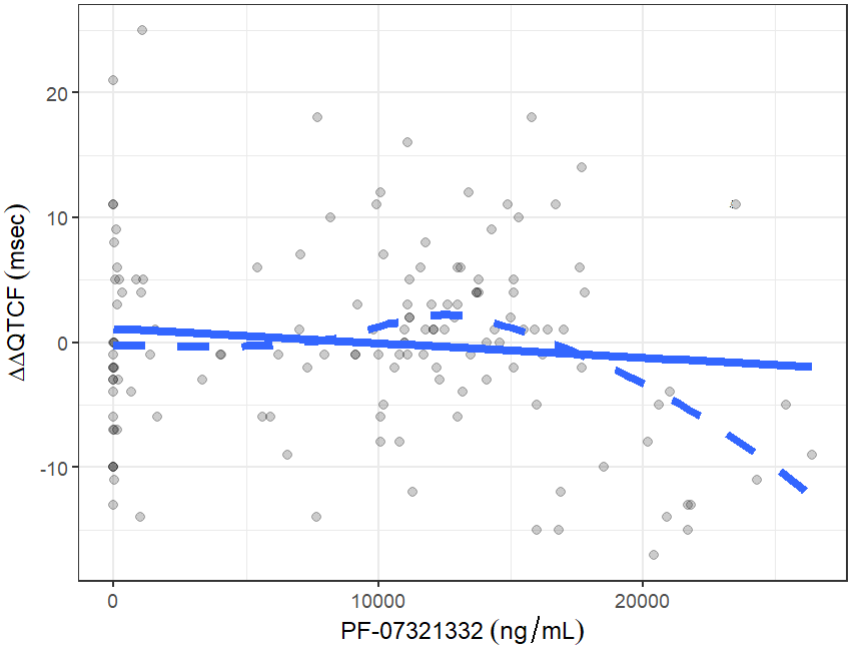
Figure 3 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 9 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 10 shows the relationship between drug concentration and ΔΔQTcF, and supports the use of a linear model.

Figure 9: Time-course of Drug Concentration (top) and QTcF (bottom)[2]



[2] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs) – Part 5..

Figure 10: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 11. Predictions from the concentration-QTcF model are provided in Table 3.

Figure 11: Goodness-of-fit Plot for QTcF

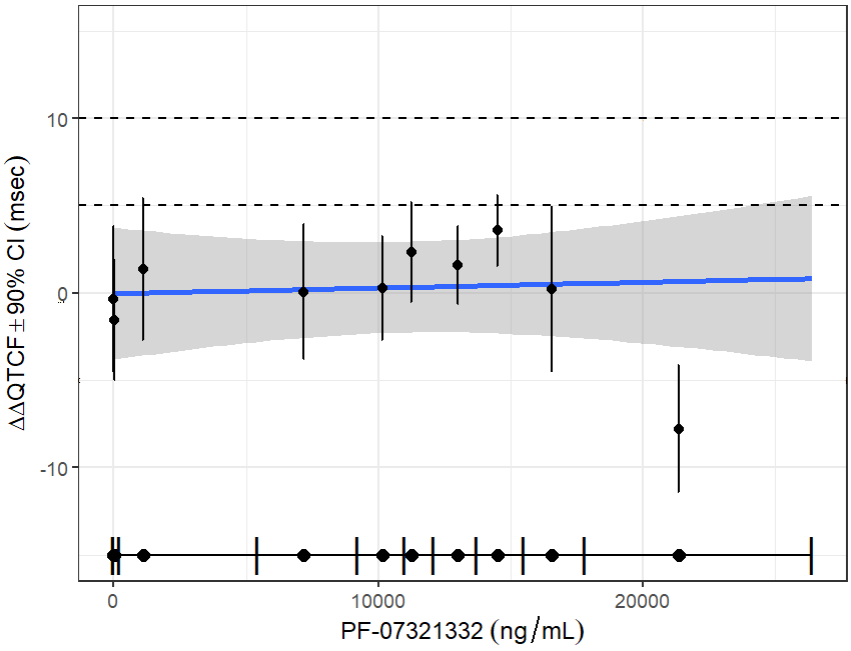


Table 3: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	PF-07321332 (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
PF-07321332 2250 mg (Suspension)/ritonavir 100 mg	1	15,943.7	0.5	(-2.4 to 3.4)

4.5.1.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

Protocol previously reviewed (DARRTS 01/28/2022).

