NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Safety of Paxlovid During Pregnancy
Protocol number	C4671037
Protocol version identifier	Protocol V4.0
Date	21 June 2023
EU Post-Authorisation Study (PAS) register number	EUPAS50117
Active substance	Combination of the oral protease inhibitors nirmatrelvir and ritonavir (ATC code J05AE30)
Medicinal product	Paxlovid
Product reference	nirmatrelvir/ritonavir
Procedure number	Marketing authorisation EMEA/H/C/005973
Marketing Authorisation Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	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 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, during pregnancy or to women with COVID-19 unexposed to any study medications 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 • Gestational hypertension • Postpartum haemorrhage • Maternal death The secondary study objective is to assess maternal exploratory outcomes that will be identified based on conditions appearing in the study population after exposure to Paxlovid.
Country(-ies) of study	• France • Spain • United Kingdom • Other countries in Europe are under evaluation

Author	Andrea Margulis, MD, ScD, FISPE, RTI Health Solutions, in collaboration with Aarhus University, University Medical Center Utrecht, and ARS Toscana, on behalf of the SIGMA Consortium Paxlovid PASS research team Cynthia de Luise, PhD, MPH, Pfizer, Inc

Marketing Authorisation Holder

Marketing Authorisation Holder	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
MAH contact person	Sophie Van De Leest Pfizer sa/nv Boulevard de la Plaine 17 1050 Bruxelles Belgium sophie.vandeleest@pfizer.com

1. TABLE OF CONTENTS

1. TABLE OF CONTENTS....4
2. LIST OF ABBREVIATIONS....6
3. RESPONSIBLE PARTIES....9
4. ABSTRACT....11
5. AMENDMENTS AND UPDATES....16
6. MILESTONES....23
7. RATIONALE AND BACKGROUND....24
7.1. Authorisations....24
7.2. European Union summary of product characteristics....24
7.3. United Kingdom summary of product characteristics....25
8. RESEARCH QUESTION AND OBJECTIVES....25
9. RESEARCH METHODS....26
9.1. Study design....26
9.1.1. Discussion of molnupiravir as an active comparator....27
9.1.2. Discussion on other drugs to treat COVID-19 as potential active comparators....28
9.2. Setting....31
9.2.1. Inclusion criteria, exclusion criteria, and follow-up....32
9.2.2. Study period....36
9.3. Variables....36
9.3.1. Exposure....36
9.3.2. Outcomes....36
9.3.3. Other variables....40
9.4. Data sources....42
9.4.1. France: French Administrative Healthcare Database (SNDS)....44
9.4.2. Spain: Catalan Information System for Research in Primary Care (SIDIAP)....46
9.4.3. United Kingdom: CPRD Aurum and Hospital Episode Statistics....47
9.4.4. Additional exploration of data sources....48
9.5. Study size....52

9.6. Data management 55
9.6.1. Record retention 56
9.6.2. Data extraction 57
9.6.3. Data processing and transformation 57
9.6.4. Data access 57
9.6.5. Data quality checks 58
9.7. Data analysis 61
9.7.1. Descriptive analyses 61
9.7.2. Unadjusted outcome measures 61
9.7.3. Adjustment for baseline imbalances 62
9.7.4. Small cell count policy 63
9.8. Quality control 63
9.9. Limitations of the research methods 64
9.10. Other aspects 66
10. PROTECTION OF HUMAN SUBJECTS 66
10.1. Patient information 67
10.2. Patient consent 67
10.3. Institutional review board/independent ethics committee 67
10.4. Ethical conduct of the study 67
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 68
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 68
13. REFERENCES 70
14. LIST OF TABLES 78
15. LIST OF FIGURES 78
ANNEX 1. LIST OF STAND-ALONE DOCUMENTS 79
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS 80
ANNEX 3. PERINATAL PHARMACOEPIDEMIOLOGY RESEARCH CHECKLIST 87
ANNEX 4. PRELIMINARY CODE LISTS TO IDENTIFY RISK FACTORS FOR PROGRESSION TO SEVERE COVID-19 88
ANNEX 5. ADDITIONAL INFORMATION 99

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEMPS	Spanish Agency of Medicines and Medical Devices [Agencia Española de Medicamentos y Productos Sanitarios]
AIFA	Italian Medicines Agency [Agenzia Italiana del Farmaco]
ALD	List of chronic conditions registered in France [Affections de Longue Durée]
ARS Toscana	Regional Health Agency of Tuscany, Italy [Agenzia Regionale di Sanità della Toscana]
ASSIR registers	Sexual and reproductive healthcare registers (Spain)
ATC	Anatomical Therapeutic Chemical (classification system)
BIFAP	Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària (Spain)
BPE	Bordeaux PharmacoEpi, Université de Bordeaux (France)
CDC	US Centers for Disease Control and Prevention
CDM	Common data model
CESREES	Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé (France)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CMA	Conditional marketing authorisation
CMUc	*Couverture médicale universelle complémentaire* indicator of low-income status (France)
CNAM	Caisse Nationale de l'Assurance Maladie (France)
CNIL	French Data Protection Commission [Commission Nationale de l'Informatique et des Libertés]
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Datalink (UK)
CPRD GOLD	General Practitioner Online Database (of CPRD)
DAP	Data access partner
DCIR	Individual outpatient healthcare data [Datamart de Consommation Inter Régime] (France)
DRE	Digital Research Environment

Abbreviation	Definition
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPhMRA	European Pharmaceutical Market Research Association
ETL	Extraction, transformation, and loading
EU	European Union
EU PAS Register	European Union Electronic Register of Post-authorisation Studies
EUROCAT	European network of population-based registries for the epidemiological surveillance of congenital anomalies
FAIR	Findability, Accessibility, Interoperability, and Re-use of digital assets
GPP	Good Pharmacoepidemiology Practices
GVP	Guideline on Good Pharmacovigilance Practices
HES	Hospital Episode Statistics
HIV	Human immunodeficiency virus
ICD-10	*International Classification of Diseases, Tenth Revision*
ICD-9	*International Classification of Diseases, Ninth Revision*
ICPC	International Classification of Primary Care
ICPE	International Conference on Pharmacoepidemiology & Therapeutic Risk Management
IDIAP Jordi Gol or IDIAP	Foundation University Institute for Primary Health Care Research Jordi Gol i Gurina (Spain)
IEC	Independent ethics committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
IT	Information technology
KM	Kaplan-Meier
LMP	First day of the last menstrual period
MAH	Marketing authorisation holder
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NHS	National Health Service
NI	Non-interventional
ONS	Office for National Statistics

Abbreviation	Definition
PASS	Post-authorisation safety study
PCR	Polymerase chain reaction
PMSI	National hospital discharge summaries database system (France)
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
RT-PCR	Reverse transcription polymerase chain reaction
RTI-HS	RTI Health Solutions, a division of RTI International, a not-for-profit research organisation
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SI-DEP	National Population Screening Information System (France)
SIDIAP	Information System for Research in Primary Care [Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària] Catalonia, Spain
SmPC	Summary of product characteristics
SNDS	French Administrative Healthcare Database [Système National Des Données de Santé] (France)
SNOMED CT	Systematized Nomenclature of Medicine–Clinical Terms
UCD	Common dispensing unit (France)
UK	United Kingdom
US	United States
VAC4EU	Vaccine Monitoring Collaboration for Europe

3. RESPONSIBLE PARTIES

The Marketing Authorisation Holder (MAH) of Paxlovid is Pfizer.

RTI Health Solutions (RTI-HS), University Medical Center Utrecht, Aarhus University, and Regional Health Agency of Tuscany, Italy (ARS Toscana), which are members of the SIGMA[1] and VAC4EU[2] consortia, are under contract with Pfizer to develop the post-authorisation safety study (PASS) programme protocol and conduct feasibility checks for the present study. Additional research partner members and collaborators are being included in the study as the country-specific reimbursement, launch timelines, and sales forecasts for Paxlovid become available.

Principal Investigator(s) of the Protocol

Name, degree(s)	Job title	Affiliation	Address
Cynthia de Luise, PhD, MPH	Senior Director, Safety Surveillance Research	Pfizer, Inc.	66 Hudson Blvd E NY, NY 10001 USA
Andrea Margulis, MD ScD, FISPE	Director, Epidemiology	RTI Health Solutions	Av. Diagonal 605, 9-1; 08028, Barcelona, Spain
Manel Pladevall-Vila, MD, MS	Senior Director, Epidemiology	RTI Health Solutions	Av. Diagonal 605, 9-1; 08028, Barcelona, Spain
Jaume Aguado, PhD	Senior Statistician, Biostatistics	RTI Health Solutions	Av. Diagonal 605, 9-1; 08028, Barcelona, Spain
Susana Perez-Gutthann, MD, PhD, FRCP, FISPE	Vice President, Global Head of Epidemiology	RTI Health Solutions	Av. Diagonal 605, 9-1; 08028, Barcelona, Spain
Vera Ehrenstein, MPH, DSc[a]	Professor	Department of Clinical Epidemiology, Aarhus University	Olof Palmes Alle 43-45, 8200 Aarhus N, Denmark
Rosa Gini, PhD	Head of the Pharmacoepidemiology Unit	Agenzia regionale di sanità della Toscana, Italy	Via Pietro Dazzi, 1, 50141 Firenze, Italy
Miriam Sturkenboom, PhD, MSc, FISPE	Head of the Department of Datascience & Biostatistics, professor	Department of Datascience & Biostatistics, University Medical Center Utrecht	Heidelberglaan 100, Utrecht, The Netherlands

a. Prof. Ehrenstein contributed to earlier versions of the protocol.

Country coordinating investigators

The list of study sites and research teams with access to data (data access partners [DAPs]) has been developed as information about the healthcare settings where Paxlovid is distributed, prescribed, and dispensed to patients in specific European countries has become available. Research partners with protocol-based access to data sources are listed below. They have reviewed and provided comments to this protocol and have confirmed interest in participating in this PASS.

Name, degree(s)	Job title	Affiliation	Address
Cécile Droz-Perroteau, PhD	Director	Bordeaux PharmacoEpi, Université de Bordeaux for SNDS (France)	146 rue Léo Saignat, Case 41, 33076 Bordeaux cedex, France
Régis Lassalle, MSc	Chief of Biostatistics and Data Management	Bordeaux PharmacoEpi, Université de Bordeaux for SNDS (France)	146 rue Léo Saignat, Case 41, 33076 Bordeaux cedex, France
Nicolas Thurin, PharmD, PhD	Scientific Officer	Bordeaux PharmacoEpi, Université de Bordeaux for SNDS (France)	146 rue Léo Saignat, Case 41, 33076 Bordeaux cedex, France
Maria Giner-Soriano, PharmD, PhD, Clinical Pharmacist	Pharmacoepidemiology researcher	IDIAP Jordi Gol, for SIDIAP (Spain)	Gran Via de les Corts Catalanes 587, àtic; 08007, Barcelona, Spain
Dan Ouchi Vernet, MSc	Senior statistician	IDIAP Jordi Gol, for SIDIAP (Spain)	Gran Via de les Corts Catalanes 587, àtic; 08007, Barcelona, Spain
Silvia Fernández García, MD, Clinical Pharmacologist	Pharmacoepidemiology researcher	IDIAP Jordi Gol, for SIDIAP (Spain)	Gran Via de les Corts Catalanes 587, àtic; 08007, Barcelona, Spain
Rosa Morros Pedrós, MD, PhD	Senior adviser, Coordinator of the Medicines Studies Unit at IDIAPJGol	IDIAP Jordi Gol, for SIDIAP (Spain)	Gran Via de les Corts Catalanes 587, àtic; 08007, Barcelona, Spain
Andrea Margulis, MD ScD, FISPE	Director, Epidemiology	RTI Health Solutions for CPRD Aurum (UK)	Av. Diagonal 605, 9-1; 08028, Barcelona, Spain
Estel Plana, MSc	Director, Biostatistics	RTI Health Solutions for CPRD Aurum (UK)	Av. Diagonal 605, 9-1; 08028, Barcelona, Spain
Manel Pladevall-Vila, MD, MS	Senior Director, Epidemiology	RTI Health Solutions	Av. Diagonal 605, 9-1; 08028, Barcelona, Spain

4. ABSTRACT

Title

Safety of Paxlovid During Pregnancy

- Protocol version 4.0, 21 June 2023
- Main author: Andrea Margulis, RTI Health Solutions, on behalf of the SIGMA Consortium Paxlovid PASS Research Team

Rationale and background

Paxlovid consists of nirmatrelvir (formerly PF-07321332), a potent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protease inhibitor, co-administered with a low dose of ritonavir, which acts as a pharmacokinetic enhancer, orally twice a day for 5 days. Paxlovid is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

The safety of Paxlovid in pregnant women is not known. The post-authorisation safety study (PASS) of Paxlovid in pregnant women is a regulatory commitment to the European Medicines Agency (EMA) and the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA).

This protocol describes a PASS to assess the safety of Paxlovid in pregnant women in European countries with data sources that have the ability to capture exposure and where the target populations, outcomes, and key covariates can be ascertained.

Research question and objectives

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 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, during pregnancy or to women with COVID-19 unexposed to any study medications 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
- Gestational hypertension
- Postpartum haemorrhage
- Maternal death

The secondary study objective is to assess maternal exploratory outcomes in outpatient and inpatient settings as available that will be identified based on conditions appearing in the study population after exposure to Paxlovid.

