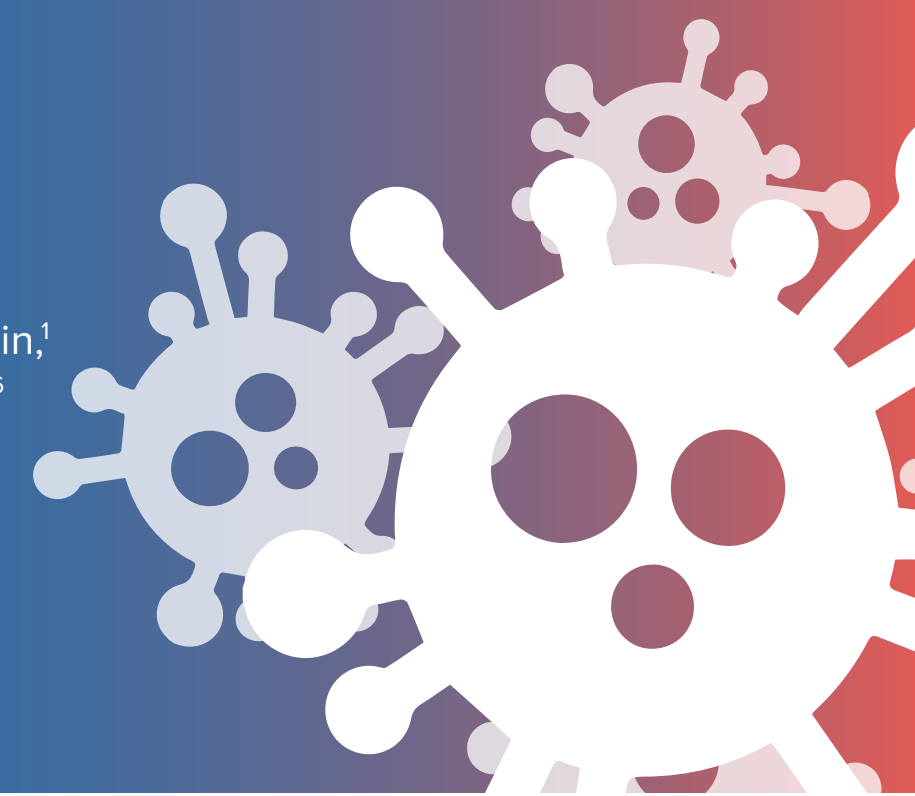


Preliminary Results From a European Post-authorisation Study to Assess the Safety of Paxlovid in Pregnancy

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BACKGROUND

- Paxlovid is an oral combination of protease inhibitors nirmatrelvir and ritonavir licensed in January 2022 in Europe. Paxlovid is used to treat COVID-19 in patients who do not require supplemental oxygen and are at increased risk for progression to severe COVID-19.¹ Here, we describe results of an interim analysis from a post-authorisation safety study (PASS) to assess the safety of Paxlovid in pregnancy. This ongoing PASS is being conducted, as there is limited evidence about the safety of Paxlovid in pregnant women. This is because clinical trials excluded pregnant patients, and summaries of product characteristics (SmPCs) from the EU and UK do not recommend its use in pregnancy.
- This PASS (EU PAS number: EUPAS50117) is a commitment to the European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA).

OBJECTIVE

- The primary study objective of this PASS is to estimate the birth prevalence, prevalence ratio, and prevalence difference of selected adverse pregnancy, offspring, and maternal outcomes in women with COVID-19 who are exposed to Paxlovid during pregnancy compared with women with COVID-19 who are exposed to molnupiravir (or other comparable medications for COVID-19), where available, or women with COVID-19 unexposed to any study medications during pregnancy.

METHODS

Data Sources

Table 1. Data Sources and Study Period Used in the Interim Analysis

Data source	Data available for the study period	Start and end dates of study period
Clinical Practice Research Datalink (CPRD) Aurum, UK	Individual-level general practitioner data (hospital data not available for the study period)	1 January 2022 through 31 January 2024
Information System for Research in Primary Care (SIDIAP), Spain	Individual-level general practitioner and hospital data	28 January 2022 through 31 December 2023
French Administrative Healthcare Database (SNDS), ^a France	Aggregated Open Medic outpatient community pharmacy data from publicly available information	28 January 2022 through 31 December 2023

SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, Catalonia, Spain; SNDS = Système National des Données de Santé.

