NON-INTERVENTIONAL (NI) PROGRESS REPORT

PASS information

Title	Use and safety of Paxlovid during pregnancy (C4671037) Use and safety of Paxlovid among patients with moderate or severe hepatic or renal impairment (C4671047)
Protocol number	C4671037 C4671047
Version identifier of the progress report	1.0
Date	14 November 2022
EU Post-Authorization Study (PAS) register number	Studies will be registered before start of data collection
Active substance	Combination of the oral protease inhibitors nirmatrelvir and ritonavir (ATC code J05AE30 to be implemented in 2023)
Medicinal product	Paxlovid
Product reference	PF 07321332/ritonavir
Procedure number	Conditional marketing authorisation EMEA/H/C/005973/000
Marketing Authorization Holder (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No

Research question and objectives	The research question for C4671037 is: what are the prevalence and comparative safety of adverse pregnancy, offspring, and maternal outcomes in women exposed to Paxlovid during pregnancy? The 2 research questions for C4671047 are: • What is the comparative safety of liver, abdominal, anaphylactic reactions, and other outcomes in patients with moderate or severe hepatic impairment exposed to Paxlovid? • What is the comparative safety of abdominal, anaphylactic reactions, and other outcomes in patients with moderate or severe renal impairment exposed to Paxlovid?
Country(-ies) of study	France, Spain, United Kingdom
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Marketing Authorization Holder(s)

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This progress report is for the programme that includes studies *Use and safety of Paxlovid during pregnancy* (C4671037) and *Use and safety of Paxlovid among patients with moderate or severe hepatic or renal impairment* (C4671047). This program was initially described in a single protocol (C4671037 version 1.0). The European Medicines Agency's (EMA's) feedback in August-September 2022 resulted in the programme being split into its 2 current studies, each with a separate protocol. This is the first progress report for the program and includes both studies.

Current plans are to use the same data sources, same active comparator, same research partners, same research partner roles, same data management processes, and similar analytic approaches for the 2 studies.

Future reports (i.e., interim and final reports) to the EMA are anticipated to be separate for each of the 2 studies. The 2 protocols (C4671037 version 2.0 and C4671047 version 1.0) are being submitted to the EMA simultaneously with this progress report.

Use and safety of Paxlovid during pregnancy (C4671037)

Study C4671037 is designed to monitor the safety profile of Paxlovid—an antiviral medication to treat adult patients with COVID-19 (coronavirus disease 2019) who do not need supplemental oxygen and who are at increased risk for progression to severe COVID-19—when used in pregnancy. This retrospective cohort study that uses prospectively collected data from France, Spain, and the United Kingdom (UK) is a non-interventional post-authorisation safety study (PASS) that will compare pregnant women exposed to Paxlovid with (1) pregnant women exposed to molnupiravir (an antiviral medication with an indication and form of administration similar to those of Paxlovid) where available and (2) unexposed pregnant women.

The protocol for this study retained the protocol number that the programme had in its initial submission to the EMA, and it is therefore currently labelled as version 2.0; this protocol includes a list of amendments relative to version 1.0.

The research question is: what are the prevalence and comparative safety of adverse pregnancy, offspring, and maternal outcomes in women exposed to Paxlovid during pregnancy?

The primary study objective is to estimate the birth prevalence, prevalence ratio, and prevalence difference of the following adverse pregnancy, offspring, and maternal outcomes in women who are exposed to Paxlovid during pregnancy compared with those in women who are exposed to molnupiravir, where available, during pregnancy, or to neither Paxlovid nor molnupiravir during pregnancy.

Pregnancy outcomes:

- Spontaneous abortion
- Elective termination
- Stillbirth
- Preterm delivery

Offspring outcomes:

- Major congenital malformations
- Intrauterine growth retardation/small for gestational age

Maternal outcomes:

- Gestational diabetes
- Postpartum haemorrhage
- Maternal death

Use and safety of Paxlovid among patients with moderate or severe hepatic or renal impairment (C4671047)

Study C4671047 is designed to monitor the safety profile of Paxlovid, when used by individuals with moderate or severe hepatic impairment or by individuals with moderate or severe renal impairment. This retrospective cohort study that uses prospectively collected data from France, Spain, and the UK is a PASS that will compare (separately for the 2 above-mentioned populations) individuals exposed to Paxlovid with (1) individuals exposed to molnupiravir (where available) and (2) unexposed individuals.

The protocol for this study received a new protocol number and is therefore labelled as version 1.0; being version 1.0, it does not include a list of amendments.

The 2 research questions are:

- What is the comparative safety of liver, abdominal, anaphylactic reactions, and other outcomes in patients with moderate or severe hepatic impairment exposed to Paxlovid?
- What is the comparative safety of abdominal, anaphylactic reactions, and other outcomes in patients with moderate or severe renal impairment exposed to Paxlovid?