Study design

The study will focus on pregnant women. Within this population, there will be a descriptive analysis and comparative analyses. Molnupiravir, an antiviral with a similar recommended usage, will be used as an active comparator in the data sources in which it is available; other drugs may be incorporated as active comparators as more information becomes available. At the time of preparing this protocol, molnupiravir was not utilised or its use was not captured by some of the data sources (eg, France and Information System for Research in Primary Care [SIDIAP] in Catalonia, Spain). Therefore, a second comparator group is included in the study: individuals with COVID-19 unexposed to any study medication. Other medications to treat COVID-19 will be considered as active comparators in the future.

The study period will start on 01 January 2022 (in alignment with regulatory authorisation and launch in Europe) and end as late as possible.

Population

The target study population will be individuals with COVID-19 exposed to Paxlovid or comparator drug molnupiravir or other comparable medications and individuals unexposed to Paxlovid, molnupiravir, or other comparable medications (the *unexposed comparison group*), while they are pregnant.

Time 0 will be the day on which individuals meet all eligibility criteria; they can start treatment with Paxlovid or molnupiravir or comparable medications within 7 days (a grace period; ie, days [0, 6] inclusive of both bounds). Unexposed individuals will be matched with individuals starting Paxlovid by time since COVID-19 diagnosis (days) and calendar time

(within ± 1 week; ie, days [−6, 6] inclusive of both bounds). Users of Paxlovid and molnupiravir (or users of comparable medications) will be matched on calendar time. Follow-up of pregnant women will start between day 1 and day 7, depending on which day matching of unexposed with exposed occurs. Follow-up will end at the earliest of 6 months after end of pregnancy, death, disenrollment or migration, end of data availability in the data source, or treatment group crossover. In addition, follow-up for each outcome in women will end at the occurrence of the given outcome. Follow-up of the offspring to assess offspring outcomes will continue through the earliest of death, disenrollment or migration, end of data availability in the data source, or 1 year of age. In addition, follow-up for each outcome in infants will end at the occurrence of the given outcome.

Variables

The exposures will be Paxlovid and the comparator molnupiravir (or any other comparable medications that may be added to the comparison group), which will be ascertained from prescription and pharmacy information or from other data banks (eg, a central COVID-19 therapy distribution registry, if Paxlovid distribution is documented in this manner). See details in the Data sources subsection.

Outcomes will be ascertained from each of the data sources based on algorithms that include diagnosis codes, medication use, procedure codes, information recorded in birth registries, and others. Planned outcomes are as follows:

- 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
  - Gestational hypertension
  - Postpartum haemorrhage
  - Maternal death

In addition, exploratory safety outcomes will be identified from the observed data using diagnostic codes in the inpatient and outpatient settings as available.

Key variables will include demographics, COVID-19 tests and diagnoses, comorbidities, comedications, COVID-19 vaccination status (as available) and health services utilisation ascertained from all the data banks linked in the selected data sources, including administrative data, coded entries, vaccination registries, birth registries, and others.

Data sources

As of 20 September 2022, the MAH has 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 is that prescribed/dispensed Paxlovid should be captured in existing electronic population data sources in France, Spain, and the UK. The Italian Medicines Agency (AIFA) established a national registry for Paxlovid and other antivirals to treat COVID-19. At the time of this writing, capture of Paxlovid dispensing/prescriptions in the existing electronic data sources commonly used for pharmacoepidemiological research in Italy at this moment is expected to be minimal. As long as the German government continues to cover payments for Paxlovid, it is expected that Paxlovid prescriptions will not be captured in the German Statutory Health Insurance data sources.

The proposed data sources are the French Administrative Healthcare Database (SNDS), SIDIAP (Catalonia, Spain), and Clinical Practice Research Datalink–Aurum (CPRD Aurum) (UK).

The UK OpenSAFELY data source and the AIFA patient registry will continue to be explored as potential supplementary data sources for this study.

The MAH will share additional information about Paxlovid supply and forecast for other European countries as it becomes available, and the research team will evaluate whether Paxlovid use is captured in the electronic data sources that allow longitudinal studies in these countries.

Study size

All individuals meeting eligibility criteria during the study observation period will be included. As the summaries of product characteristics (SmPCs) recommend against use in pregnancy, Paxlovid exposure in this population is anticipated to be small.

Data analysis

Study data will be analysed as a cohort. Descriptive baseline characteristics will include tabulations of age, sex, comorbidities, selected concurrent medications, COVID-19 vaccination status, history of COVID-19, current COVID-19 status and setting of Paxlovid

use (among Paxlovid users). Comparative analyses will be based on the estimation of risk/prevalence, risk/prevalence ratios, and risk/prevalence differences. Comparative analyses will control for measured confounding within each data source. Aggregated results from each data source will be combined using meta-analytic techniques as numbers allow. If a study population is too small, analyses will be only descriptive; pooling of results from various data sources will be undertaken only if at least 3 independent data points are available.

Milestones

- Protocol C4671037 V1.0 submission: 31 May 2022 (including pregnant population, population with moderate or severe hepatic impairment and population with moderate or severe renal impairment in a single document)
- Protocol C4671037 V2.0 submission: 29 November 2022 (pregnant population)
- Progress report submission: 29 November 2022
- Interim report 1: 14 months after protocol endorsement; interim report 1 estimated for quarter 4 2024*
- Interim report 2: 24 months after protocol endorsement; interim report 2 estimated for quarter 4 2025*
- Final report: final report estimated for 31 March 2026*

* Protocol endorsement from EMA is expected in quarter 4 2023. Milestones will be updated once protocol endorsement date is known.

5. AMENDMENTS AND UPDATES

Key changes after submission to the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency of protocol C4671037, titled *Use and safety of Paxlovid during pregnancy and among patients with moderate or severe hepatic or renal impairment* (V1.0, dated 20 May 2022), are listed below. Minor (eg, wording) changes are not listed.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
3	21 Jun 2023	4 6	Milestones were updated: protocol endorsement is anticipated in quarter 3 2023	Update based on regulatory timeline for this amendment.
		9.3.2.1	Exploratory outcomes will be sought in outpatient data, inpatient data, and data from emergency visits; the outpatient component was added in this amendment.	In response to EMA queries on C4671037 Protocol Amendment 2; EMEA/H/C/005973/MEA/008.1, dated 07 June 2023
		10.1 10.2	Changes in the text of the protection of human subjects section have been implemented to use the right terminology according to EU legislation applicable to the protection of human subjects and also to reflect accurately the structure of the data that will be used in the study.	To use the right terminology to define the structure of the data that will be used in the study.
		9 12	Clarifications of the content of interim report 1, interim report 2, and the final report and to describe specific elements that will be included in those reports.	In response to EMA queries on C4671037 Protocol Amendment 2; EMEA/H/C/005973/MEA/008.1, dated 07 June 2023
2	14 Apr 2023	Cover page 4 Annex 2	Removed “Use and” from title.	Drug utilisation will no longer be included in this study.
		Cover page 4 8	The study objectives have been reworded to explicitly mention that additional comparator drugs might be incorporated into the study.	In response to comment 2 in Final Assessment Report for non-imposed non-interventional PASS protocol, Post-Authorisation Measure 009; EMEA/H/C/005973/MEA/008, dated 23 February 2023 (hereafter in this table, 2023 CHMP/PRAC Final Assessment Report)

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Cover page 4 8 9.1 12	Other treatments for COVID-19 will be considered to identify the study active comparator cohort. This is reflected now in the objectives. Counts of individuals exposed to such drugs will be presented in interim reports.	In response to comment 4 in the 2023 CHMP/PRAC Final Assessment Report
		Cover page 4 8 9.3.2	Gestational hypertension has been added to maternal outcomes.	In response to comment 3 in the 2023 CHMP/PRAC Final Assessment Report
		Cover page 4 8 9.3.2 9.9	Exploratory outcomes have been incorporated into the study and the study objectives. Limitations have been noted.	In response to comments 3 and 13 in the 2023 CHMP/PRAC Final Assessment Report
		4 6 9.1 9.7 12	The paediatric study report, which was a deliverable in protocol version 2.0, was eliminated. A stratified analysis that will explore use in the paediatric population was added.	In response to comment 1 in the 2023 CHMP/PRAC Final Assessment Report
		4 7	Explicit mentions of the companion PASS on populations with moderate or severe hepatic or renal impairment have been removed.	In response to comment 2 in the 2023 CHMP/PRAC Final Assessment Report
		4 9.2 9.2.1	The text describing the start and end of follow-up has been modified for clarity, including the note to Figure 1.	In response to comment 8 in the 2023 CHMP/PRAC Final Assessment Report
		None (Section 7.4 in version 2.0)	This section was removed.	The content of this section was considered not informative.
		9.1 9.2 9.2.1 9.9	The eligibility criteria and their graphic depiction have been modified so that all pregnant women with COVID-19 are eligible for this study (regardless of having other conditions that may put them at increased risk for progression to severe COVID-19). The exposure window for starting treatment was extended from the previous 0-3 days.	In response to several comments in the 2023 CHMP/PRAC Final Assessment Report

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.2.1 9.4	For the purpose of this study, the start of pregnancy will be the first day of the last menstrual period. Other pregnancy periods have been specified. Processes to estimate the first day of the last menstrual period have been expanded.	In response to comment 10 in the 2023 CHMP/PRAC Final Assessment Report
		9.2.1 9.4.3	It has been clarified that COVID-19 test results are available in CPRD Aurum. It has also been clarified that the Pregnancy Register and the Mother-Baby Link are available in CPRD Aurum.	In response to comment 17 in the 2023 CHMP/PRAC Final Assessment Report
		9.2.1	The interval for matching exposed and unexposed has been expanded; the reasons for and advantages of matching in this setting have been restated for clarity and completeness.	In response to comment 9 in the 2023 CHMP/PRAC Final Assessment Report
		9.2.2	It is now specified that exploratory outcomes require linkage to HES data.	In response to comments 3 and 11 in the 2023 CHMP/PRAC Final Assessment Report
		9.3 Annex 4	The medical conditions that are risk factors for progression to severe COVID-19 have been updated; code lists to identify them are provided in Annex 4.	Updated list: to align with current knowledge. Addition of code lists: in response to comment 14 in the 2023 CHMP/PRAC Final Assessment Report
		9.3.2	A description of the period during which codes to ascertain outcomes will be sought was added.	In response to comment 19 in the 2023 CHMP/PRAC Final Assessment Report
		9.4.2	Details on how information on COVID-19 tests is available for research in SIDIAP have been added.	In response to comment 16 in the 2023 CHMP/PRAC Final Assessment Report
		9.4.4.1	The term “PASS-DUS” has been removed from this section. The AIFA description has been updated.	In response to comment 18 in the 2023 CHMP/PRAC Final Assessment Report
		9.7.4	The text for masking small cell counts was modified to explicitly denote both bounds of the masked range; eg, ”1 ≤ n ≤ 10” will be used instead of “n ≤ 10.”	Further described in response to comment 20 in the 2023 CHMP/PRAC Final Assessment Report

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	10 Nov 2022	All protocol	Protocol version 1.0 included 3 populations: pregnant women, individuals with moderate or severe hepatic impairment, and individuals with moderate or severe renal impairment. The protocol was divided into 2: one including the population of pregnant women (the present protocol C4671037), and one including the populations of individuals with moderate or severe hepatic impairment and individuals with moderate or severe renal impairment (protocol C4671047).	Committee for Medicinal Products for Human Use (CHMP) Outcome of procedure EMEA/H/C/005973/MEA/009 received on 15 September 2022
		Cover page 4 8 9 Throughout	The objective related to drug utilisation was removed. This component included a description of women of childbearing age, which was removed per request of the Agency. As a consequence, the description of the population that would be involved in that analysis and the analyses were removed; the labels "PASS-DUS" and "PASS-safety," no longer needed, were removed.	Addressing comment 6 in Final Assessment Report for non-imposed non-interventional PASS protocol - Post-Authorisation Measure 009; EMEA/H/C/005973/MEA/009, dated 15 September 2022 (hereafter in this table, 2022 CHMP/PRAC Final Assessment Report)
		Cover page 4 8 9.3	Maternal outcomes are now specified in the objectives: postpartum haemorrhage, gestational diabetes, and maternal death. Other outcomes are now also listed.	Addressing comment 19 in 2022 CHMP/PRAC Final Assessment Report
		Cover page 4 8 9.3	Outcomes categories were pregnancy outcomes, outcomes in live births, and maternal outcomes. Without modifying the outcomes themselves, they were recategorised as pregnancy outcomes, offspring outcomes, and maternal outcomes. In addition, the outcome labels were homogenised (eg, congenital anomalies and birth defects).	Outcome categories were modified to clarify the unit of analysis for each outcome. Outcome labels were homogenised for clarity.
		3	Updated principal investigator table.	To account for study team updates

