

NON-INTERVENTIONAL STUDY TYPE 1 FINAL REPORT ABSTRACT

Title: Safety of Paxlovid During Pregnancy

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Rationale and background: Paxlovid contains nirmatrelvir and ritonavir. Nirmatrelvir is an oral protease inhibitor that blocks the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19). Ritonavir slows the metabolism of nirmatrelvir to prolong its activity. On 31 December 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) issued a conditional marketing authorisation (CMA) for Paxlovid in Great Britain. Paxlovid was authorised for use in the European Union (EU) for the treatment of COVID-19 following the granting of a CMA by the European Commission on 28 January 2022, which converted into a full marketing authorisation on 24 February 2023. At that time, Paxlovid was indicated in the EU and UK to treat COVID-19 in adults who do not require supplemental oxygen and who have increased risk for progressing to severe COVID-19. In November 2025, the EU indication was expanded to paediatric patients aged 6 years or older weighing at least 20 kg. Use of Paxlovid in pregnancy is not recommended. There is limited evidence about the safety of Paxlovid in pregnant women. Therefore, this non-interventional study addressed the safety of Paxlovid in pregnant women. The size of the exposed pregnant population was anticipated to be very small because of the recommendation against using Paxlovid during pregnancy or becoming pregnant during treatment with Paxlovid in the EU and UK summaries of product characteristics (SmPCs). None of the other European Medicines Agency (EMA)–approved drugs to treat COVID-19 are recommended for use in pregnancy. This non-interventional study is designated as a post-authorisation safety study and is a commitment to the EMA and MHRA.

Research question and objectives: The primary study objective was 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 those in women with COVID-19 who are exposed to molnupiravir (or other comparable medications for COVID-19), where available, or to women with COVID-19 unexposed to any study medications during pregnancy.

The secondary study objective was to assess maternal exploratory outcomes that were identified based on conditions appearing in the study population after exposure to Paxlovid.

Study design: This non-interventional study had a cohort design.

Setting: The study included populations from 3 data sources in France, Spain, and the UK making use of secondary data collected primarily for healthcare purposes as follows: (1) SNDS (French Administrative Healthcare Database [Système National Des Données de Santé]) in France; (2) SIDIAP (Information System for the Development of Research in Primary Care) [Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària] in Catalonia, Spain; and (3) Clinical Practice Research Datalink (CPRD) Aurum in the UK. The study period was from January 2022 until as late as possible in each data source: 31 December 2023 in SNDS, 30 June 2024 in SIDIAP, and 31 August 2024 in CPRD Aurum.

Subjects and study size, including dropouts: The study population comprised pregnant women with documented COVID-19 who had at least 12 months of inclusion in the data source population before time zero (which is defined below) and were users of Paxlovid, or comparator medication molnupiravir or other comparable medications, or were unexposed to study medications, and their offspring. For pregnancies treated with Paxlovid or comparator medication, time zero was the date of first prescription/dispensing of treatment during the pregnancy. For unexposed pregnancies, time zero was the date on which they were matched to an exposed pregnancy. Follow-up started for all women on day 0. Follow-up ended at the earliest of death; disenrollment, migration, or end of data availability in the data source; 6 months after end of pregnancy; or artificial censoring due to treatment crossover. Follow-up of the offspring continued through the earliest of death; end of data availability in the data source, disenrollment, or migration; or 1 year of age. In addition, in outcome-specific analyses, follow-up ended at the occurrence of the outcome being evaluated.

Variables: Exposure was identified from prescriptions/dispensings for Paxlovid, molnupiravir, remdesivir, tixagevimab/cilgavimab, anakinra, regdanvimab, tocilizumab, casirivimab/imdevimab, and sotrovimab. In France, Paxlovid, anakinra, and tocilizumab dispensings were observed. Remdesivir, anakinra, and tocilizumab dispensings were observed in Spain. In the UK, Paxlovid, molnupiravir, and tocilizumab prescriptions were observed.