For the population of individuals with moderate or severe hepatic impairment, the primary objective is:

- To assess the safety of Paxlovid relative to the comparator populations who used molnupiravir for COVID-19 and to unexposed patients with COVID-19 with respect to hospitalisations or emergency room visits for the following:
    - Hepatic transaminase elevations, clinical hepatitis, or jaundice
    - Severe vomiting, nausea, diarrhoea, or abdominal pain
    - Dysgeusia, headache, or hypertension
    - Anaphylactic reactions

For the population of individuals with moderate or severe renal impairment, the primary objective is:

- To assess the safety of Paxlovid relative to the comparator population who used molnupiravir for COVID-19 and to unexposed patients with COVID-19 with respect to hospitalisations or emergency room visits for the following:
    - Severe vomiting, nausea, diarrhoea, or abdominal pain
    - Dysgeusia, headache, or hypertension
    - Anaphylactic reactions

Research partners for this programme (C4671037 and C4671047)

As of 23 November 2022, all collaborations listed in Table 1 are in place. All the institutions and data sources are participating in both C4671037 and C4671047. This programme is a collaboration between the marketing authorisation holder (MAH) and the SIGMA Consortium (https://sigmaconsortium.eu/), of which the research partners listed below are members. Researchers from the listed institutions have participated in the development of previous and current versions of the study protocols. Aarhus University also collaborated in the development of protocol C4671037 version 1.0.

Table 1. SIGMA Consortium research partners for this programme

Role in PASS implementation	Data source	Collaborating institution
Research partner with protocol-based access to data	SNDS (France)	Bordeaux PharmacoEpi, Université de Bordeaux
Research partner with protocol-based access to data	SIDIAP (Spain)	IDIAP Jordi Gol

Table 1. SIGMA Consortium research partners for this programme

Role in PASS implementation	Data source	Collaborating institution
PI/coordinating centre & research partner with protocol-based access to data	CPRD (United Kingdom)	RTI Health Solutions
Programming centre	None for this program	Agenzia regionale di sanità della Toscana, Italy
Co-PI centre & programming centre	None for this program	Department of Datascience & Biostatistics, University Medical Center Utrecht

CPRD = Clinical Practice Research Datalink; IDIAP = Foundation University Institute for Primary Health Care Research Jordi Gol i Gurina (Spain); PASS = post-authorisation safety study; PI = principal investigator; SIDIAP = Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària); SNDS = French Administrative Healthcare Database.

As of 23 November 2022, all contracts with the research partners for protocol development have been signed and all research partners have confirmed their interest in participating in the implementation of the 2 PASSs. Immediate next steps, once the protocols are endorsed by the EMA, include contracting for study implementation, research partners' obtaining the necessary institutional and ethical approvals, registering the studies in the EU PAS Register, developing the statistical analysis plans, and obtaining data cuts for interim analyses, which will include updates on the number of users of Paxlovid and molnupiravir and outcome counts for the first interim report. To enable completion of these steps before the first interim report is due to the EMA, the submission dates of the interim reports are anchored on the date of protocol endorsement by the EMA.

Challenges for this programme (C4671037 and C4671047)

The main challenges for this program include the following:

- *Identifying exposure* is a key uncertainty at the time of preparation of this document. In some data sources, Paxlovid distribution is using the channels that trigger a record in routinely available electronic health records or healthcare claims. This criterion was used to select the data sources. The MAH and the research team are in close communication sharing information about country-specific distribution channels and sales volume, as this information becomes available.

- *Size of target populations*. The target populations include individuals who should not receive Paxlovid per the SmPC. For this reason, it is expected that the number of Paxlovid-exposed individuals in the target populations will be small. In the case that the study populations are too small to support comparative analyses, descriptive analyses will be conducted instead. Plans for these analyses will be incorporated into the statistical analysis plans.

Distribution of Paxlovid in Europe

As of 30 September 2022, the MAH confirmed that Paxlovid has been supplied to France, Germany, Italy, Spain, Slovenia, Sweden, and the UK, initially or continuing under special government contracts, resulting in different distribution and reimbursement channels being used and subsequent challenges capturing its prescription and distribution.

Current information on prescribed or dispensed Paxlovid should be captured in existing electronic population data sources in France, Spain, and the UK. Currently, the proposed data sources are SNDS (France), SIDIAP (Catalonia, Spain), and CPRD Aurum (UK). Counts are presented in Table 2. For more details, please refer to protocols C4671037 and C4671047, Section 9.4, Data Sources.