5.2 REVIEW OF SUPPORTING NONCLINICAL DATA

The sponsor is developing nirmatrelvir for the treatment of COVID-19. Nirmatrelvir (MW: 499.54 Da) inhibits SARS-CoV-2 and human coronavirus 3CL protease inhibitor. Nirmatrelvir is intended to be administered with ritonavir as a booster to enhance the systemic exposures of nirmatrelvir. Previously the IRT agreed the sponsor's strategy to use an integrated clinical (Study #C4671001) and integrated nonclinical assessment (hERG study 22LJ022 and in vivo QT study 20GR275) to support the QT assessment under ICH E14 Q&A 5.1, and recommended using dofetilide, moxifloxacin and ondansetron as the reference compounds in the proposed hERG assay. The sponsor now submitted the hERG raw data for review.

5.2.1 In vitro hERG assay

5.2.1.1 Sponsor's results

The GLP hERG study report 22LJ022 (CRO study number: 211129.QHJ, link) describes the potential effects of nirmatrelvir on the hERG current in HEK293 cells. Another hERG study report 22LJ025 (CRO study number: 220210.QHJ, link) evaluates the potential effects of three reference drugs dofetilide, ondansetron, moxifloxacin, and on hERG current. The hERG current was assessed at near-physiological temperature (35-37^{o}C), using the hERG current protocol recommended by the FDA (link). A full blocker (1 µM E-4031) was added at the end of the experiment to assess the contribution of the non-hERG currents. Solution samples were collected from the outflow of the perfusion apparatus on the day of experiment for drug concentration verification. According to the sponsor's responses to the information request (link), solution samples were collected at the end of the perfusion tube (before the recording chamber) using the same batch of the solution in the experiment. The sponsor provided a picture of the chamber showing that the tip of the perfusing tube is located in the middle of the cell chamber, indicating the patched cell can directly receive perfusion solution from the tube. The timing of sample collection ranged from 14 mins to 2 hours before the start of the hERG recording, which were within the formulation stability period which was assessed in extracellular (EC) or perfusion solution (~28 hours). The analysis results met the acceptance criteria (100 ± 15% of nominal concentrations). Therefore, the nominal concentrations were used to describe the drug effects.

Nirmatrelvir inhibited hERG current by (Mean ± SEM; n = 4) 4.6 ± 3.7% at 30 µM and 12.6 ± 0.7% at 300 µM. The IC50 for the inhibitory effect of nirmatrelvir on hERG potassium current could not be calculated but was estimated to be greater than 300 µM. Positive control drug ondansetron inhibited hERG current by (Mean ± SEM; n = 4) 17.1 ± 1.2% at 0.3 µM, 41.8 ± 1.1% at 1 µM, 63.6 ± 3.4% at 3 µM and 86.2 ± 1.7% at 10 µM. The IC50 of ondansetron on hERG potassium current was 1.53 µM (Hill coefficient = 0.93)

In another hERG assay (22LJ025), reference drug ondansetron inhibited the hERG current by 35.0%, 55.8%, 74.0% and 90.5% at 0.3, 1, 3 and10 µM, respectively. The IC50 of ondansetron on hERG potassium current was 0.71 µM (Hill coefficient = 0.76).

Reference drug moxifloxacin inhibited the hERG current by 15.4%, 40.4%, 56.6% and 76.7% at 10, 30, 100 and 300 µM, respectively. The IC50 of moxifloxacin on hERG potassium current was 64.5 µM (Hill coefficient = 0.78).