Primary, prespecified outcomes were categorised as follows: (1) pregnancy outcomes: spontaneous abortion, elective termination, stillbirth, preterm delivery (overall, iatrogenic, and spontaneous); (2) infant outcomes: major congenital malformations (MCM), intrauterine growth retardation/small for gestational age; and (3) maternal outcomes: gestational diabetes, gestational hypertension, postpartum haemorrhage, and maternal death.

Exploratory, data-driven outcomes were constructed from diagnosis codes documented among eligible Paxlovid-exposed women in the 30 days after exposure; occurrence of these outcomes was then assessed among Paxlovid-exposed women and unexposed women in the 30 days after time zero.

Descriptive variables included age, calendar time at time zero, gestational month at time zero, duration of enrolment before cohort entry, socioeconomic status, and variables

reflecting race/ethnicity, history of overweight or obesity, history of smoking, alcohol consumption, history of alcohol-related disease, COVID-19-related diagnosis and vaccination, healthcare utilisation, comorbidities that confer high risk for progression to severe COVID-19, and maternal and obstetric morbidity.

To address confounding, eligible time zero from unexposed women and Paxlovid-exposed women were matched with a variable matching ratio of 1 Paxlovid-exposed woman to up to 5 unexposed women on days between COVID-19 diagnosis and time zero, calendar time at time zero, and gestational month at time zero. Paxlovid-exposed women and women exposed to active comparator medications were planned to be matched 1:1 on calendar time at time zero and gestational month at time zero. Furthermore, the following variables were included in propensity score models for control of confounding: number of risk factors for progression to severe COVID-19 (categorised as 0 or ≥ 1), age (< 35 or ≥ 35 years), number of indicators of maternal and obstetric morbidity (0, 1, or ≥ 2), and history of smoking (yes/no). The number of variables to incorporate in the propensity score model was limited by the small number of Paxlovid-exposed pregnancies.

The main summary measures were attrition and outcome counts, prevalence proportions (PPs) and adjusted prevalence ratios (PRs), and prevalence differences (PDs) with their 95% confidence intervals (CIs). Comparative analyses (ie, PD and PR) were conducted for outcomes with at least 5 events in the 2 exposure groups combined. Aligned with data privacy regulations in France requiring small counts between 1 and 10 to be masked as 1-10, small counts and the corresponding proportions were masked, as well as other numbers that would allow back-calculation of masked numbers.

Imbalance of characteristics between exposure groups was assessed with absolute standardised differences. The PP of pregnancy and maternal outcomes was the number of pregnancies with a record of the outcome of interest divided by the total number of pregnancies in the matched cohort. For offspring outcomes, calculations were based on the number of offspring. Unadjusted PRs and PDs were calculated as the ratio or the difference, respectively, in the prevalence of the outcome between the Paxlovid exposure group and the unexposed group. Stabilised weights for the inverse probability of treatment initiation at time zero (ie, based on the propensity scores) were used to calculate the adjusted PRs and PDs.

In sensitivity analysis, a subset of completed pregnancies with unknown outcome were incorporated as cases and non-cases of spontaneous abortion, as appropriate. Additionally, we explored the effect measure modification of the adjusted PR and adjusted PD by concomitant use of medications with contraindications or interactions per the EU SmPC (yes/no).

Results:

SNDS (France)

Descriptive data: From among 36,611 pregnancies identified in SNDS (France) during the study period, 13,846 (37.8%) had at least 1 documented COVID-19 episode during the

pregnancy episode in the study period, and 74 pregnancies had at least 1 Paxlovid dispensing. Overall, 24 Paxlovid-exposed eligible pregnancies were matched with 112 unexposed pregnancies. There were 1-10 and 82 linked infants in the Paxlovid-exposed and unexposed pregnancies, respectively. No pregnancies exposed to active comparator medications were eligible for the study in SNDS.

The mean (SD) age at time zero was 33.0 (4.5) years among Paxlovid-exposed pregnancies and 31.4 (5.5) among the unexposed pregnancies. Paxlovid use was observed between Q2 2022 and Q2 2023. Time zero occurred in each gestational month among the Paxlovid-exposed and unexposed pregnancies. However, aligned with data privacy regulations, the proportions of Paxlovid-exposed pregnancies with time zero in each gestational month were masked. Time zero occurred in 40.2% and 10.7% of the unexposed pregnancies in gestational month 1 and gestational month 7, respectively.