^a Aggregated, publicly available data were obtained because individual-level data extraction had not been approved at the time of analysis.

Study Population and Follow-Up

- Pregnancies and mother-infant pairs were identified with electronic algorithms in:
 - SIDIAP: ConcePTION pregnancy algorithm²
 - CPRD: CPRD Aurum pregnancy algorithm³ and mother-infant linkage algorithm
- Pregnancies in SNDS were not identified for this analysis, as information on pregnancy was not available.
- Data provided by CPRD were further cleaned by RTI Health Solutions (RTI-HS) to remove implausible pregnancy episodes and deduplicate overlapping pregnancy episodes.
- Eligibility criteria are presented as part of the cohort attrition in Figure 1.
- Follow-up started the date of first prescription/dispensing of Paxlovid or the comparator medication during pregnancy (time zero) and ended at the earliest of 6 months after the end of pregnancy (age 1 year for offspring), end of study period (Table 1), outcome (Table 2), disenrollment, or death.

Exposure

- Study medication:** Paxlovid.
- Active comparators** are medications approved by EMA for the treatment of COVID-19, as available: remdesivir, tixagevimab/cilgavimab, anakinra, regdanvimab, tocilizumab, casirivimab/imdevimab, and sotrovimab; and molnupiravir, which was used for the treatment of COVID-19 for some time but which was not approved by the EMA. No active comparators were available for this analysis in SIDIAP.

Outcomes

Table 2. Primary and Exploratory Outcomes

Type of outcome	Outcomes ^a
Primary	Pregnancy outcomes <ul style="list-style-type: none">Spontaneous abortion^bElective terminationStillbirth^cPreterm delivery^d (all, iatrogenic, and spontaneous) Offspring outcomes <ul style="list-style-type: none">Major congenital malformationsIntrauterine growth retardation/small for gestational age Maternal outcomes <ul style="list-style-type: none">Gestational diabetesGestational hypertensionPostpartum hemorrhageMaternal death
Exploratory	Empirically assessed from diagnoses in eligible Paxlovid-exposed individuals in the 30 days after exposure

^a Outcomes were defined through diagnostic codes, procedures, medicinal product prescriptions or dispensings, information collected in other data banks in the selected data sources, and as part of the pregnancy-identifying algorithms.

^b Spontaneous abortion defined as foetal loss before 20 completed weeks of gestation.

^c Stillbirth defined as foetal loss on or after 20 completed weeks of gestation.

^d Preterm delivery defined as birth before 37 completed weeks of gestation.

Common Data Model

- The ConcePTION common data model⁴ and common descriptive analytics were used to generate the counts in SIDIAP and CPRD.

Analysis

This interim analysis aimed to describe:

- Aggregated counts of eligible Paxlovid-exposed pregnancies, pregnancies exposed to comparator medications as available in each data source, and aggregated outcome counts from SIDIAP (Spain) and the CPRD (UK).
- Aggregated counts of sold boxes and users, by age group and sex, for Paxlovid and comparator medications that were in use in the general population in SNDS (France). This is because aggregated publicly available data from Open Medic were used for SNDS from which pregnancies could not be identified.

According to small cell count restriction rules in CPRD, counts between 1 and 4 have been masked as 1≤n≤4, and any other descriptive data that could allow back-calculation to a small count have been suppressed or masked as not reportable.

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RESULTS

- In SNDS (publicly available aggregated counts), 206,069 patients in the general population in years 2022 and 2023 had ≥ 1 Paxlovid dispensing (≈70% aged ≥ 60 years; > 55% female); fewer patients used anakinra (5895; ≈ 40% aged ≥ 60 years, ≈ 50% female) or tocilizumab (22,306; ≈ 60% aged ≥ 60 years, ≈ 70% female). Each year, patients were dispensed, on average, approximately 1 box of Paxlovid and 7 and 20 boxes for tocilizumab and anakinra, respectively (Table 3).
- Figure 1 presents cohort attrition in SIDIAP and CPRD:
 - No eligible pregnancy exposed to Paxlovid was identified in SIDIAP or in CPRD.
 - In CPRD, 1≤n≤4 were exposed to molnupiravir and had unknown outcomes. No other primary or exploratory study outcomes were observed.