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		4 6	The milestone section now provides one date for the start of the data collection and only 1 date for the end of data collection. The milestones also reflect that timelines might need to be modified depending on the dates of protocol endorsement.	Addressing comment 2 in 2022 CHMP/PRAC Final Assessment Report
		7.4	This is a new section in the background to describe findings from the literature pertaining to the study.	For completeness
		7	It is now explicit that lactation is investigated in the C4671039 PK study; the feasibility of studying lactation in the PASS will be subsequently assessed if substantial transfer into breast milk is found.	Addressing comment 4 in 2022 CHMP/PRAC Final Assessment Report
		Cover page 4 8	Objectives are now explicit in terms of what the comparator populations are for the pregnant women population.	Addressing comment 7 in 2022 CHMP/PRAC Final Assessment Report
		9.1.2	Discussion on drugs that could be used as active comparators (in addition to molnupiravir) has been added.	Addressing comment 8 in 2022 CHMP/PRAC Final Assessment Report
		4 9.1 12	The feasibility assessment for this programme was expanded to include a characterisation of the study populations by exposure status; this is to be included in interim reports.	Addressing comment 10 and comment 15 in 2022 CHMP/PRAC Final Assessment Report
		9.1.1 9.2 9.2.1.1 9.2.1.2 9.9	Sections 9.2.1.1 and 9.2.1.2 were removed. Some text from those sections was relocated to Sections 9.1.1 (new in this protocol version) and 9.9. Inclusion and exclusion criteria were modified. Section 9.2 was restructured.	Addressing comment 14 in 2022 CHMP/PRAC Final Assessment Report
		9.1	Table 1 was restructured to remove the drug utilisation component and to reflect the study populations per the Agency´s request.	Addressing comment 11 in 2022 CHMP/PRAC Final Assessment Report
		9.1	The text related to target trial emulation in Section 9.1 was removed.	Addressing comment 12 in 2022 CHMP/PRAC Final Assessment Report
		9.2	The age-related inclusion criterion for safety analyses was removed (study participants had to be aged 18 years or older).	To include in the study a population as broad as possible

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.2	The figure for the drug utilisation component was removed; the figure for the safety component was modified to reflect each population, as needed.	Addressing comments 13 and 15 in 2022 CHMP/PRAC Final Assessment Report
		9.2 9.9	Inclusion and exclusion criteria were modified to require documented COVID-19 from all individuals in the study; criteria are now stated as bullet points. The limitations associated with this inclusion criterion have been expanded.	Addressing comments 14 and 15 in 2022 CHMP/PRAC Final Assessment Report
		9.2	Pregnancy identification processes were described for each proposed data source.	Addressing comment 16a in 2022 CHMP/PRAC Final Assessment Report
		9.2.2	Table added to show the study period in each data source, incorporating lag and timing of data updates.	Addressing comment 17 in 2022 CHMP/PRAC Final Assessment Report
		9.3.2	Major congenital malformations will be identified using EUROCAT definitions.	Addressing comment 18 in 2022 CHMP/PRAC Final Assessment Report
		9.3.2	Table 5 mentioned a sensitivity analysis that would consider all pregnancies (including all pregnancies with unknown outcome) to be pregnancy terminations. This sensitivity analysis was removed (it is retained in relation with spontaneous abortions).	This was an oversight in the previous version of the protocol; it had been decided that this analysis would be removed (it might increase the misclassification of terminations rather than decrease them)
		9.3.2	Column header in Table 5 was modified.	Addressing comment 20 in 2022 CHMP/PRAC Final Assessment Report
		9.3.3	The obstetric comorbidities, previously indicated through a reference, are now enumerated (from the same reference).	For clarity
		9.4	Information was added indicating that the Spanish data source BIFAP is not available for studies funded by pharmaceutical companies.	Addressing comment 23 in 2022 CHMP/PRAC Final Assessment Report
		9.4	This section was expanded to include new information on Paxlovid supplies to countries in the European Union.	For completeness

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.5	Additional calculations on the estimated size of the study population and anticipated study precision for various outcomes was included.	Addressing comment 24 in 2022 CHMP/PRAC Final Assessment Report
		9.7	Propensity score matching with ratio up to 1:5 will be considered for control of confounding.	Addressing comment 25 in 2022 CHMP/PRAC Final Assessment Report
		9.7.2	For major congenital malformations, live birth and total prevalences per the EUROCAT definition will be calculated.	Addressing comment 26 in 2022 CHMP/PRAC Final Assessment Report
		Annex 3	A checklist for complete reporting in perinatal pharmacoepidemiology research was added. This is a new annex.	For completeness

AIFA = Italian Medicines Agency; CHMP = Committee for Medicinal Products for Human Use (of the European Medicines Agency); COVID-19 = coronavirus disease 2019; CPRD = Clinical Practice Research Datalink; EUROCAT = European network of population-based registries for the epidemiological surveillance of congenital anomalies; HES = Hospital Episode Statistics; PASS = post-authorisation safety study; PASS-DUS = drug utilisation component of the PASS; PK = pharmacokinetics; PRAC = Pharmacovigilance Risk Assessment Committee (of the European Medicines Agency); SIDIAP = Information System for Research in Primary Care.

6. 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)
Protocol C4671037 V2.0 submission	29 November 2022 (pregnant population)
Registration in the EU PAS Register	14 December 2022
Progress report submission	29 November 2022
Start of data collection[a]	Quarter 4 2023[b]
Interim report 1	14 months after protocol endorsement; interim report 1 estimated for quarter 4 2024[b]
Interim report 2	26 months after protocol endorsement; interim report 2 estimated for quarter 4 2025[b]
End of data collection[a]	Quarter 4 2025[b]
Final study report	31 March 2026[b]

CHMP = Committee for Medicinal Products for Human Use (of the European Medicines Agency);
PRAC = Pharmacovigilance Risk Assessment Committee (of the European Medicines Agency).

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."[3] Simple counts are not part of this definition. End of data collection is "the date from which the analytical data set is completely available." [3]

b. Protocol endorsement is anticipated in quarter 3 2023. Deliverable dates will be updated once protocol endorsement date is known.

7. RATIONALE AND BACKGROUND

Paxlovid contains nirmatrelvir (formerly PF-07321332) and ritonavir copackaged. Nirmatrelvir is an oral protease inhibitor that blocks the activity of 3-chymotrypsin-like cysteine protease, an enzyme required for 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 in a way that allows nirmatrelvir to remain active in the body for longer periods of time and at higher concentrations. Nirmatrelvir is expected to retain activity against the Omicron variant.[4]

The safety of Paxlovid in pregnant women is not known. The post-authorisation safety study (PASS) of Paxlovid in pregnant women is a regulatory commitment to the European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). This protocol addresses the safety of Paxlovid in pregnant women. Lactation is not included in the PASS of pregnant women but is investigated in the C4671039 pharmacokinetics study; if this study demonstrates transfer into breast milk to a relevant extent, then the feasibility of studying lactation in the PASS will be assessed.

This non-interventional study is designated as a PASS and is a commitment to EMA and MHRA.

7.1. Authorisations

On 22 December 2021, the US Food and Drug Administration issued an Emergency Use Authorization for Paxlovid.[5] On 31 December 2021, the UK MHRA issued a conditional marketing authorisation (CMA) for Paxlovid in Great Britain.[6] 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.[7] The CMA was converted to full marketing authorisation on 24 February 2023.

7.2. European Union summary of product characteristics

The indication of Paxlovid in the EU is "for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19."[8] The recommended dosage is 300 mg of nirmatrelvir (two 150-mg tablets) and 100 mg ritonavir (one 100-mg tablet) taken together orally every 12 hours for 5 days. Paxlovid should be started as early as possible after the COVID-19 diagnosis and within 5 days of symptom onset. The 5-day treatment should be completed even if the patient requires hospitalisation due to COVID-19 progression after starting Paxlovid treatment.

Women of childbearing potential should avoid becoming pregnant during Paxlovid treatment and in the 7 days after completing the treatment course. Ritonavir may reduce the efficacy of combined hormonal contraceptives; patients who use them should be advised to use an effective alternative contraceptive method or an additional barrier contraception method during treatment and until the following menstrual cycle.

Regarding use in pregnancy, the summary of product characteristics (SmPC) indicates that no data exist from the use of Paxlovid in pregnant women. Lower foetal body weights were observed in rabbit tests with PF-07321332. The SmPC also indicates that Paxlovid is not recommended during pregnancy and in women of childbearing potential who do not use contraception, unless the clinical condition requires it. Regarding use in breast-feeding women, the SmPC indicates that no data are available on the use of Paxlovid in breast-feeding women and that "*it is unknown whether PF-07321332 is present in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breast-fed newborn/infant or on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment and as a precautionary measure for 7 days after completing Paxlovid."*

7.3. United Kingdom summary of product characteristics

The indication of Paxlovid in the United Kingdom **(**UK) is: "*Paxlovid is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19,"*[9] like in the EU.

The UK SmPC states that women of childbearing potential should avoid becoming pregnant during treatment (no reference to any period after treatment) and recommends advising patients who use combined hormonal contraceptives to employ alternative contraceptive methods or a barrier method during treatment and until after 1 complete menstrual cycle afterward. In the UK SmPC, the recommendation against use in pregnancy is stronger than in the EU (*"Paxlovid is not recommended during pregnancy and in women of childbearing potential not using effective contraception"*), with no consideration of the patient´s clinical condition.

Like in the EU, the UK SmPC states that *"A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Paxlovid and for 7 days after the last dose of Paxlovid."*

8. RESEARCH QUESTION AND OBJECTIVES

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 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, see Section 9.1.2), where available, or to women with COVID-19 unexposed to any study medications 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
- Gestational hypertension
- Postpartum haemorrhage
- Maternal death

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

9. RESEARCH METHODS

9.1. Study design

The study population is described in Table 1.

Table 1. Study population

Study population	General description
Women who are pregnant and have COVID-19 (and their offspring where appropriate)	The process for identifying pregnancies and pregnancy start dates is specific to each data source. Included in the study will be users of Paxlovid, users of the comparator medication molnupiravir or other comparable medications for COVID-19 (when available, see Section 9.1.2), and the unexposed pregnant individuals, all with COVID-19.

The study will have a cohort design and will make secondary use of multiple sources of data from electronic health records and/or claims data in European countries. Data sources currently selected have the ability to capture Paxlovid exposure where the target populations, study outcomes, and key covariates can be ascertained.

The feasibility component of this research programme will provide counts of the target population, separately for Paxlovid users, users of molnupiravir, users of other comparable medications (Section 9.1.2, Table 2), and the unexposed comparator group. Relevant patient characteristics will be presented for each exposure group in the target population to allow an assessment of the feasibility of comparative analyses.

Molnupiravir has been preliminarily selected as an active comparator for this study because its indication is similar and users are anticipated to be comparable to Paxlovid users in terms of COVID-19 severity at treatment start and risk for progression to severe COVID-19[10] (see additional discussion in Section 9.1.1). At the time of preparing this protocol, molnupiravir was not utilised in the populations covered by some selected data sources or its use was not captured by the data sources (eg, France and Information System for Research in Primary Care [SIDIAP] in Catalonia, Spain). Therefore, a second comparator group is included in the study: pregnant individuals with COVID-19 who had not received any study medication. Challenges are discussed in Section 9.9. Strategies to reduce confounding will be applied. Briefly, individuals will be described, and safety outcomes will be assessed in comparative analyses, if feasible. Pooling of results using meta-analytic techniques is planned. Analyses are outlined in Section 9.7, and details will be included in the statistical analysis plan (SAP).

Reports will include a progress report with a description of project start-up and subsequent activities, the evolution of the identified challenges for this study, and the list of anticipated data sources (per an ongoing feasibility assessment on Paxlovid distribution channels in various countries); 2 annual interim reports with results of the feasibility component (described previously) and preliminary outcome counts; and a final report with the results of the safety component.

A checklist to confirm that all key methods elements for perinatal pharmacoepidemiology research are addressed explicitly in this protocol is included in Annex 3.

9.1.1. Discussion of molnupiravir as an active comparator

Molnupiravir was not authorised in the EU at the time of writing this protocol. However, EMA issued advice indicating that it could be used, like Paxlovid, to treat adult patients with COVID-19 who do not need supplemental oxygen and who are at increased risk for progression to severe COVID-19.[10] Like Paxlovid, molnupiravir is to be administered within 5 days of symptom onset and taken for 5 days. Molnupiravir should not be administered in pregnancy or to individuals who can become pregnant and are not using contraception.[10] Some countries in the EU, eg, Italy, have made it available for use,[11] and the Spanish Health Agency included it among available treatment options.[12] On 23 February 2023, EMA's Committee for Medicinal Products for Human Use (CHMP) issued a negative opinion on the

marketing authorisation filing for molnupiravir for the treatment of COVID-19 in adults because "the clinical benefit of Lagevrio in the treatment of adults with COVID-19 who are not receiving supplemental oxygen and who are at increased risk of developing severe COVID-19 could not be demonstrated."[13]

Molnupiravir was approved by the MHRA in the UK in November 2021.[14] The approved indication is consistent with the language in EMA's advice described above.[15]

Because of the similar indication and mode of use, molnupiravir users are anticipated to be comparable to Paxlovid users in terms of COVID-19 severity at treatment start and risk for progression to severe COVID-19. Molnupiravir can be used in patients with hepatic or renal impairment, which can result in channelling of patients with these problems to molnupiravir and away from Paxlovid. This was confirmed in OpenSAFELY data: 0.7% of Paxlovid users had liver disease and less than 0.5% had kidney disease, while 4.9% of molnupiravir users had liver disease and 11.2% had kidney disease.[16]

9.1.2. Discussion on other drugs to treat COVID-19 as potential active comparators

Other drugs that are used to treat COVID-19 have characteristics that make them less than optimal comparators for this study. Details are presented in Table 2. Other drugs that may be approved before the final analyses start will be assessed for suitability as additional comparators.