The proportion of Paxlovid-exposed pregnancies across all socioeconomic status quintiles was masked as 4.2% to 41.7%, except for no pregnancies observed in quintile 3. Unexposed pregnancies were similarly distributed across socioeconomic status quintiles, ranging from 0.9% to 8.9% (1 masked proportion) to 14.3% in each quintile, and a lower proportion in quintile 5 (highest deprivation). A few Paxlovid-exposed pregnancies (4.2%-41.7%) had a history of alcohol-related disease, whereas none of the unexposed pregnancies did. History of smoking or history of overweight or obesity were present in 4.2% to 41.7% of Paxlovid-exposed pregnancies and in 0.9% to 8.9% of unexposed pregnancies. Due to masking of small numbers, it was not possible to determine whether there was an imbalance in the distribution of these variables among the 2 groups. It should be noted that data on some confounding variables (eg, race/ethnicity and body mass index) were not available in the SNDS database.

A total of 4.2% to 41.7% of Paxlovid-exposed pregnancies and 24.1% of unexposed pregnancies had been diagnosed with COVID-19 before the current episode. Both the Paxlovid-exposed and unexposed pregnancies had a mean (SD) of 0.9 (1.0) days between the start of the current COVID-19 episode and time zero; in both groups, the most frequent number of COVID-19 vaccines received was 3; over two-thirds of the Paxlovid-exposed group had received 3 doses, whereas more than half of the unexposed group had received 3 doses. The mean (SD) days from the most recent COVID-19 vaccination to time zero was 160.5 (41.4) days for the Paxlovid-exposed pregnancies and 172.5 (26.7) days for the unexposed pregnancies. All Paxlovid-exposed and unexposed pregnant women had non-severe COVID-19 at time zero.

In the year before the current pregnancy, 50.0% of Paxlovid-exposed pregnancies and 36.6% of unexposed pregnancies had more than 4 primary care visits, whereas 58.3% of Paxlovid-exposed pregnancies and 45.5% to 53.6% of unexposed pregnancies had more than 4 outpatient specialist visits. More than 66% and 79% of the Paxlovid-exposed and unexposed pregnancies had no emergency department visits or hospitalisations, respectively. A total of 87.5% to 100% Paxlovid-exposed pregnancies and all unexposed pregnancies had no intensive care unit (ICU) stays. However, 4.2% to 41.7% of the Paxlovid-exposed

pregnancies had 2 ICU stays compared with none from the unexposed pregnancies. Overall, masking due to low numbers made it difficult to ascertain whether the 2 groups differed numerically in healthcare utilisation and the extent of any difference.

Risk factors for progression to severe COVID-19 were more frequent among Paxlovid-exposed pregnancies than among unexposed pregnancies, with median (Q1, Q3) of 1 (1, 2) and 0 (0, 1) risk factors, respectively. Also, a higher percentage of Paxlovid-exposed pregnancies had at least 1 indicator of maternal morbidity (Paxlovid, 37.5%; unexposed, 9.8%). Use of medications with contraindications or potential interactions during the 90 days before or at time zero per the Paxlovid EU SmPC was higher among the Paxlovid-exposed pregnancies than among the unexposed pregnancies (Paxlovid, 58.3%; unexposed, 18.8%). All results for other medication groups of interest were masked due to small cell counts; therefore, it was difficult to ascertain whether these 2 groups had an imbalance in the use of certain medications groups.

Control of confounding: Due to small numbers, only 4 variables were included in the propensity score (number of risk factors for progression to severe COVID-19, age, number of maternal comorbidities, and history of smoking), and weighting was only partially successful in creating comparable cohorts. Weighting resulted in a more balanced distribution of some patient characteristics. Age and history of smoking, although included in the propensity score, remained unbalanced with absolute standardised differences > 0.1, along with several other variables not included in the propensity score (eg, socioeconomic status, emergency department visits, hospitalisations). Therefore, the possibility of residual confounding could not be ruled out.