Table 2. Study feasibility: Paxlovid distribution in Europe

Country	Capture in data sources
France	Medic'AM: 12,634 dispensed boxes in Feb-Jun 2022 EPI-PHARE report: 12,179 individuals received Paxlovid between 4 Feb and 29 Jun 2022
Germany	Not available
Italy	AIFA Register: 81,709 treatments as of 2 Nov 2022
Slovenia	Not available
Spain	SIDIAP: 353 Paxlovid prescriptions for 339 individuals between 7 Apr and 30 Jun 2022
Sweden	Not available
United Kingdom	CPRD Aurum: 400 prescriptions as of 13 Sep 2022 OpenSAFELY: 10,850 individuals as of 7 Oct 2022

AIFA = Italian Medicines Agency [Agenzia Italiana del Farmaco]; CPRD = Clinical Practice Research Datalink; SIDIAP = Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) Catalonia, Spain.

Next steps – Milestones

Table 3. Use and safety of Paxlovid during pregnancy (C4671037): Study milestones

Milestone	Planned/actual date
Protocol C4671037 v1.0 submission	31 May 2022 (actual; including pregnant population, population with moderate or severe hepatic impairment, and population with moderate or severe renal impairment in a single protocol)
Final CHMP/PRAC feedback	15 September 2022 (actual)
Protocol C4671037 v2.0 submission	November 2022 (pregnant population)
Regulatory protocol endorsement anticipated	Quarter 1 or quarter 2 of 2023
Registration in the EU PAS Register	Study will be registered prior to start of data collection
Progress report submission	November 2022
Start of data collection[a]	Quarter 4 of 2023[b]
Interim report 1	12 months after protocol endorsement; interim report 1 estimated for quarter 2 of 2024[b]
Interim report 2	24 months after protocol endorsement; interim report 2 estimated for quarter 2 of 2025[b]
End of data collection[a]	Quarter 2 of 2025[b]
Paediatric study report (as applicable if Paxlovid is used by pregnant individuals younger than 18 years old[3])	6 months after the end of data collection for the final report[a]
Final study report	28 November 2025[b]

CHMP = Committee for Medicinal Products for Human Use; EU PAS Register = European Union Electronic Register of Post-authorisation Studies; PRAC = Pharmacovigilance Risk Assessment Committee.
Note: Contracts for study implementation between the sponsor and research organisation(s), data source selection, and approvals by data protection, data custodian, ethics, and scientific review bodies, several of which require a final or endorsed protocol, are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

a. Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts".[1] Simple counts are not part of this definition. End of data collection is "the date from which the analytical data set is completely available". [1]
b. Protocol endorsement is anticipated in quarter 1 or quarter 2 of 2023. Deliverable dates will be updated once protocol endorsement date is known.

Table 4. Use and safety of Paxlovid among patients with moderate or severe hepatic or renal impairment (C4671047): Study milestones

Milestone	Planned/actual date
Protocol C4671037 v1.0 submission	31 May 2022 (actual; including pregnant population, population with moderate or severe hepatic impairment, and population with moderate or severe renal impairment in a single protocol)
Final CHMP/PRAC feedback	15 September 2022 (actual)
Protocol C4671047 v1.0 submission	November 2022 (population with moderate or severe hepatic impairment, and population with moderate or severe renal impairment)
Regulatory protocol endorsement anticipated	Quarter 1 or quarter 2 of 2023
Registration in the EU PAS Register	Study will be registered prior to start of data collection
Progress report submission	November 2022
Start of data collection[a]	Quarter 4 of 2023[b]
Interim report 1	12 months after protocol endorsement; interim report 1 estimated for quarter 2 of 2024[b]
Interim report 2	24 months after protocol endorsement; interim report 2 estimated for quarter 2 of 2025[b]
End of data collection[a]	Quarter 2 of 2025[b]
Paediatric study report (as applicable if Paxlovid is used in this population)	6 months after the end of data collection for the final report[a]
Final study report	28 November 2025[b]

CHMP = Committee for Medicinal Products for Human Use; EU PAS Register = European Union Electronic Register of Post-authorisation Studies; PRAC = Pharmacovigilance Risk Assessment Committee.
Note: Contracts for study implementation between the sponsor and research organisation(s), data source selection, and approvals by data protection, data custodian, ethics, and scientific review bodies, several of which require a final or endorsed protocol, are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

a. Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts".[1] Simple counts are not part of this definition. End of data collection is "the date from which the analytical data set is completely available".[1]
b. Protocol endorsement is anticipated in quarter 1 or quarter 2 of 2023. Deliverable dates will be updated once protocol endorsement date is known.

REFERENCE

1. EMA. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (EMA/813938/2011 Rev 3). 13 October 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf. Accessed 30 July 2021.

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