Table 2. Other EMA-approved drugs to treat COVID-19

Drug	Indication and mode of administration	Pregnancy	Comments
Remdesivir[17]	• Adults and children with pneumonia requiring supplemental oxygen • Adults and children who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intravenous	Should not be used during pregnancy; women of childbearing potential must use effective contraception during treatment	• Second indication comparable to that of Paxlovid • Intravenous medications are expected not to be well captured in the proposed data sources (which were selected based on the known distribution of Paxlovid)
Tixagevimab/ cilgavimab[18]	• COVID-19 preexposure prophylaxis in adults and adolescents • Treatment of adults and adolescents with COVID-19 who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intramuscular[18] or intravenous[19]	Should be used in pregnant women only if the potential benefit to the mother justifies the potential foetal risk	• Second indication comparable to that of Paxlovid • If use of this product were captured for its treatment indication, it could be included among potential comparators
Anakinra[20]	• Rheumatoid arthritis, periodic fever syndromes, familial Mediterranean fever, and other conditions • COVID-19 treatment in adults with pneumonia requiring supplemental oxygen who are at risk for progressing to severe respiratory failure determined by plasma levels ≥ 6 ng/mL of soluble urokinase plasminogen activator receptor • Subcutaneous injection	Avoid the use during pregnancy and in woman of childbearing potential not using contraception	The multiple indications and the COVID-19 indication for patients who have a more severe COVID-19 than those anticipated to receive Paxlovid, and the fact that the COVID-19 use might be in hospitalised patients, make this product not suitable as a comparator drug
Regdanvimab[21]	• Treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intravenous infusion	Should be used in pregnant women only if the potential benefit to the mother justifies the potential foetal risk	Intravenous medications are expected to be not well captured in the proposed data sources

Table 2. Other EMA-approved drugs to treat COVID-19

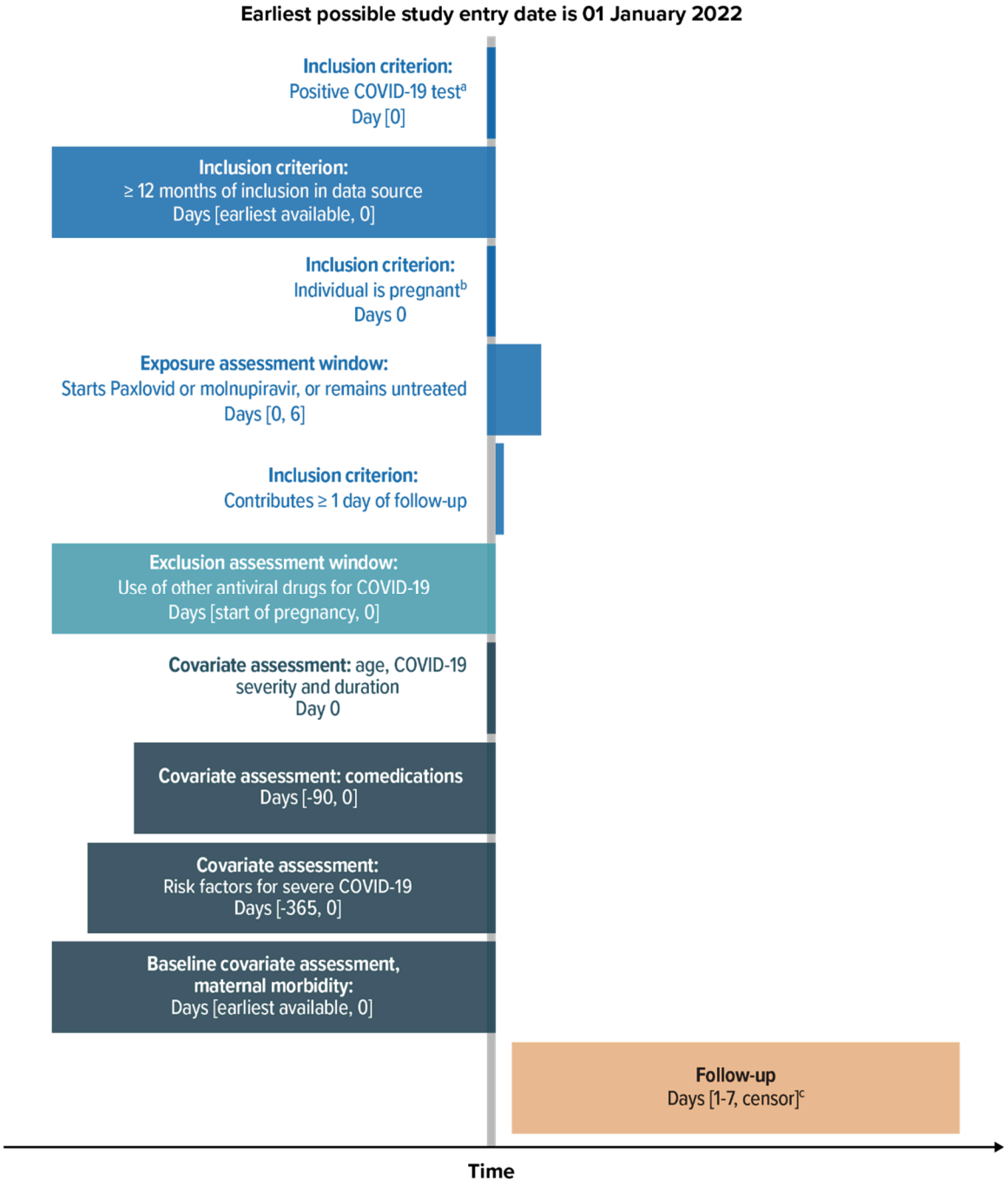
Drug	Indication and mode of administration	Pregnancy	Comments
Tocilizumab[22]	• Rheumatoid arthritis, juvenile idiopathic polyarthritis, and other conditions • Treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation • Intravenous infusion	Should not be used in pregnancy unless necessary	The multiple indications and the fact that the COVID-19 use might be in hospitalised patients make this product not suitable as a comparator drug
Casirivimab / imdevimab[23]	• COVID-19 postexposure prophylaxis • Treatment of COVID-19 in adults and adolescents who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intravenous infusion or subcutaneous injection	Use only if the potential benefit justifies the potential risk for the mother and the foetus	• Second indication comparable to that of Paxlovid • If use of this product were captured for its treatment indication, it could be included among potential comparators
Sotrovimab[24]	• Treatment of adults and adolescents with COVID-19 who do not require oxygen supplementation and are at increased risk for progression to severe COVID-19 • Intravenous infusion	Should be used only if the expected benefit to the mother justifies the potential foetal risk	Intravenous medications are expected to be not well captured in the proposed data sources

Source of drug list: EMA, COVID-19 treatments. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/covid-19-medicines. Accessed 12 June 2023

9.2. Setting

Figure 1 provides an overview of the data elements that will be ascertained for eligibility and the timing of ascertainment. Additional details are provided in the following sections.

Figure 1. Overview of the timing for covariate ascertainment



a. Including positive test, documented diagnosis or documented entry in a COVID-19 registry, reflecting a COVID-19 diagnosis.
b. Each woman needs to be pregnant at day 0 for inclusion; for pregnancy outcomes that require information on end of pregnancy, only pregnancies with known outcome will be included.
c. For pregnant women, follow-up will end at the earliest of 6 months after end of pregnancy, death, disenrollment or migration, end of data availability in the data source, or treatment group crossover. In addition, follow-up for each outcome in women will end at the occurrence of the given outcome. Follow-up of the offspring to assess offspring outcomes will continue through the earliest of death, disenrollment or migration, end of data availability in the data source, or 1 year of age. In addition, follow-up for each infant outcome will end at the occurrence of the given outcome.

Note: Figure based on Schneeweiss et al[25]

9.2.1. Inclusion criteria, exclusion criteria, and follow-up

Inclusion and exclusion criteria

This target population will comprise pregnant individuals with documented COVID-19 who had at least 12 months of inclusion in the data source population and were users of Paxlovid or comparator medication molnupiravir or remained unexposed. At least 1 day of follow-up will be required for inclusion in the study. Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Woman is pregnant (no age restriction) at the time of COVID-19 diagnosis
- Woman has documented COVID-19
- Woman has at least 12 months of inclusion in the data source at the time of starting a study medication or becoming eligible
- Woman started treatment with Paxlovid or comparator medication within 7 days of the COVID-19 diagnosis or did not start those treatments during those 7 days
- Woman contributed at least 1 day of follow-up. Note: Women who test positive at screening at hospital admission for delivery will not be included in the study population, as they will not contribute to follow-up.

Exclusion criterion

Patients meeting any of the following criteria will not be included in the study:

- Received Paxlovid, comparator medication, or other medications listed in Table 2 earlier in the pregnancy

Pregnancies with foetuses with major or minor malformations or chromosomal abnormalities, and multifoetal pregnancies will be included in the study. Women can contribute more than one pregnancy to the study.

After the eligibility criteria are applied, the target population will include pregnant individuals starting Paxlovid or molnupiravir or other comparator medication during the study period and pregnant individuals unexposed to any study medication.

Time 0 will be the day on which individuals meet all eligibility criteria (Figure 1); they will have 7 days after COVID-19 diagnosis to start treatment with Paxlovid or molnupiravir or other comparator medication (this is often described as a grace period; ie, days [0, 6] inclusive of both bounds). Unexposed individuals will be matched with individuals starting Paxlovid by time since COVID-19 diagnosis (days) and calendar time (within ± 1 week; ie, days [−6, 6] inclusive of both bounds). Matching at this stage intends to (1) increase comparability of treatment groups regarding time since start of disease, including potential changes in severity over time, (2) balance immortal time by imposing the observed immortal time before treatment among the treated onto the untreated patients,[26] and (3) ensure that treated and untreated patients are contemporary (calendar time is a proxy for prevalence of circulating variants, preferred therapeutic approaches, etc). Paxlovid and molnupiravir users (or users of another comparator medication) will be matched on calendar time. If insufficient matches are found because of the restriction imposed by the period of 1 week around the COVID-19 diagnosis for matching, the period will be extended. This change, if applicable, will be described in the final report together with sensitivity analyses of the impact of extending the period.

Follow-up

Follow-up of pregnant women will start between day 1 and day 7, depending on which day matching of exposed and unexposed occurs (Figure 1). Follow-up will end at the earliest of 6 months after end of pregnancy, death, disenrollment or migration, end of data availability in the data source, or treatment group crossover. *Treatment group crossover* is defined in this study as the situation in which individuals who entered the study as unexposed start treatment with Paxlovid or molnupiravir (or comparable medication, see Section 9.1.2), when users of molnupiravir (or comparable medication) start treatment with Paxlovid, or when Paxlovid users start treatment with molnupiravir (or comparable medication). In addition, follow-up for each outcome will end at the occurrence of the given outcome. The 6 months after the end of pregnancy will be used to assess pregnancy outcomes.

Follow-up of the offspring to assess offspring outcomes will continue through the earliest of death, disenrollment or migration, end of data availability in the data source, or 1 year of age. In addition, follow-up for each infant outcome will end at the occurrence of the given outcome.

Starting treatment with drugs to treat COVID-19 that are not Paxlovid or comparator drug molnupiravir or comparable medications (as available, see Section 9.1.2) will not result in censoring.

Pregnancy identification

The process of identifying pregnancies and pregnancy start dates is specific to each data source. In some data sources (eg, SNDS), pregnancies are identified only when they end because the records available for research include only information that is generated at that time (eg, via a birth registry). In other data sources (eg, Clinical Practice Research Datalink [CPRD]), pregnancies can be identified using both records for pregnancy outcomes and records for ongoing pregnancies, such as codes for diagnostic tests and services that are indicated only during pregnancy.[27] The latter is the preferred approach for this study and will be used to the extent possible. When using records for ongoing pregnancies, pregnancies with unknown outcome will be identified, including pregnancies whose expected date of delivery is after the last available date in the data cut (likely ongoing pregnancies) and pregnancies for which delivery has occurred but the outcome is not documented in the data source. Reasons why pregnancy outcomes may not be documented after the delivery date among individuals who continue to be present in the data source include missing data (eg, delivery occurred in a hospital and is not or is not yet documented in primary care records [if using primary care data]) or because the pregnancy ended in an elective termination or spontaneous abortion and is not documented in the data source.[27,28] In some data sources (such as CPRD), one can assume that a large proportion of the pregnancies that started well before the end of data availability and have an unknown outcome are spontaneous abortions.[29] This will be addressed in a sensitivity analysis on the outcome definitions (Section 9.7).

Pregnancy periods

For the purpose of this study, start of pregnancy will be the first day of the last menstrual period (LMP). The first trimester will include time from LMP through day 97 (97 days is 13 weeks + 6 days), inclusive of both bounds; the second trimester will go from day 98 (14 weeks + 0 days) through day 195 (27 weeks + 6 days), inclusive of both bounds; and the third trimester will go from day 196 (28 weeks + 0 days) through delivery.