Reference drug dofetilide inhibited the hERG current by 19.4%, 34.3%, 59.2% and 90.0% at 3,10, 30 and 100 nM, respectively. The IC50 of dofetilide on hERG potassium current was 17.9 nM (Hill coefficient = 0.98)

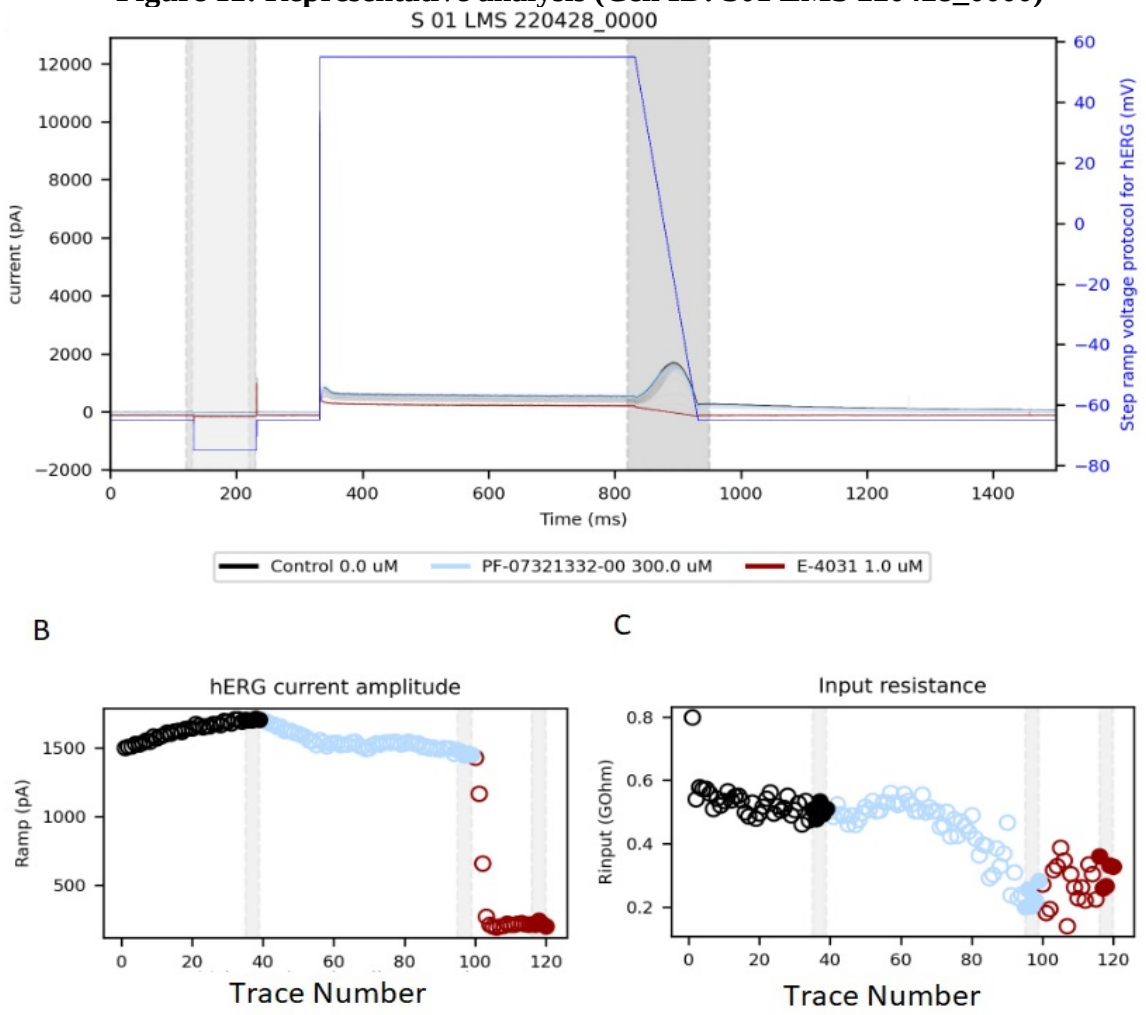
5.2.1.2 Reviewer's assessment

Original electrophysiology records for the hERG assay was provided by the sponsor. The records were analyzed to assess data quality and verify study report conclusions. For data quality assessment, current from all traces were examined to verify stability, and time course plots were constructed to verify that current amplitude in control solution were stable prior to drug application, and that drug effects reached steady state.

The hERG current was assessed at near-physiological temperature (35-37^{o}C), at the stimulating frequency of 0.2 Hz (every 5 seconds), using the recommended hERG voltage protocol that is available at IRT's website (link). The positive control ondansetron was evaluated at four concentrations (0.3, 1, 3 and 10 µM) to allow for the estimation of the IC50 against hERG channel. A full hERG blocker (1 µM E-4031) was added at the end of the experiment to assess the non-hERG currents evoked by the voltage protocol. Solution samples were collected from outflow of perfusion apparatus at the time of experiment for drug concentration verification. Sample collected from the end of the perfusion tube is acceptable since the tip of perfusion tube is placed adjacent to the patched cell and the solution directly perfuse or feed the cell. The analysis results met the acceptance criteria (100 ± 15% of nominal concentrations). Therefore, the nominal concentrations were used to describe the drug effects.