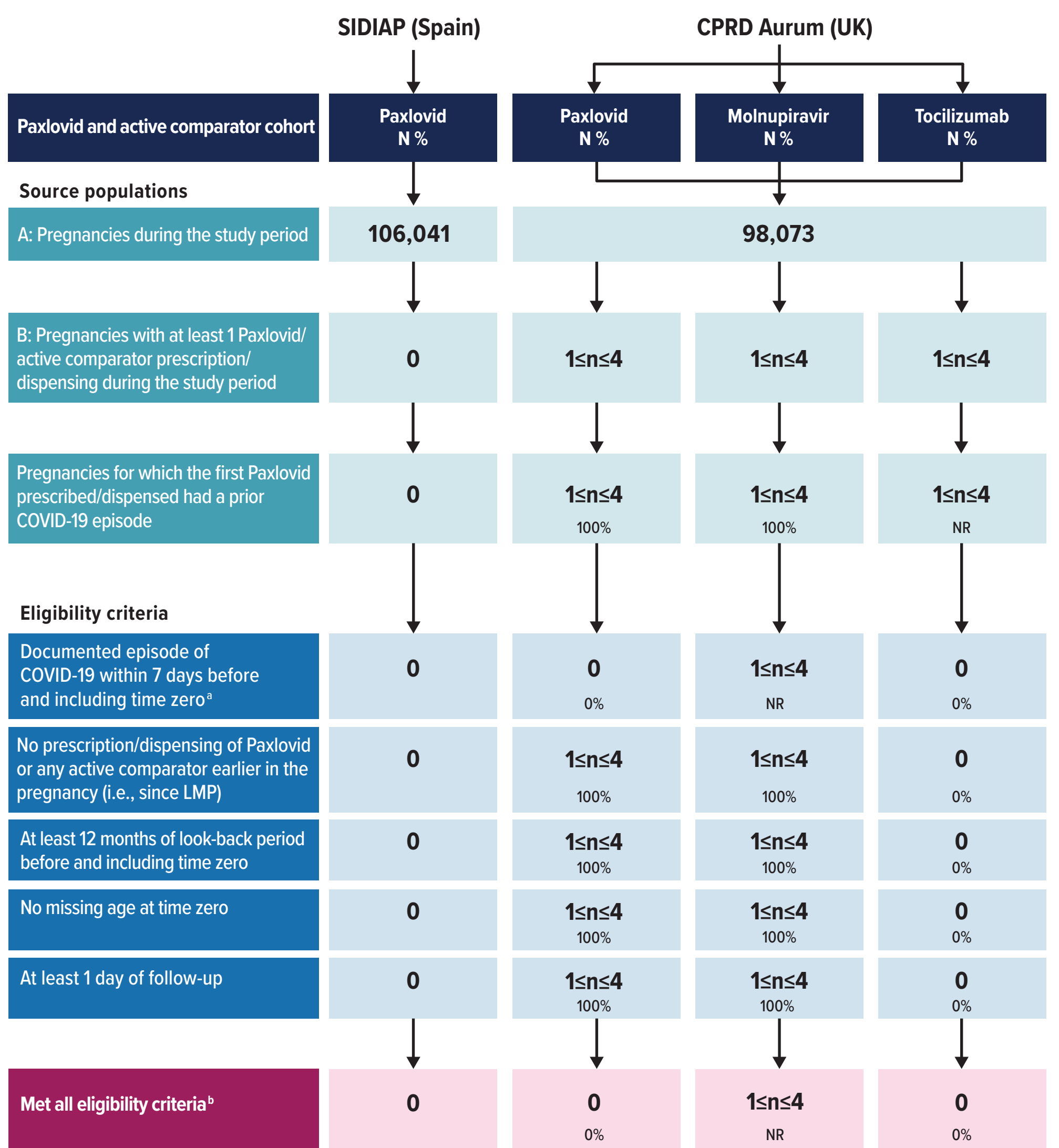
Table 3. Number of Patients With at Least 1 Dispensing for Paxlovid or Active Comparator Medications and Number of Dispensed Boxes (SNDS, 2022-2023)