Pregnancy identification and mother-infant linkage in SNDS (France)

Algorithms are available in SNDS to identify pregnancies and to link mothers to infants.[30,31] Following the publication by Blotière et al (31), the pregnancy identification algorithm identifies pregnancies based on discharge diagnoses and medical procedures associated with pregnancy outcomes (live births, stillbirths, elective abortions, therapeutic abortions, spontaneous abortions, and ectopic pregnancies) recorded in the French national insurance database (DCIR) or the French hospital discharge database (PMSI). In the Blotière et al (31) study, when records indicated different outcome dates within a certain timeframe, the later record was retained (ie, 28 weeks for births, 6 weeks for terminations). Records with unknown women identifiers were removed (some records cannot be linked to other records in the data source), as were duplicate records. Then, pregnancy termination codes that appeared during a pregnancy episode ending in a delivery were removed; pregnancy terminations in the first 10 weeks after a delivery were also removed. Finally, pregnancy outcomes were categorised into live births, stillbirths, spontaneous and other types of abortions, and abnormal products

of conception. Information on time since LMP, gestational age, the date of the first prenatal medical examination, dates of the ultrasounds, and date of the pregnancy outcome were used to estimate the dates of the beginning and end of pregnancy.

Linkage between maternal and neonatal data for births occurring at or later than 22 weeks of gestation is possible within the PMSI using a common identifier that is recorded for both the delivery stay and the birth stay. Follow-up of infants after birth is possible through linkage of the infant to the social security numbers of the parents.

Pregnancy identification and mother-infant linkage in SIDIAP (Spain)

An algorithm to identify pregnancies has been previously used within SIDIAP.[32-35] The algorithm uses diagnosis codes recorded in primary healthcare records during pregnancy and information recorded in the sexual and reproductive healthcare registries, including LMP, gestational week, expected date of delivery, actual date of delivery or termination, and pregnancy outcomes. The algorithm has been described in a conference abstract.[35] First, early pregnancy records are identified, including LMP records, positive pregnancy test, and records indicating gestational week. Then, duration of pregnancy is estimated based on LMP, episode end date, and end-of-pregnancy codes; pregnancies with unlikely duration are removed. Last, the pregnancy outcome is identified from *International Classification of Diseases, Tenth Revision* (ICD-10) codes; duplicates are discarded. Approximately 50% to 60% of pregnant women in Catalonia are attended in the sexual and reproductive healthcare centres that contribute data to SIDIAP. Approximately 70% of infant records can be linked to maternal records and used for research.

Pregnancy identification and mother-infant linkage in CPRD Aurum (UK)

CPRD has developed algorithms for pregnancy identification and mother-infant linkage. The process was first implemented in the General Practitioner Online Database (CPRD GOLD) and has now been implemented in CPRD Aurum.[36-38] The pregnancy identification algorithm uses SNOMED CT (Systematized Nomenclature of Medicine—Clinical Terms) codes, Read codes, data source–specific identifiers for antenatal care, pregnancy outcomes (including delivery and pregnancy loss), and postnatal care to identify patients who have had a pregnancy. The pregnancy identification algorithm first classifies pregnancy outcome records into distinct pregnancy episodes (combining multiple records related to the same pregnancy). The start of each of pregnancy is then estimated based on information on gestational age, estimated date of delivery, or estimated LMP (if available) or is imputed based on a default gestational age (depending on the outcome type). Next, additional pregnancies without an outcome recorded are identified using antenatal records. For pregnancies without a recorded outcome, pregnancy end is estimated using the latest record during the pregnancy, and pregnancy start is estimated based on information on gestational age, estimated date of delivery, or estimated date of conception or LMP (if available) or by subtracting 4 weeks from the earliest antenatal record during the pregnancy.

Mother-infant linkage within the CPRD is conducted using a probabilistic algorithm that uses data recorded in the primary care medical record.[39,40] Mother-infant pairs are linked using

family number or household identifier (which identifies individuals within the same family), maternity information from the mother's primary care record (used to identify deliveries and delivery dates), and the birth month/year of newly registered infants. A data cleaning process removes matches that are likely incorrect.

9.2.2. Study period

The study period will start on 01 January 2022 (in alignment with regulatory authorisation in Europe) and end as late as possible, based on the calendar period coverage at the time of the last data extraction. Please see Table 3, which shows the anticipated dates during which data will be observed for each study report. The latest available data at the time of the data extraction will be used.

Table 3. Dates for start of study period and end of data availability for each study report in each data source

Data source	Start of study period	Anticipated end of data availability		
	Date of authorisation: 01 January 2022	Interim report 1	Interim report 2	Final report
CPRD Aurum[a]	01 January 2022	Q3 2023	Q3 2024	Q3 2024
SIDIAP	01 January 2022	30 June 2023	30 June 2024	30 June 2024
SNDS	01 January 2022	31 December 2022	31 December 2023	31 December 2023

HES = Hospital Episode Statistics; Q*n* yyyy = quarter of the calendar year.
Note: Interim report 1 has an anticipated data cut in Q4 2023; interim report 2 and final report in Q4 2024
a. In analyses using CPRD Aurum, HES linkage is required to ascertain exploratory outcomes. As of June 2023, the latest release of HES data covers the period April 1997 to March 2021. This lag time of coverage may delay the start of the analysis or limit the availability of data for analysis.

9.3. Variables

9.3.1. Exposure

The main exposure of interest will be Paxlovid, which will be ascertained from prescription and pharmacy information reflecting prescriptions issued (eg, CPRD) or dispensed (eg, French Administrative Healthcare Database [SNDS]) or from other data sources (eg, a central Paxlovid distribution registry if Paxlovid distribution is documented in this manner). See Section 9.4 for details.

The periods of pregnancy during which exposure will be ascertained (often described as exposure windows) are specific to each outcome, reflecting the period at risk for each outcome; they are listed in Section 9.3.2.

9.3.2. Outcomes

The outcomes will be the prespecified outcomes listed in Table 4 plus the exploratory outcomes (see Section 9.3.2.1). They will be ascertained using coded diagnoses, procedures,

medical product prescriptions or dispensings, and information collected in other data banks in the selected data sources. Codes for pregnancy and prespecified maternal outcomes will be sought during maternal follow-up and within the outcome-specific at-risk periods noted in Table 5, taking into consideration that availability of codes might be delayed relative to the occurrence of the outcome. Codes for exploratory maternal outcomes will be sought for a fixed period after start of follow-up, as described in Section 9.3.2.1. Major congenital malformations will be identified up to infant age 1 year. Validated algorithms for outcome identification, if available, will be used. To further explore validity and adjust algorithms as needed for selected study outcomes, a random sample of patient profiles, ie, the electronic information ordered chronologically, could be reviewed.

A more detailed description of the outcomes and the subsets of pregnancies among which each outcome will be ascertained is presented in Table 5.

In this study, the first occurrence of each outcome during follow-up will be considered a study outcome, and outcome occurrence will determine end of follow-up for that outcome, as described in Section 9.2.1.

Table 4. Study outcomes in the target population

Study population	Study outcomes
Individuals who are pregnant (and their offspring, as appropriate)	Pregnancy outcomes • Spontaneous abortion • Elective termination • Stillbirth • Preterm delivery (all, iatrogenic, and spontaneous) Offspring outcomes • Major congenital malformations • Intrauterine growth retardation/small for gestational age Maternal outcomes • Gestational diabetes • Gestational hypertension • Postpartum haemorrhage • Maternal death

Table 5. Identification of pregnancy-related outcomes and outcome-specific exposure windows

Outcome	Description of outcome, outcome-specific at-risk window, and outcome-specific exposure window	Pregnancies among which the outcome will be ascertained	Source records
Spontaneous abortions	Foetal loss before 20 completed weeks of gestation. The period during which this outcome can occur is before 20 completed weeks; individuals will be considered exposed if drug use occurs during this period. Sensitivity analysis: In data sources where we can assume that pregnancies with unknown outcome are neither live births nor stillbirths, in a sensitivity analysis, all pregnancies with unknown outcome and an estimated delivery date of ≥ 3 months before data extraction among women included in the data source at the time of data extraction will be considered a spontaneous abortion.	All pregnancies with known outcome; for sensitivity analysis, all pregnancies	Maternal records
Elective terminations	Nonspontaneous termination of pregnancy, including ectopic pregnancies, termination due to foetal anomalies or any other cause. The at-risk period for this outcome is the time during which these can occur, which varies by jurisdiction. Because it is expected that elective terminations will occur in early pregnancy, the at-risk period will be before 20 completed weeks; individuals will be considered exposed if drug use occurs during this period.	All pregnancies with known outcome	Maternal records
Stillbirths	Foetal loss on or after 20 completed weeks of gestation. The period during which this outcome can occur is on or after 20 completed weeks; individuals will be considered exposed if drug use occurs any time during pregnancy.	All pregnancies with known outcome Although pregnancies that end earlier than 20 completed weeks are not at risk for this outcome, the outcome will be ascertained among all pregnancies with known outcome for comparability with other studies.	Maternal records
Preterm delivery	Live birth before 37 completed weeks. The period during which this outcome can occur is the time during which a delivery can result in a live birth, but before 37 completed weeks. Individuals will be considered exposed if drug use occurs before 37 completed weeks.	Pregnancies ending with live birth	Maternal records

Table 5. Identification of pregnancy-related outcomes and outcome-specific exposure windows

Outcome	Description of outcome, outcome-specific at-risk window, and outcome-specific exposure window	Pregnancies among which the outcome will be ascertained	Source records
Preterm delivery: iatrogenic	This is the subset of preterm deliveries in which the delivery is initiated for maternal or foetal conditions.	Pregnancies ending with live birth	Maternal records
Preterm delivery: spontaneous	These are the remaining preterm deliveries.	Pregnancies ending with live birth	Maternal records
Major congenital malformations	Structural changes with significant medical, social, or cosmetic consequences for the affected individual that typically require medical intervention.[41] The EUROCAT definitions will be followed.[42] Minor (per the EUROCAT classification[41]) and unspecified anomalies; chromosomal abnormalities, genetic syndromes or sequences; or endocrine, metabolic, immunologic, or haematologic anomalies will not be included in this definition. Organogenesis occurs during the first trimester; individuals will be considered exposed if drug use occurs before or at completed week 13 from the LMP.	All pregnancies resulting in a live birth Congenital anomalies can occur in pregnancies that end in other pregnancy outcomes, but no information is typically available regarding the presence of congenital anomalies in stillbirths or spontaneous abortions.	Maternal and infant records (infant records until 1 year of age)
Intrauterine growth retardation/ small for gestational age	Foetal or birth weight below the 10th percentile for gestational age and sex Individuals will be considered exposed if drug use occurs any time during pregnancy (and before the first code indicating the presence of the outcome).	Pregnancies ending with live birth	Maternal and possibly infant records (depending on the data source)
Gestational diabetes	Diabetes that is first diagnosed during pregnancy. This outcome can occur typically after 24 completed weeks. Individuals will be considered exposed if drug use occurs any time during pregnancy (and before the first code indicating the presence of the outcome).	All pregnancies reaching the gestational age at which diagnosis is typical (eg, 24 completed weeks)	Maternal records
Gestational hypertension	Hypertension that is first diagnosed during pregnancy, with or without proteinuria or seizures. This outcome is typically diagnosed after 20 completed weeks. Individuals will be considered exposed if drug use occurs any time during pregnancy (and before the first code indicating the presence of the outcome).	All pregnancies reaching the gestational age at which diagnosis is typical (eg, 20 completed weeks)	Maternal records

Table 5. Identification of pregnancy-related outcomes and outcome-specific exposure windows

Outcome	Description of outcome, outcome-specific at-risk window, and outcome-specific exposure window	Pregnancies among which the outcome will be ascertained	Source records
Postpartum haemorrhage	Abundant haemorrhage after delivery; will be ascertained from delivery to 6 days after delivery. Individuals will be considered exposed if drug use occurs any time during pregnancy.	All pregnancies with known outcome	Maternal records
Maternal death	Death during pregnancy Individuals will be considered exposed if drug use occurs any time during pregnancy.	All pregnancies	Maternal records

EUROCAT = European network of population-based registries for the epidemiological surveillance of congenital anomalies; LMP = first day of the last menstrual period.

9.3.2.1. Exploratory outcomes

A group of empirically identified outcomes (hereafter, "exploratory outcomes") will also be assessed. These outcomes will be identified from diagnosis codes from outpatient diagnoses (as available in each data source), hospitalisation discharge diagnoses and emergency department diagnoses documented in the participating data sources among eligible Paxlovid-exposed individuals. These will be events that are recorded up to 1 month after the Paxlovid dispensing date in individuals who are eligible for the study. Events that are included among the prespecified outcomes will be removed from the preliminary list. The resulting list will be reviewed by the research team to determine whether any item does not merit assessment. The exploratory outcomes will be analysed within the planned cohort design along with the other study outcomes. Events selected from data sources using the same coding system will be included in all data sources using the same coding system if they are found in more than 1 data source. Events identified using SNOMED CT will be assessed in CPRD Aurum only, and the same approach will be followed in other data sources using unique coding systems. Analyses will be conducted only if a minimum number of cases are observed in the study population, as specified for the prespecified outcomes. Results of analyses on exploratory outcomes will not be meta-analysed.