Representative analysis from one cell of hERG study (Cell ID: S 01 LMS 220428_0000) is shown in Figure 12. The panel A shows recorded traces of each treatment group from this cell. The voltage waveform used to evoke hERG current is shown in blue. The small hyperpolarizing voltage pulse from -80 to -90 mV is designed to calculate input resistance according to Ohm's law. Two shaded gray areas on the left show measurement cursors used to calculate baseline currents at -80 mV and at -90 mV, respectively. The gray shade on the right highlights the region where peak hERG tail current was measured. Traces recorded in control solution are shown in black, following 300 µM nirmatrelvir application in light blue; and 1 µM E-4031 in red at the end of the experiment. Time course plots for peak ramp current and input resistance are shown on panels B and C, respectively.

Figure 12**: Representative analysis (Cell ID: S01 LMS 220428_0000)**



The hERG current amplitudes from the last 5 traces acquired in control (black solid circles) and in drug solution (light blue solid circles represent drug concentration at 300 µM) were then averaged to calculate % inhibition by that concentration.

Results (with E-4031 subtraction) of nirmatrelvir, positive control and reference drugs on hERG current are summarized in Table 4.

Table 4: Effects of nirmatrelvir, positive control and reference drugs on hERG current

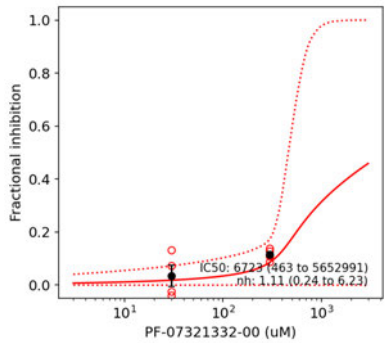
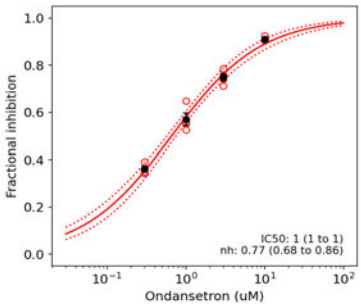
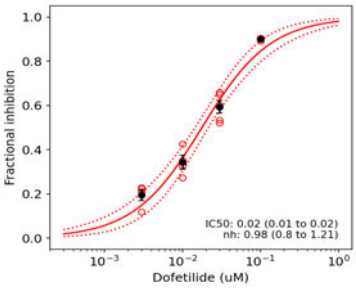
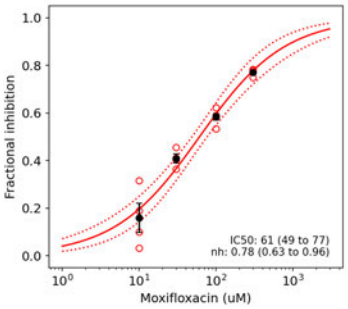
Test article	N	Inhibition (fraction)	SEM	IC50
nirmatrelvir 30 µM	4	0.03	0.04	>300 µM
nirmatrelvir 300 µM	4	0.12	0.01	
Ondansetron A 0.3 µM	4	0.17	0.01	1.45 µM
Ondansetron A 1 µM	4	0.42	0.01	
Ondansetron A 3 µM	4	0.65	0.01	
Ondansetron A 10 µM	4	0.88	0.01	
Ondansetron B 0.3 µM	4	0.36	0.01	0.662 µM
Ondansetron B l µM	4	0.57	0.03	