Medication	2022			2023		
	Patients	Boxes	Boxes per patient ^a	Patients	Boxes	Boxes per patient ^a
Paxlovid	83,102	85,164	1.0	122,967	126,596	1.0
Tocilizumab	9961	68,738	6.9	12,345	87,407	7.1
Anakinra	2724	57,013	20.9	3171	61,492	19.4

Note: Data for years 2022 and 2023 are sourced from Open Medic.

^a Boxes per patient are calculated by dividing the number of dispensed boxes by the number of patients. A higher number of boxes dispensed per patient suggests that the medication is used for a chronic indication and not for COVID-19.

Figure 1. Cohort Attrition in SIDIAP and CPRD Aurum



LMP = first day of the last menstrual period; NR = not reportable (masked to prevent back-calculation of masked small count).

Note: Presented are the medications for which records were present in the data source for the study population. In Spain, molnupiravir was not dispensed, and in SIDIAP, no active comparators were available for this analysis.

^a The different eligibility criteria were applied independently and are not mutually exclusive.

^b The denominator is the count in the row labelled B.

DISCUSSION

- SIDIAP and CPRD provided information on medication use among eligible pregnant patients. Use in pregnancy in SNDS will be assessed in a future report, which is due in December 2025.
- In SIDIAP and CPRD, no eligible pregnancies were exposed to Paxlovid; in CPRD only 1≤n≤4 were exposed to molnupiravir.
- CPRD: The use of Paxlovid has been primarily captured in CPRD Aurum since late June 2023, thus limiting the ability to identify pregnancies that reached term (37 completed weeks of gestation) given that the study period ended 31 January 2024. Earlier UK data might be available from OpenSAFELY, but OpenSAFELY was not available for participation at the time.
- SNDS: 206,069 patients in the general population had at least 1 dispensing of Paxlovid in years 2022 and 2023. Anakinra and tocilizumab had fewer users than Paxlovid. Additionally, the user profile of anakinra and tocilizumab differed from Paxlovid's, as expected, given their approved indications in rheumatology. This is an important consideration for eligibility (e.g., requiring documentation of COVID-19 before treatment) and confounding control.

DISCLOSURES

This study was funded by Pfizer Inc. and is conducted by the SIGMA Consortium. AVM, JA, KB, AEC, MF, CR, and NSM are employees of RTI-HS, which is a unit of RTI International, an independent, nonprofit organisation that conducts work for government, public, and private organisations, including pharmaceutical companies. The authors received no compensation other than annual salary from employer. CLAN, YM, LN, MS, and HDJ are salaried employees at UMCU, which receives institutional research funding from pharmaceutical companies and regulatory agencies, administered by UMCU. CC was a salaried employee at UMCU at the time this project was performed. MGS, DO, MF, and SFG are employees of IDIAPJGol. They are working on other projects funded by pharmaceutical companies in the institution that are not related to this study and with no personal profit. RG, GR, and DM are employed or consultants of ARS, a public research center whose budget is partially supported by studies funded by public or private organisations. CDP, JJ, DS, and NHT are researchers at BPE, a research platform of the University of Bordeaux and its subsidiary ADERA, which performs financially supported studies for public and private partners. RTI-HS, UMCU, ARS, and BPE conduct studies in compliance with the ENCePP Code of Conduct. SG, CDL, and JL are employees and stockholders of Pfizer. This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. The protocol was approved by CPRD Research Data Governance (study ID: 24-003851).

CONCLUSIONS

Although the study period was relatively short, the lack of Paxlovid-exposed pregnancies in SIDIAP (Spain) and CPRD Aurum (UK) is in alignment with the recommendations in the EU and UK SmPCs of not using Paxlovid during pregnancy. Future reports will include a longer study period and individual-level data of pregnant patients from SNDS in France.