9.3.3. Other variables

In addition, the following study variables will be included:

- Demographics

- Conditions that will be ascertained to identify increased risk for progression to severe COVID-19:[43] asthma, cancer, cerebrovascular disease, chronic kidney disease, chronic lung diseases (only bronchiectasis, chronic obstructive pulmonary disease [COPD], interstitial lung disease, pulmonary embolism, pulmonary hypertension), chronic liver diseases (only cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease,

autoimmune hepatitis), cystic fibrosis, type-1 diabetes, type-2 diabetes, disabilities (see list in Annex 4), heart conditions (including heart failure, coronary artery disease and cardiomyopathies), human immunodeficiency virus (HIV) infection, mental health conditions (only mood disorders [including depression] and schizophrenia spectrum disorders), neurologic conditions (only dementia), obesity (body mass index ≥ 30 kg/m^2), primary immunodeficiencies, smoking (current or former), solid organ or blood stem cell transplantation, tuberculosis, use of immunosuppressive medications including corticosteroids.
Conditions associated with suggestive higher risk will also be ascertained:[43] overweight (body mass index ≥ 25 kg/m^2 but < 30 kg/m^2), sickle cell disease and substance use disorders.
Increased risk for progression to severe COVID-19 will be ascertained in the 12 months before time 0.
From the noted reference,[43] not incorporated will be physical inactivity (because it is not ascertainable in the selected data sources) and pregnancy (because all patients will be pregnant). Codes to identify these variables are presented in Annex 4.

For the purpose of this PASS, individuals at increased risk for progression to severe COVID-19 will be individuals with COVID-19 diagnosis or registration in a COVID-19 registry and at least 1 risk factor listed in the previous paragraph (acknowledging that prescribing physicians may not base their assessment on exactly these variables).

- Characteristics to identify maternal morbidity: preeclampsia/eclampsia, chronic congestive heart failure, congenital heart disease, pulmonary hypertension, chronic ischaemic heart disease, sickle cell disease, multifoetal gestation, cardiac valvular disease, systemic lupus erythematosus, HIV, drug abuse, placenta previa, chronic renal disease, pre-existing hypertension, previous C-section, gestational hypertension, alcohol abuse, asthma, pre-existing diabetes mellitus.[44]

- Comedications, including medications listed as contraindicated or with potentially significant interactions with Paxlovid in the EU SmPC,[8] Section 4.3 and Table 1, or the UK SmPC,[9] Table 1 and Table 2. Use of these medications will be quantified in the 3 months before Paxlovid use to provide information on the number of patients who may be at risk for simultaneous use of Paxlovid and these medications; please see caveats in Section 9.9.

- COVID-19 diagnoses, days since current infection, COVID-19 severity at start of treatment.

- COVID-19 vaccination status, as available.

Baseline information will be obtained from records before drug initiation or Paxlovid eligibility.

9.4. Data sources

As of 20 March 2023, the MAH confirmed that Paxlovid has been supplied to Denmark, France, Germany, Italy, the Netherlands, Norway, Slovenia, Spain, 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 is that prescribed/dispensed Paxlovid should be captured in existing electronic population data sources in Denmark, France, Spain, and the UK. Currently, the proposed data sources are SNDS (France), SIDIAP (Catalonia, Spain), and CPRD Aurum (UK). Exposure counts are presented in Table 6.

Table 6. Study feasibility: Paxlovid in European data sources/registries

Country	Distribution by MAH or capture in data sources
Denmark	400 packages sold in 2022 as of 04 April 2023
France	Medic'AM: 12,634 dispensed boxes in February-June 2022 EPI-PHARE report: 50,818 individuals received Paxlovid between 04 February and 27 October 2022[45]
Italy	AIFA Registry: 120,156 treatments as of 22 March 2023[46]
Spain	SIDIAP: 1323 Paxlovid prescriptions to 1233 individuals from 07 April to 31 December 2022
United Kingdom	CPRD Aurum: 500 prescriptions as of 13 January 2023 OpenSAFELY: 14,350 individuals as of 19 January 2023[16]

AIFA = Italian Medicines Agency; CPRD = Clinical Practice Research Datalink (United Kingdom); MAH = marketing authorisation holder; SIDIAP = Information System for Research in Primary Care (Spain).

In France, Paxlovid received early access authorisation on 20 January 2022 and has been made available for prescription since 03 February 2022[47] in outpatient settings (a specific procedure needs to be completed by general practitioners and community pharmacists) and inpatient settings (including emergency care). To date, only dispensings from the outpatient setting (community pharmacies) are captured in SNDS; for inpatients and emergency room visits, the drug is directly provided to the hospital by health authorities, and patient exposure is not captured. In July 2022, access to Paxlovid was extended to the following groups of patients: patients who are immunocompromised (regardless of age or vaccination status), patients at high risk of severe disease due to comorbidities when they have an incomplete vaccination status (ie, when they are unvaccinated at any age, have not received a booster at any age, or have not received a second booster if aged > 60 years), and patients aged > 60 years with or without comorbidities when their vaccination schedule is incomplete (absence of second booster, in particular).[48] Molnupiravir is not available in France.

In Spain, dispensing of Paxlovid is taking place in community pharmacies through validated prescriptions; it is expected that all Paxlovid prescriptions recorded in SIDIAP will be captured. The Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios [AEMPS]) informs that novel antivirals are distributed through the normal channels.[12] For Paxlovid (authorised), due to the interactions and special

warnings for use, a special validation is required. Each autonomous region (eg, Catalonia) establishes its own validation, and the validation process should be shorter than 24 hours. Risk factors that health professionals should consider when deciding to prescribe Paxlovid, as well as considerations related to drug-drug interactions, were put forward by the Catalonian government.[49] Molnupiravir is not approved, but in case its use is considered, access will be on a case-by-case basis through an application for special use of medications. For patients eligible for antivirals, the AEMPS treatment graph indicates that they can be treated with Paxlovid or remdesivir or, alternatively, with molnupiravir. SIDIAP will contribute data (from Catalonia) to this study. BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària), which collects longitudinal medical records from various regions in Spain and is administered by AEMPS, is not available for studies funded by pharmaceutical companies.

The MAH will share additional information about Paxlovid supply and forecast for other European countries as it becomes available, and the research team will evaluate whether this allows capture of Paxlovid in additional electronic data sources in these countries.

- In Denmark, Paxlovid has been supplied. Distribution started in 2022, and data for 2022 indicate that 400 courses were sold in 2022 (Table 6).
- The Italian Medicines Agency (AIFA) established a national registry for Paxlovid and other antivirals for COVID-19. At this time, and while direct Italian government funding rather than funding through individual region occurs, capture of Paxlovid dispensing/prescriptions in the established electronic data sources that are commonly used for PASSs in Italy (eg, regional or local health unit data sources) is expected to be minimal. Initially, Paxlovid could only be prescribed and dispensed in selected centres in each Italian region (modality 1). As of April 2022, Paxlovid can be dispensed in pharmacies with a prescription also by general practitioners (modality 2). The counts, but not the clinical characteristics of the patients receiving Paxlovid under modality 2 are captured in the AIFA registry (D Striano, Pfizer Italy, email communication, 13 May 2022).
- As long as the German government continues to cover Paxlovid payments, it is expected that Paxlovid prescriptions will not appear in the German Statutory Health Insurance data sources, which is based on prescriptions reimbursed by the insurers.
- The Netherlands had a supply of about 15,000 packs, leading to a small study size.
- Norway had a supply of about 25,000 packs, leading to a small study size.
- Slovenia had a supply of about 19,000 packs, leading to a small study size.
- In Sweden, Paxlovid will be prescribed and distributed in hospitals, and therefore will not be captured in the Swedish registers typically used for pharmacoepidemiology research.

- The UK OpenSAFELY data source is proposed for exploration as a supplementary data source for the PASS.

9.4.1. France: French Administrative Healthcare Database (SNDS)

SNDS contains individual-level pseudonymised information on all outpatient reimbursed claims from all main French healthcare insurance schemes linked to the national hospital discharge summaries database and the national death register. It currently covers the overall French population—about 67 million individuals—from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires, capturing data from 2011.[50] Medical history data goes back to 2006 for 86% of the population. The following information is available for each individual:

- Demographics and general information: sex, date of birth, area/region of residence. Socioeconomic status can be derived from the presence of CMUc (*Couverture médicale universelle complémentaire*), which indicates full insurance coverage due to low-income status and deprivation index and a composite indicator that gives information on patient socioeconomic status based on its geographic residence.

- Registration for chronic conditions and date of first diagnosis of the condition: These conditions are itemised in a list of 3448 ICD-10 codes (Affections de Longue Durée [ALD]). Registration with an ALD is obtained at the request of a patient's practitioner and is validated by the health insurance system physician. Registration of chronic conditions may not be complete because patients are already registered for a related disease, or because the treatment is cheap, or because of stigma concerns.

- Occupational accidents and diseases.

- Medication dispensed in primary or secondary outpatient pharmacies, recorded as dispensed preparation packs, with dates (prescription and dispensing): Drug information includes ATC (Anatomical Therapeutic Chemical) code, CIP (Presentation Identifier Code) code (French pharmacy coding system), and EPhMRA (European Pharmaceutical Market Research Association) code; description of packs in number of tablets and strength; the number of packs dispensed; date of prescription and nature of prescriber, date of dispensing, and the dispensing pharmacy (anonymised). Information on underlying medical indication is not available.

- Medication dispensed in-hospital, recorded as dispensed units, with dates: available only for drugs prescribed out of the cost-coding system, mainly expensive drugs (eg, targeted cancer therapies and monoclonal antibodies). Drug information includes ATC code, UCD (common dispensing unit) code, and EPhMRA code. Information on underlying medical indication is not available.

- Date and nature of physician and paramedical (nurses, physiotherapist) encounters with procedures; outpatient diagnoses are not recorded.

- Date and nature of all laboratory test requests, without results.

- Hospital discharge summaries from PMSI (French national hospital discharge summaries database system): ICD-10 diagnosis codes for main and associated diagnoses for all medical, obstetric, and surgical hospitalisations, including date and duration of hospitalisation, medical procedures, diagnosis-related group, and the cost-coding system.

- Medical history data: available going back to 2006 for 86% of patients and to 2011 for all patients in the SNDS database.

- Date of death, through linkage with the national death registry, without the cause of death.[50]

- There is a well-defined algorithm to identify pregnancies and deliveries in SNDS only when they end. Mother-child linkage has been available in the SNDS since 2012, allowing identification of the newborn and follow-up within the database to conduct long-term pregnancy safety studies.[30,31]

Exposure to COVID-19 vaccines will be obtained through a linkage of the SNDS to the SI Vaccin COVID, the information system implemented by the Caisse Nationale de l'Assurance Maladie (CNAM), to enable the preparation, management, and monitoring of the COVID-19 vaccination campaign. It captures, among other things, vaccine brand and date of injection.[51]

If possible, results of all antigenic and reverse transcription polymerase chain reaction (RT-PCR) COVID-19 tests carried out in France—whether positive or negative—will be retrieved from the National Population Screening Information System (SI-DEP), a secure platform resulting from a partnership between the Ministry of Solidarity and Health, Public Assistance–Paris Hospitals. Linkage of the SI-DEP to the SNDS is currently ongoing at the national level under the supervision of CNAM.[52] While the linkage of the SI-DEP to the SNDS has been anticipated by the French law, issues related to the linkage are being addressed. The SNDS data holder is currently working on improving the linkage process, but the release date has not been communicated yet. The fact that a test has been performed is well captured by the database even in the absence of this linkage.

Outpatient diagnoses are not captured in the SNDS.

By law, it is not possible to go back to the patient to collect additional information. Most outcomes are identified with hospital diagnosis codes. For some studies, independent expert validation using reconstituted electronic health records using all information in the database, ie, assembling a chronological listing of diagnoses, procedures, and medications recorded for a patient, can be conducted.[53]

Complete and consolidated SNDS data are released in the third quarter of the following year included in each period. Access to SNDS data is strictly regulated by French law and needs approval from the committee on health data research (Comité éthique et scientifique pour les

recherches, les études et les évaluations dans le domaine de la santé [CESREES]) and from the French Data Protection Commission (CNIL). The process typically requires 6 to 12 months before data extraction by the CNAM database operator: 3 to 5 months are required for this regulatory process, and 3 to 6 months to receive the extracted data. Data extraction requests at several timepoints over the study period can be anticipated from the study protocol, eg, once every year until the end of the study.

9.4.2. Spain: Catalan Information System for Research in Primary Care (SIDIAP)

SIDIAP was created in 2010 by the Catalan Health Institute and the IDIAP Jordi Gol Institute (IDIAP). It includes information collected since 01 January 2006 during routine visits at 378 primary care centres that are part of the Catalan Health Institute in Catalonia (northeast Spain), which has 3414 participating general practitioners. SIDIAP has pseudoanonymised records for 5.8 million individuals (75% of the Catalan population) and is representative of the Catalan population.[54]

The SIDIAP data comprise the clinical and referral events registered by primary care health professionals (eg, general practitioners, paediatricians, gynaecologists, and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results. The SIDIAP data can also be linked to other data sources, such as the hospital discharge database, on a project-by-project basis. Health professionals gather this information using ICD-10 codes, ATC codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, and blood and urine test results. SIDIAP includes all routine childhood and adult immunisations, including the antigen and the number of administered doses. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. The SIDIAP database is updated every 6 months.[54]

Recent reports have shown SIDIAP data to be useful for epidemiological research. SIDIAP is listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database (https://www.encepp.eu/encepp/viewResource.htm?id=104903).