Ondansetron B 3 µM	4	0.75	0.02	
Ondansetron B 10 µM	4	0.91	0.00	
Dofetilide 3 nM	4	0.20	0.03	0.0178 µM
Dofetilide 10 nM	4	0.34	0.03	
Dofetilide 30 nM	5	0.59	0.03	
Dofetilide 100 nM	4	0.90	0.00	
Moxifloxacin 10 µM	4	0.16	0.06	61 µM
Moxifloxacin 30 µM	4	0.41	0.02	
Moxifloxacin 100 µM	5	0.58	0.01	
Moxifloxacin 300 µM	4	0.77	0.01	

While there are numerical differences in the results from FDA's independent analysis compared to the sponsor's, these do not change overall conclusions. That is, FDA's independent analysis of the submitted electrophysiology data shows that nirmatrelvir inhibited the hERG current by 3% and 12% at 30 and 300 µM, respectively. The IC50 of nirmatrelvir on hERG current is expected to be larger than 300 µM. The positive control ondansetron inhibited the hERG current with an IC50 of 1.45 µM, which is similar to the IC50 observed in the reference data (0.66 µM) and the mean IC50 value (1.33 µM) of ondansetron on hERG current from FDA (DARS lab) in the HESI-BAA project. The

concentration-response curves of nirmatrelvir and positive control ondansetron on hERG currents are summarized in Figure 13.

Figure 13**: Effects of nirmatrelvir and reference drugs on hERG current**

Nirmatrelvir	**Ondansetron**
	
Dofetilide	**Moxifloxacin**
	

5.2.1.3 **Summary**

The comparisons of sponsor's hERG assay and the best practice recommendations by the new ICH S7B Q&A 2.1 are summarized in Table 5.

Table 5: Comparison of sponsor's hERG assays with the new draft ICH S7B Q&As best practice recommendations

Best Practice Elements	Deviations/limitations	Impact from Deviations
Temperature (35-37°C)	None	
Voltage protocol	None	
Recording quality	None	
IC50 Calculation	Two concentrations were tested. The highest tested concentration was 300 µM due to solubility issues	Unable to determine the IC50
Concentration verification	None	
Positive Control	None	

Best Practice Elements	Deviations/limitations	Impact from Deviations
Negative Control (vehicle)	None	
Good Laboratory Practice	None	

Table 6: Safety Margins of nirmatrelvir and reference drugs on hERG Current

Drug	High clinical Cmax or critical concentration (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (µM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Nirmatrelvir	10800	69%	3348	>300 (1158)	499.63	>44x (173x)
Dofetilide	0.37	64%	0.133	0.0178	442	59x
Ondansetron	247	73%	66.69	0.66	293	2.9x
Moxifloxacin	1866	40%	1119.6	61	401	21.8x

Nirmatrelvir high clinical $C_{max,ss}$: 10800 ng/mL. Critical concentration: concentration associated with 10 msec mean QTc prolongation. The estimated IC50 values were 1158 and 18266 µM, when extrapolated from the data at 30 and 300 µM using hill coefficient of 1.5 and 0.5, respectively. The lowest estimated IC50 (1158 µM with h=1.5) is used for hERG safety margin calculation.