Outcome data: There were no events of spontaneous abortion, stillbirth, MCM, intrauterine growth retardation/small for gestational age, gestational hypertension, postpartum haemorrhage, or maternal death among the Paxlovid-exposed pregnancies. There were 1-10 events for the other primary (prespecified) outcomes (ie, elective terminations and preterm delivery [overall, iatrogenic, and spontaneous]), and gestational diabetes. The cohort sizes of Paxlovid-exposed pregnancies differed for each outcome due to different eligibility specifications, ranging from 1-10 to 24.

No events of gestational hypertension, postpartum haemorrhage, or maternal death occurred in the unexposed pregnancies, and there were 1-10 events for the other primary outcomes (ie, spontaneous abortions, elective terminations, preterm delivery [overall, iatrogenic, and spontaneous], stillbirths, MCM, intrauterine growth retardation/small for gestational age, and gestational diabetes). The cohort sizes of unexposed pregnancies eligible for each of these outcomes ranged from 17 to 112.

Regarding the exploratory (data-driven) outcomes, among Paxlovid-exposed pregnancies, 5 exploratory (data-driven) outcomes were observed in 1-10 pregnancies each: unspecified thrombocytopenia, vaginismus, urinary device problems, excessive weight gain in pregnancy and excessive foetal growth, and complications of labour and delivery. Among unexposed pregnancies, 4 exploratory (data-driven) outcomes were observed: urinary device problems,

excessive weight gain in pregnancy and excessive foetal growth, pregnancy-related anaemia (ie, 1-10 pregnancies each), and complications of labour and delivery (23 [21.5%] pregnancies).

Comparative analyses of pregnancy, infant, and maternal outcomes (primary outcomes):

Five prespecified outcomes met the criterion of having at least 5 events in the 2 exposure groups combined and were analysed comparatively: compared with unexposed pregnancies, Paxlovid-exposed pregnancies had a higher adjusted prevalence of elective termination (PR = 3.1 [95% CI, 0.5, 6.8]; PD = 24.3 [-5.2, 52.8]), overall preterm delivery (PR = 1.7 [0.3, 3.3]; PD = 13.4 [-24.8, 41.5]), and iatrogenic preterm delivery (PR = 4.8 [0.7, 23.2]; PD = 21.2 [-1.9, 55.7]) and a lower adjusted prevalence of spontaneous preterm delivery (PR = 0.4 [0.0, 1.2]; PD = -7.8 [-34.0, 3.6]). For the outcome intrauterine growth retardation/small for gestational age, the adjusted prevalence among the exposed group was 0 and among the unexposed group was greater than 0 (masked); the PR was 0 (0, 0) and the PD was not reportable due to masking.

Comparative analyses of exploratory outcomes: Three exploratory outcomes met the criterion for comparative analysis. The PR for excessive weight gain in pregnancy and excessive foetal growth was 1.8 (95% CI, 0.0, 12.6), and the PD was 3.4 (-4.3, 16.8); for complications of labour and delivery, the estimates were 1.1 (0.1, 2.0) and 2.5 (-24.4, 22.3), respectively, and for pregnancy-related anaemia, these estimates were 0 and not reportable, respectively.

In summary, no clear pattern of increased or decreased risks was observed when taking into consideration that there were no events of the primary outcomes spontaneous abortions, stillbirths and MCM among the Paxlovid-exposed pregnancies and only a limited number of events (1-10) among the unexposed pregnancies (suggesting no increased risk among the Paxlovid-exposed pregnancies) and the noted results from comparative analyses for other outcomes.

SIDIAP (Spain)

Because no Paxlovid-exposed pregnancies were eligible for the study, no further analyses beyond attrition were conducted using the data from SIDIAP.

CPRD Aurum (UK)

Because no Paxlovid-exposed pregnancies were eligible for the study, no further analyses beyond attrition were conducted using the data from CPRD.

Discussion: Paxlovid use during pregnancy was found to be low. The low use of Paxlovid in pregnancy in France, Spain, and the UK is consistent with the recommendations provided in the EU and UK SmPCs.