Information on pregnancy and pregnancy outcomes recorded by gynaecologists and midwives is available from the ASSIR registers (sexual and reproductive healthcare registers). Approximately 50% to 60% of pregnant women in Catalonia are attended in the sexual and reproductive healthcare centres, where pregnancy-related information, including dates of pregnancy start and end, pregnancy outcomes, and other information, is captured. Approximately 70% of infant records can be linked to maternal records and used for research.

To facilitate research on COVID-19, SIDIAP has included within the data available for research information on COVID-19 tests conducted within the Catalan public primary care

system, including test type (eg, antigen test), date, and result.[55] No additional linkages are needed.

Study applications need to be approved by the SIDIAP Scientific Committee and the IDIAP Ethics Committee.

9.4.3. United Kingdom: CPRD Aurum and Hospital Episode Statistics

The CPRD in the UK collates the pseudonymised computerised medical records of general practitioners, who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. Accordingly, general practitioners are responsible for primary healthcare and specialist referrals, and they also document information about specialist referrals and hospitalisations. General practitioners act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care, as necessary. Secondary care teams also provide information to general practitioners about their patients, including key diagnoses. The data recorded in CPRD include demographic information, prescription details, clinical events, outpatient laboratory test results, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. Data validation with original records (eg, specialist letters) is also available, although response rates since the pandemic period have been extremely low. CPRD has 2 primary care components: CPRD GOLD (practices that use Vision software) and CPRD Aurum (practices that use EMIS software). CPRD Aurum is expanding and can be linked to several additional data banks; the MAH will use it for the present PASS.

The CPRD Aurum data set comprises only English practices.[56] Most of the data are coded using SNOMED CT codes. As of November 2022, CPRD Aurum contained data on 15,713,221 current acceptable patients (ie, active patients available for research) and 46,761,868 patients, including deceased and transferred-out patients.[56] Data include demographics, all general practitioner/healthcare professional consultations (eg, phone calls, letters, emails, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments (including all prescriptions), all data referrals to other care providers, hospital discharge summary (date and codes), hospital clinic summary, preventive treatment and immunisations, and death (date and cause). The Hospital Episode Statistics (HES) database contains details of all admissions to National Health Service (NHS) hospitals in England (Accident & Emergency, Admitted Patient Care, Outpatients). CPRD Aurum records are linked to HES using a combination of the patient's NHS number, sex, and date of birth. Additional linked data sets include Death Registration data from the Office for National Statistics (ONS), which includes information on the official date and causes of death (using ICD codes), Mother-Baby Link, and an algorithm-based Pregnancy Register. The Mother-Baby Link and the Pregnancy Register, initially implemented in CPRD GOLD, have also been implemented in CPRD Aurum.[38,40]

COVID-19 tests results are available in CPRD Aurum without additional linkages, including results from PCR (polymerase chain reaction) tests.[57] Other COVID-19–related data sets could be explored.

Study applications need to be submitted to and approved by the CPRD Research Data Governance. RTI Health Solutions also needs to complete an institutional review board (IRB) application for non-human research status determination.

9.4.4. Additional exploration of data sources

9.4.4.1. Italy: AIFA National Italian Patient Registry (exploratory)

Paxlovid users in Italy are being registered in a national registry mandated by AIFA. More details about the AIFA registry for patients receiving COVID-19 oral antiviral agents and its data collection form is provided in Annex 5. The form covers information to be collected at enrolment and 1 section that needs to be completed via telephone follow-up 1 month later. The baseline form collects demographic and comorbidity information appropriate to identify the patients of interest to describe drug utilisation, including specific questions on pregnancy and renal and hepatic impairment. AIFA does not collect data to support the safety analyses that are described in this protocol; at this time, individual-level data is not available to external researchers.

AIFA issues periodic reports on use of COVID-19 oral antiviral treatments in aggregated form (ie, no individual-level data are available); these reports are publicly available.[46,57] As of 22 March 2023 (report 31), 120,156 Paxlovid treatment courses had been administered in Italy, as well as 64,231 molnupiravir treatment courses. Therefore, the information in this patient registry is of great interest to inform the Paxlovid PASS, although the aggregated nature of the released data and the data access avenues may preclude incorporating it into the PASS.

Typically, after a new AIFA patient registry becomes available to prescribers, the corresponding MAH has access to a weekly report with the number of new prescriptions and of closed treatments. According to an agreement (pending to finalise) between the Italian pharmaceutical companies' association and AIFA, the new reports available to companies will have more information, always in aggregated form. In the context of regulatory activities such as a PASS or post-authorisation efficacy study, some limited flexibility for the customisation of the reports exits. However, in the context of an emergency use approval, the current situation, only the public reports are available to the Paxlovid MAH.

We continue to monitor the situation via communications with the Paxlovid MAH affiliate in Italy, who has established communications with the AIFA registry contacts who have confirmed that at this stage, the AIFA registry cannot participate in the Paxlovid PASS since the new agreement between the Italian pharmaceutical association and AIFA is estimated to be executed toward the end of 2022. The plan is to reach out to AIFA early in 2023 to explore whether at that time the information collected in the patient registry could be leveraged for the Paxlovid PASS. In the meantime, we will use the information available in publicly available reports.

Linkages of the Italian national registry to regional or local health unit data sources are not expected at this time.

Originally Paxlovid could only be prescribed and dispensed in selected centres in each Italian region (described as *modality 1* in Section 9.4). As of April 2022, Paxlovid can be dispensed in pharmacies with a prescription also by general practitioners (described as *modality 2* in Section 9.4). The counts, but not the clinical characteristics of these patients are captured in the AIFA registry (D Striano, Pfizer Italy, email communication, 13 May 2022).

9.4.4.2. Italy: Regional and local health unit data sources (exploratory)

The Italian National Healthcare System is organised at the regional level: the national government sets standards for assistance and tax-based funding for each region, which regional governments are responsible for providing to all their inhabitants.

Italian regional and local health unit data sources have played a strong role in PASS, in particular for medications dispensed in community pharmacies reimbursed by the regions, but it is unclear at this point whether Paxlovid will be captured in these data sources. The national codes associated with market authorisation exist, but currently, per national regulations, general practitioners will only be able to identify eligible patients and refer them to one of the regional centres that will prescribe and dispense Paxlovid. These centres are hospitals or hospital-like facilities. Pathways to identify eligible patients and facilitate access to Paxlovid are determined by each region.

We monitor the capture of Paxlovid prescriptions via data sources from regional and local health units via the ARS Toscana and the province of Caserta in Campania.

- Tuscany is an Italian region, with approximately 3.6 million inhabitants. The ARS Toscana is a research institute in the Tuscany region. The ARS Toscana data source comprises all information collected by the Tuscany region to account for the healthcare delivered to its inhabitants. Moreover, ARS Toscana collects data from regional initiatives. All data in the ARS Toscana data source can be linked at the individual level through a pseudoanonymous identifier. The ARS Toscana database routinely collects primary care and secondary care drug prescriptions for outpatient use and is able to link them at the individual level with hospital admissions, emergency care admissions, records of exemptions from copayment, diagnostic tests and procedures, causes of death, the mental health services register, the birth register, the spontaneous abortion register, and the induced terminations register. A pathology register is available, mostly recorded in free text, but with morphology and topographic SNOMED CT codes. Mother-child linkage is possible through the birth register.

- Similar information is available for the province of Caserta, in Campania, with approximately 1 million inhabitants.

9.4.4.3. United Kingdom: OpenSAFELY (exploratory)

OpenSAFELY[58,59] is a secure platform for analysis of electronic health data records in England stemming from a collaboration between the University of Oxford, the London School of Hygiene and Tropical Medicine, the TPP and EMIS suppliers of electronic health

records, and NHS England. NHS England handles information governance and permissions. The collaboration was developed to support urgent research in the context of the COVID-19 emergency. Data are maintained within the secure environments of the servers where they reside and are not allowed to move from their original location. In addition, researchers cannot manipulate raw data; instead, they must use the OpenSAFELY tools and information technology (IT) systems to write their analysis code and then run it against dummy data provided by OpenSAFELY. When the code is ready, it is executed by OpenSAFELY; researchers view the study results, tables, and graphs.

OpenSAFELY has strict open-source and transparency policies. The open-source policy limits the software and IT systems that can be used for the analysis. Currently the platform supports only statistical analysis code written with Stata, R, or Python; it requires that researchers use and are knowledgeable of the Git and GitHub IT systems. Those systems are aligned with best practices regarding task management and code review. The transparency policy determines that all analysis code executed in the platform is shared for review and re-use by other investigators using the platform.

OpenSAFELY includes data on around 24 million individuals whose general practitioners use the TPP SystmOne primary care clinical information system (44% of the English population). The collaboration is also currently developing support for the practices using the EMIS system, which would bring the patient population covered to a total of 58 million people in England.

The reason for proposing to use OpenSAFELY is that it complements the proposed CPRD Aurum, and its use would largely increase the size of the study population. OpenSAFELY has access to the same linkages as CPRD Aurum plus access to outpatient hospital appointments and in-hospital treatments for COVID-19. Another important advantage of OpenSAFELY is that the lag times are shorter than in CPRD Aurum; eg, the lag for HES linkages with OpenSAFELY is 1 to 2 months compared with 11 months with CPRD Aurum. A caveat is that the research team has no previous experience using this data source, and the OpenSAFELY support team does not act as a data research partner for its data. Therefore, the research team is exploring how to integrate OpenSAFELY into the present PASS.

Table 7 describes the main features of OpenSAFELY and CPRD Aurum.

Table 7. Main features of OpenSAFELY and CPRD Aurum

Feature	OpenSAFELY	CPRD Aurum
UK population[0]	66,647,112	66,647,112
Database population	24 million (100% in England)	13 million (99% in England)
Electronic healthcare system	TPP SystmOne (40% of English population) EMIS (under development)	EMIS (56% of English population)

Table 7. Main features of OpenSAFELY and CPRD Aurum

Feature	OpenSAFELY	CPRD Aurum
Database type	Primary healthcare electronic medical record database plus complete linkage to HES and other data	Primary healthcare electronic medical record database plus high-coverage linkage to HES and other data
Linked data sets	• Hospital Admissions • Intensive care admissions (COVID-19 only) • Emergency attendances • Death registry • COVID-19 test results • Deprivation data • In-hospital deaths (COVID-19 only) • In-hospital treatments for COVID-19 • Outpatient hospital appointments	• Hospital admissions (including COVID-19) • Intensive care admissions (COVID-19) • Emergency attendances • Death registry • COVID-19 test results • Deprivation data/socioeconomic measures • Cancer registry and treatment • Mental health services • Mother-Baby Link and Pregnancy Register algorithms (currently only in CPRD GOLD; in development in CPRD Aurum)
Drug dictionary codes/ therapeutic classification	dm+d	dm+d and Gemscript
Disease and procedure coding system(s)	CTV3 Read codes and, for EMIS, SNOMED CT and local EMIS® codes; ICD-10 for HES linkages	SNOMED CT and local EMIS® codes; ICD-10 for HES linkages
Lag time linkages for HES	1-2 month	Currently at least 11 months
Access	• Only approved users • Project approval required from NHS England	• Through paid CPRD licence • Subject to protocol approval via CPRD's Research Data Governance Process
In-hospital treatments for COVID-19	Yes	No (plan to reach out to explore whether these linkages would be possible)
Laboratory test results	Yes, from primary care health records	Yes, from primary care health records
Data Security	OpenSAFELY does not allow moving patient data outside the secure environments where they already reside. Data reside centrally, and analysis programmes also run centrally. Analysis programmes are written by researchers.	Data are downloaded locally, and researchers have access to pseudonymised patient data in electronic repositories protected by each institution under the requirements of a licence and/or data use agreement with CPRD.
Can analytical files be downloaded locally?	No, only dummy data sets that can support the programming of analytical code	Yes
Software required to run analysis	Stata, R, or Python	Any

Table 7. Main features of OpenSAFELY and CPRD Aurum

Feature	OpenSAFELY	CPRD Aurum
Knowledge and implementation of other IT systems required?	Git/GitHub	None
Open access policy	• All platform activity is publicly logged. All code for data management and analysis is shared centrally, under open licences and by default, for scientific review and efficient re-use.	All scripts and codes lists are kept by the investigators running the different studies according to their institution's policies.
Transparency	• All projects started within OpenSAFELY are visible to the public. • OpenSAFELY requires all researchers to archive and publish their analytic code, changes are shared publicly.	• A list of approved projects using CPRD data is publicly available from CPRD´s site (https://cprd.com/approved-studies-using-cprd-data). • A list of publications using CPRD data is publicly available from CPRD's site (https://cprd.com/bibliography)

COVID-19 = coronavirus disease 2019; CPRD = Clinical Practice Research Datalink (United Kingdom); HES = Hospital Episode Statistics; ICD-10 = *International Classification of Diseases, Tenth Revision*; IT = information technology; NHS = National Health Service; UK = United Kingdom.

a. UK population as of 01 January 2019 (estimated; this is the last available estimate).[60]

9.5. Study size

In this study, the duration of the observation period is bound by the dates for producing regulatory reports. For the safety component, all individuals meeting the study´s eligibility criteria during the study period will be included.