5.2.2 In vivo study

5.2.2.1 Sponsor's results

The in GLP vivo study (20GR275) assessed the potential effects of nirmatrelvir on ECG parameters administered as a twice per day (BID) dose at 40 (20 BID) and 150 (75 BID) mg/kg/day via oral gavage in conscious, unrestrained, radio-telemetry implanted male cynomolgus monkeys, which is summarized in Table 7. Prior to initiation of the CV phase, all animals received a single oral dose of nirmatrelvir at 150 (75 BID) mg/kg/day for provision of a PK profile (PK phase). CV phase started 8 days after PK phase. Telemetered data including ECG traces were continuously recorded from all animals for a minimum of 45 minutes prior to dosing and continuing through at least 22 hours post-dose. ECG data was binned into 1-minute bins, and then averaged into 15 min bins. Values for each telemetry endpoint were averaged into four post-dose periods for each dose level (0.75 – 5.5 h, 7.25 – 9 h, 9.25 – 16 h, 16.25 – 20.5 h). Individual animal correction was used for QT correction using vehicle control data and a linear slope.

The mean (± SD) Cmax at 150 (75 BID) mg/kg/day was 14.7 ± 9.24 µg/mL. The free Cmax were 6.4 µg/mL (the protein binding was 56.5% in monkeys). Nirmatrelvir decreased the QTc-intervals by 4.4 ms and 6.8 ms at 40 mg/kg/day and 150 mg/kg/day doses, respectively. No positive drugs were used in the study. The reported minimum

detectable difference was reported as 9.3 msec based on power analysis of historical studies.

Table 7: Summary of in vivo QT study

QT Study							
Exposure	The 150-mg/kg (75-mg/kg-BID) dose provides a 1.9-fold margin over high clinical exposures (unbound)						
Design	Crossover: vehicle, solvate (MTBE) control + 2 dose levels of PF-07321332; N = 8						
Species	Cynomolgus monkey (male); telemetry instrumented						
Historical QTcI sensitivity	MDD: 9.1 msec (reference range 2.5th–97.5th percentile; 3.9–16.7 msec) from power analysis of historical studies						
ECG collection	~24-hour telemetry (conscious animals)						
ECG reading methodology	Fully automated; animal-specific library/template						
PK collection	Predose and approximately 6 HPD during CV phase at all doses; same-study animals predose and at 0.5, 1, 2, 4, 6 (before PM dose), 7, and 24 HPD in a standalone PK phase @ 150 mg/kg (75 mg/kg BID)						
Analysis Methods							
Data Reduction Method	0.75–5.5, 7.25–9.0, 9.25–16.0, 16.25–20.5 HPD; super-intervals						
Analysis methodology	By-time using ANOVA						
HR correction method	QTcI based on vehicle data (QT vs RR; linear slope) for each animal generating an IACF						
ECG Findings	Transient QTc decrease (−5 to −7 msec; during 7.25–16.0 HPD) at 150 mg/kg (75 mg/kg BID)						
Summary Findings							
Dose (mg/kg)	QTcI effect size after 2nd BID dose 9.25–16.0 HPD mean (95% CI)	Parent concentration at 6 HPD (µg/mL) during CV phase	C_{max} total (µg/mL) during PK phase	C_{max} unbound (µg/mL)	Fu (PPB) species	High clinical C_{max} (unbound) (µg/mL)	Exposure ratio
MTBE control	−0.36 (−7.17, 6.44)	NA	NA	NA	0.310 (0.69) Human	3.4 10.9 (total)	1.9 1.3 (total)
40 (20 BID)	−4.38 (−11.19, 2.42)	0.0334	NA	NA			
150 (75 BID)	−6.82 (−13.63, −0.01)	0.308	14.7	6.4	0.435 (0.565)		