This report identified 24 Paxlovid-exposed pregnancies in the SNDS database from France during the study period from January 2022 to December 2023. These pregnancies were

successfully matched with 112 unexposed pregnancies. No pregnancies exposed to active comparator medications were eligible for the study in SNDS. No eligible Paxlovid-exposed pregnancies were identified in SIDIAP (Spain) or in CPRD (the UK); therefore, no further analyses were conducted in these 2 data sources.

In the SNDS database, the 24 pregnant women who were prescribed Paxlovid were slightly older, as indicated by the higher mean age, and had more risk factors for progression to severe COVID-19 and indicators of maternal morbidity; also, a higher proportion used medications contraindicated or potentially leading to interactions with Paxlovid than unexposed pregnant women. Furthermore, masking due to low numbers made it difficult to ascertain whether there was an imbalance in the distribution of other variables such as healthcare utilisation in the year before current pregnancy, socioeconomic status, or history of overweight or obesity between the Paxlovid-exposed and unexposed pregnancies.

The cohort sizes of Paxlovid-exposed and unexposed pregnancies differed for each outcome due to outcome-specific eligibility specifications and were very small. Outcome counts were also small in both cohorts, generally ranging from 0 to 1-10 (masked). No spontaneous abortions, stillbirths, MCM, intrauterine growth retardation/small for gestational age, gestational hypertension, postpartum haemorrhage, or maternal death were observed among Paxlovid-exposed pregnancies or their infants. Due to small study size, only the following outcomes met the criteria for comparative analysis in the SNDS database: (1) pregnancy outcomes: elective termination and preterm delivery (overall, spontaneous and iatrogenic), (2) infant outcome: intrauterine growth retardation/small for gestational age, and (3) exploratory outcomes: excessive weight gain in pregnancy and excessive foetal growth, complications of labour and delivery, and pregnancy-related anaemia. The adjusted PR and PD estimates suggested potentially increased risk for elective termination, overall preterm delivery, iatrogenic preterm delivery, and excessive weight gain in pregnancy and excessive foetal growth and a potentially reduced risk for spontaneous preterm delivery, intrauterine growth retardation/small for gestational age, and pregnancy-related anaemia in the Paxlovid-exposed group compared with the unexposed group. However, all risk estimates were imprecise, as shown by wide 95% confidence intervals.

Furthermore, the study did not identify any pregnancies exposed to active comparator medications. Therefore, Paxlovid-exposed pregnancies could not be compared with any active comparator group and comparisons were made with only unexposed pregnancies. The unexposed pregnancies may not represent an optimal comparator group due to inherent differences between the unexposed pregnant women and the Paxlovid-exposed pregnant women (ie, unexposed pregnant women did not require any treatment for COVID-19 whereas the Paxlovid-exposed pregnancies required treatment for COVID-19 despite Paxlovid being not recommended for use during pregnancy).

The study matched the Paxlovid-exposed and unexposed pregnancies on the following 3 variables: days after COVID-19 diagnosis until time zero, calendar time at time zero, and gestational age at time zero in 30-day months counting from the first day of the last menstrual period (LMP). However, because of the small number of Paxlovid-exposed

pregnancies, only the following 4 variables could be adjusted for in the propensity score model via inverse probability of treatment weighting: (1) number of risk factors for progression to severe COVID-19 (categorised as 0 or ≥ 1), age (< 35 or ≥ 35 years), number of maternal and obstetric morbidities (0, 1, or ≥ 2), and history of smoking (yes/no). Therefore, residual confounding by several key factors could not be ruled out.

In conclusion, a limited number of Paxlovid-exposed pregnancies was identified in the French SNDS database and no Paxlovid-exposed pregnancies were identified in the Spanish SIDIAP and UK CPRD databases in this study. This finding is consistent with the EU and UK SmPCs, which do not recommend using Paxlovid in pregnancy and recommend preventing pregnancy during treatment. Due to the limited number of Paxlovid-exposed pregnancies identified in the SNDS database, the resulting risk estimates in the comparative analyses lacked precision and did not provide evidence of increased or decreased risk for pregnancy, infant or maternal outcomes compared with unexposed pregnancies.

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