Source: QT evaluation report, Supplemental Table 12

Reviewer's comment: *The QTc assessment in the in vivo QTc study was based on data binning and the width of the windows were broad relative to the concentration time-profile, bringing into question the sensitivity of the windowed-based analysis. To address this limitation, we considered the full time-profile as provided on page 35 of the report, which did not suggest large changes in the QTc interval. There was too limited data to establish similarity in the PK profile between the CV and PK phase (i.e., a single trough measurement) and the PK sampling following the second dose likely missed Tmax, which adds uncertainty to how the exposures in the in vivo QT study compares to clinical exposure. Overall, the in vivo monkey study (20GR275) suggests no QTc prolongation at concentrations that are expected to exceed high clinical exposures.*

5.2.3 Non-clinical Summary

In summary, the hERG assay meet most of the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1 (link). The hERG results showed that nirmatrelvir has a hERG safety margin of > 44x (12% inhibition at 300 µM). The estimated IC50 and safety margin of nirmatrelvir on hERG channel are 1158 µM and 173x by fitting data to hill equation with a hill slope of 1.5, respectively. Reference drugs dofetilide, ondansetron and moxifloxacin have hERG safety margins of 59x, 2.9x and 21.8x, respectively. The hERG safety margin of nirmatrelvir is larger than the safety margins of those reference drugs. The results of hERG assay suggest that nirmatrelvir

has a low risk for QT prolongation by directly inhibiting the hERG current at high clinical exposure**.**

No QTc prolongation was observed at exposures anticipated to exceed high clinical exposure in the in vivo monkey study.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	August 29, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 217188
Product Name and Strength:	Paxlovid 300 mg;100 mg and 150 mg;100 mg Dose Pack (Nirmatrelvir 300 mg[a]; Ritonavir 100 mg tablets) and (Nirmatrelvir 150 mg; Ritonavir 100 mg tablets)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer
FDA Received Date:	June 29, 2022
TTT ID #:	2022-33
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph.
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD
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[a] packaged as two 150 mg Nirmatrelvir tablets.

1 REASON FOR REVIEW

As part of the approval process for Paxlovid (nirmatrelvir;ritonavir) dose pack under NDA 217188, the Division of Antivirals (DAV) requested that we review the proposed Paxlovid prescribing information (PI), patient prescribing information (PPI), carton labeling and container labels for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Paxlovid is currently authorized for emergency use under EUA 105 for the treatment of mild to moderate coronavirus disease in patients 12 years of age and older weighing at least 40 kg.

Under EUA, Paxlovid is available in the following presentations:

-Paxlovid 300 mg;100 mg Dose pack (30 tablets divided in 5 daily-dose blister cards)

-Paxlovid 150 mg;100 mg Dose pack (20 tablets divided in 5 daily-dose blister cards) for patients with moderate renal impairment (eGFR ≥30 to < 60 mL/min)

DMEPA is currently monitoring ongoing wrong dose medication error reports that are occurring with Paxlovid presentations under the EUA. We note that the majority of the ongoing wrong dose medication errors have occurred during patient self-administration and often describe patients taking the wrong dose or wrong tablets due to confusion with the packaging or labeling. On June 27, 2022, DMEPA sent an Information Request (IR) to Pfizer requesting they provide their mitigation strategies to address the ongoing wrong dose errors due to the packaging configurations. As a result, the EUA Fact Sheet for Patients, Parent and Caregivers was revised to address areas of vulnerability to medication errors. In addition, Pfizer also issued a Dear Health Care Provider (DHCP) letter and provided a commitment to investigate alternative packaging for Paxlovid. We are continuing to monitor these wrong dose errors and consider additional mitigation strategies to minimize the ongoing errors under the EUA.

We note that for the proposed NDA 217188, [redacted] (b) (4) (Paxlovid 300 mg;100 mg and 150 mg;100 mg Dose Packs) are proposed by the Applicant.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND CONCUSIONS

Paxlovid is currently authorized for emergency use under EUA 105. Under EUA review, DMEPA has previously evaluated the Fact Sheet for Healthcare Providers (FS for HCP), Fact Sheet for Patients, Parent and Caregivers (PFS), proposed carton labels, container labeling and product packaging of the two Paxlovid Dose Packs. Our evaluation of the NDA prescribing information (PI) and patient prescribing information (PPI) did not identify areas of vulnerability that may lead to medication errors. However, the PI and PPI should be revised to reflect recent revisions made to the EUA FS for HCP and PFS. We will collaborate with DAV to align these labels.

Our evaluation of the proposed container labels, carton labeling, and blister card packaging configuration identified areas of vulnerability to medication error. We continue to receive wrong dose medication error reports occurring during patient-self administration (see 1.1) and we recommend that the Applicant revise the product design and/or packaging configuration to address the wrong dose medication errors. (b) (4) Therefore, an alternative packaging configuration, such as single dose blister cards, should be developed that will maximize safe use and support all dosing regimens in the product labeling. As such, we defer any comments on the proposed container labels and carton labeling until the packaging configuration for product marketing is finalized to address the wrong dose medication errors. We provide an information request to Pfizer in Section 4 below for inclusion in the 74-day letter.

4 RECOMMENDATIONS FOR PFIZER

We note your submission dated July 12, 2022 which provided a mitigation plan in response to the Information Request (IR) dated June 27, 2022 from FDA to address the ongoing wrong dose

[b] Re: EUA 105 Response to Information Request. New York (NY): Pfizer Global Regulatory Affairs. 2022 JUL 12. Available from: \\CDSESUB1\evsprod\EUA000105\0166\m1\us

medication errors with Paxlovid under EUA 105. You stated that evaluations are underway to "*evaluate potential blister card label prototypes to determine if changes to the blister card could improve patient medication use and address potential patient confusion*". Based on the ongoing reports of wrong dose medication errors, we continue to have concerns (b) (4) For example, you may consider developing single dose blister cards, that will maximize safe use and support all dosing regimens in product labeling under NDA 217188. Depending on revisions to the packaging configuration, additional data such as data from a human factors study, may be needed to ensure that the proposed packaging supports safe and effective use.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Paxlovid that Pfizer submitted on June 29, 2022.

Table 2. Relevant Product Information for Paxlovid	
Initial Approval Date	N/A authorized for use under EUA 105 in 12/2021
Active Ingredient	nirmatrelvir copackaged with ritonavir
Indication	Treatment of adult (b) (4) who are at high risk for progression to severe COVID-19.
Route of Administration	Oral
Dosage Form	Tablet
Strength	150 mg nirmatrelvir and 100 mg ritonavir
Dose and Frequency	300 mg nirmatrelvir (2 tablets of 150 mg) and 100 mg ritonavir (one 100 mg tablet) twice daily for 5 days or For moderate renal impairment (eGFR ≥30 to <60 mL/min): 150 mg nirmatrelvir (1 tablets of 150 mg) and 100 mg ritonavir (one 100 mg tablet) twice daily for 5 days
How Supplied	Paxlovid 300 mg;100 mg Dose pack (b) (4) Paxlovid 150 mg;100 mg Dose pack (b) (4)
Storage	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 11, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Paxlovid and EUA 105. Our search did not identify any reviews with outstanding issues or recommendations

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Paxlovid labels and labeling submitted by Pfizer.

- Container label(s) and Carton labeling received on June 29, 2022
- Prescribing Information and Patient Prescribing Information (Image not shown) received on June 29, 2022, available from \\CDSESUB1\evsprod\NDA217188\0001\m1\us

F.2 Label and Labeling Images

Container label(s)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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