The number of treatments prescribed in various countries is presented in Section 9.4. Numbers by exposure group in each data source will be obtained in interim analyses.

The size of the exposed pregnant population is anticipated to be very small, given the strong recommendation against using Paxlovid during pregnancy or becoming pregnant during treatment with Paxlovid in the EU and UK SmPCs (Section 7). All other EMA-approved drugs to treat COVID-19 are also not recommended for use in pregnancy (Sections 9.1.1 and 9.1.2). It is likely that only relatively common outcomes will be observed with some certainty, given that the anticipated size of the study population is small.

For orientation regarding the study size, information from 2 data sources is provided. OpenSAFELY[16,61] reports that, of 93,860 individuals aged 12 years old or older who were eligible for COVID-19 treatment from 11 December 2021 through 28 February 2022, 57.2% were women and 34.8% were aged 12 to 49 years old (note: the publication reports a total of 93,870 potentially eligible patients, but the addition of age-specific counts in Table 3 of the referenced paper results in the number that we report here). If the distribution of sex were the

same across age categories, one could expect 93,860 × 0.572 × 0.348 = 18,684 eligible women aged 12 to 49 years (numbers of individuals are rounded down to nearest smaller integer). Extending these assumptions to treated individuals, 1156 women 12 to 49 years old would have been treated with Paxlovid and 906 with molnupiravir. Pregnancy rates have been reported as 10.3% in women aged 15 to 44 years in the United States in 2005;[62] assuming that this number can be applied as a percentage to the previously mentioned subtotals, one might estimate that, in OpenSAFELY from mid-December 2021 to mid-April 2022, 1924 eligible women were pregnant, of whom 119 were treated with Paxlovid and 93 were treated with molnupiravir. These numbers are likely overestimates because the age categories reported by OpenSAFELY include teenage and perimenopausal women (who would have a lower pregnancy rate than the source population for referenced pregnancy rate) and, more importantly, because the SmPCs for Paxlovid and molnupiravir recommend against use in pregnancy. OpenSAFELY reports on antiviral use even in patients for whom a positive COVID-19 test is not documented: "… patients who received treatment (see below) were also included in the population even if they were not identified as meeting eligibility criteria (eg, having no positive SARS-CoV-2 test)".[61] Patient counts reported in the referenced publication[61] are somewhat lower than in the previous report,[16] despite the observation periods being practically identical.

In SNDS, 50,818 individuals received Paxlovid between 04 February and 27 October 2022;[45] 4,806 of whom were women aged younger than 50 years. Also assuming that 10.3% are pregnant, estimations result in 495 pregnant women treated with Paxlovid; again, this is likely an overestimate, especially knowing that the mean age at Paxlovid use among individuals (of any sex) younger than 50 years of age was 38.6 years.

Table 8 contains precision estimates for proportions of Paxlovid-exposed women that we might observe for the target population. The numbers of patients represent numbers of Paxlovid users that we might observe in the study. For example, if the study identifies 10,000 Paxlovid users and 5% are pregnant, the 95% confidence interval (CI) will be (4.6%-5.4%).

Table 8. Precision (95% confidence intervals) expected for proportions of Paxlovid users in the target population

No. of patients	Potentially observed percentage of Paxlovid users in the target population					
	1%	5%	10%	20%	30%	40%
1000	(0.5-1.8)	(3.7-6.5)	(8.2-12.0)	(17.6-22.6)	(27.2-32.9)	(36.9-43.1)
2000	(0.6-1.5)	(4.1-6.0)	(8.7-11.4)	(18.3-21.8)	(28.0-32.1)	(37.8-42.2)
3000	(0.7-1.4)	(4.2-5.8)	(8.9-11.1)	(18.6-21.5)	(28.4-31.7)	(38.2-41.8)
4000	(0.7-1.4)	(4.3-5.7)	(9.1-11.0)	(18.8-21.3)	(28.6-31.4)	(38.5-41.5)
5000	(0.7-1.3)	(4.4-5.6)	(9.2-10.9)	(18.9-21.1)	(28.7-31.3)	(38.6-41.4)
10,000	(0.8-1.2)	(4.6-5.4)	(9.4-10.6)	(19.2-20.8)	(29.1-30.9)	(39.0-41.0)

Note: Confidence intervals were calculated using the Clopper-Pearson method for the binomial distribution.[63]

Table 9 provides some precision estimates that can be anticipated for comparative analyses for various study sizes that may be observed in the present study, for reference. Calculations for this table assumed that the true relative risk is 1 and that study population will have 3 unexposed pregnant women in the comparison group for each Paxlovid-exposed pregnant woman; this is based on the comparison with unexposed women. For example, if the study size were 280 Paxlovid-exposed pregnant women and 840 unexposed pregnant women, comparative analyses might result in a risk ratio 95% CI whose upper limit is under 3.0 with 0.8 probability for major congenital malformations.

Table 9. Study sizes needed for the upper limit of the risk ratio 95% confidence intervals to be below selected thresholds with a probability of 0.8 among pregnant women

Outcome	Assumed prevalence	Upper limit of 95% confidence interval	Exposed:unexposed pregnant women
Small for gestational age	10%[a]	5	37:111
		4	50:150
		3	80:240
		2.5	115:345
		2	200:600
Major congenital malformations	3%[64]	5	130:390
		4	177:531
		3	280:840
		2.5	405:1215
		2	705:2115
Stillbirth	0.6%[65]	11	300:900
		8	400:1200
		5	675:2025
		3	1440:4320
		2.5	2065:6195
		2	3610:10,830

Note: Outcomes are listed in order of decreasing prevalence. Assumptions underlying these calculations:

- No difference in risk between the exposed and unexposed (ie, risk ratio = 1).
- Ratio of exposed to unexposed was 1:3.
- Probability that the upper limit of 95% CI will be as stated = 0.8.
- Calculations were done using the "Study Size" tool in Episheet [66]

a. Assumed prevalence of 10% based on definition of birth weight below 10th percentile for gestational age.

9.6. Data management

This study will be conducted in a distributed manner, using a common protocol, common data model (CDM), and common analytics programmes based on existing health data, as far as possible. We count on a hybrid approach, where some of the data access partners (DAPs) may be able to run a script that is provided and others may need to run analyses themselves. The following steps will be implemented when access to individual-level data is possible:

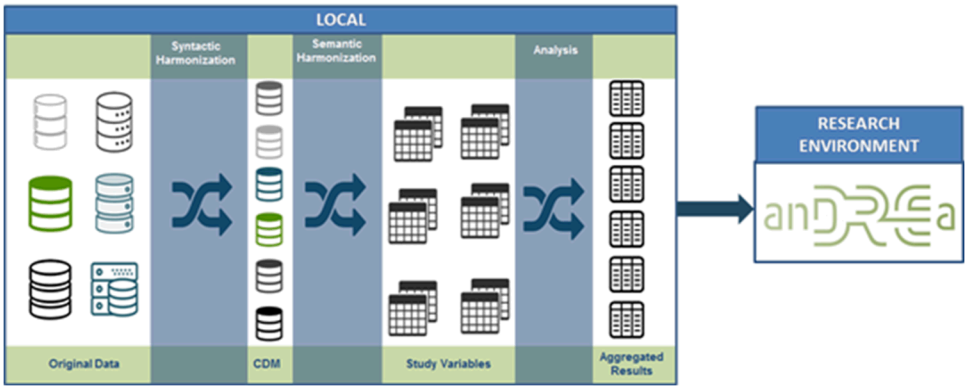
1. Extraction, transformation, and loading (ETL) of data to a CDM. To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation will be used. The CDM that will be used has been developed during the IMI-ConcePTION project.[67] In this CDM, data are represented in a common structure, but the contents of the data remain in their original format. The ETL design for each study is shared in a searchable Findability, Accessibility, Interoperability, and Re-use of digital assets (FAIR) catalogue. The Vaccine Monitoring Collaboration for Europe (VAC4EU) FAIR data catalogue is a metadata management tool designed to contain searchable metadata describing organisations that can provide access to specific data sources. Data quality checks will be conducted to measure the integrity of the ETL, as well as internal consistency within the context of the CDM (see Section 9.8).

2. Second, to reconcile differences across diagnostic terminologies, a shared semantic foundation is built for the definition of events under study by collecting relevant concepts in a structured fashion using a standardised event definition template. This is conducted by mapping relevant disease concepts to ICD-10, ICD-9 (*International Statistical Classification of Diseases, Ninth Revision*), SNOMED CT, READ, or International Classification of Primary Care (ICPC) terminologies starting with a modified version of the ADVANCE Codemapper in VAC4EU.[68] Codes can be tagged as being specific (narrow) or possible (broader) allowing for variation of the sensitivity of the event definition. Codes that are produced are reviewed by the DAPs and study team and listed in a study code lists using a VAC4EU R function, which subsequently gets incorporated in the R script for data transformation.

3. Third, following conversion to harmonised study variable sets, R and SAS scripts for the calculation of incidence and prevalence will be distributed to DAPs for local deployment. The aggregated results produced by these scripts will then be uploaded to the Digital Research Environment (DRE) for pooled analysis and visualisation (see Figure 2). The DRE, which is made available through the University Medical Center Utrecht (https://www.andrea-consortium.org/), is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate (https://www.andrea-consortium.org/azure-dre/).

In case access to individual-level data is not possible, and only count/aggregated data can be used, we will provide the DAP with the shell tables that need to be filled and the exact definitions using a code book.

Figure 2. Data management plan



9.6.1. Record retention

Validation of the quality control of the statistical analysis will be documented by the coordinating centre. The final study protocol and amendments, the final statistical report, statistical programmes, aggregated results, and output files will be archived on a study-specific, secure central server.

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, DAPs will keep all study-related records, including analysis files, syntaxes, ETL specifications, output of data quality checks and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone call reports). The records will be retained by DAPs according to local regulations or as specified in the vendor contract, whichever is longer. DAPs must ensure that the records continue to be stored securely for so long as they are retained. It is the responsibility of the coordinating centre to inform the other investigators or institutions regarding when these documents no longer need to be retained.

For requests for access to data for audit purposes, only aggregated data from all DAPs will be available on the DRE. The audit trail will consist of a detailed description of the methods to extract and process the records from the data sources. Access to raw data at each data source research centre will require the data requestor to obtain a licence or apply for approval at a research committee and to fulfil the conditions required under the governance rules of each data source.

If the DRE environment becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified; the study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless the coordinating centre and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

The coordinating centre must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6.2. Data extraction

Each DAP will create ETL specifications using the standard ConcePTION ETL design template for v2.2 (accessible via this link: https://docs.google.com/document/d/1SWi31tnNJL7u5jJLbBHmoZa7AvfcVaqX7jiXgL9uAWg/edit). Following completion of this template and review by the study team, each DAP will extract the relevant study data locally using its software (eg, Stata, SAS, R, Oracle). These data will be loaded into the ConcePTION CDM structure in csv (comma-separated value) format. These data remain local (see Figure 2).

9.6.3. Data processing and transformation

Data processing and transformation will be conducted using R (and SAS quality-control code) against the syntactically harmonised CDM. The scripts will first transform the data in the syntactically harmonised CDM to semantically harmonised study variables (see Figure 2). Following creation of study variables, the data will be characterised. This characterisation will include calculation of code counts and incidence rates, as well as benchmarking within the data source (over time), between data sources, and externally (against published estimates). Subsequently, code to conduct analysis against semantically harmonised study variables will be distributed and run locally to produce aggregated results. The scripts for these processing and analysis steps will be developed and tested centrally and sent to the DAPs.

The scripts will be structured in modular form to ensure transparency. Functions to be used in the modules will be either standard packages or packages specifically designed, developed, and tested for multidatabase studies. Scripts may be double-coded in SAS and R, and quality checks will be thoroughly documented.

The DAPs will run the code locally and send aggregated analysis results to the DRE using a secure file transfer protocol. In the DRE, results will be further plotted, inspected (for quality assessment), and pooled (if needed) for final reporting.

All final statistical computations will be performed on the DRE using R. For the quality-control scripts, SAS (SAS Institute; Cary, North Carolina) will be used. DAPs will have access to the workspace for script verification.

Aggregated results, ETL specifications, and a repository of study scripts will be stored in the DRE.

9.6.4. Data access

Within the DRE, each project-specific area consists of a separate secure folder called a "workspace." Each workspace is secured behind a firewall. Each workspace can be accessed only by users specific to its respective data source. Access to this workspace is possible only

with double authentication using an identification code and password together with the user's mobile phone for authentication. Upload of files is possible for all researchers with access to the workspace within the DRE. The DRE offers tools to control and monitor which activities take place within projects, in compliance with General Data Protection Regulations and Good Clinical Research Practices.

Download of files is possible only after requesting and receiving permission from a workspace member with an "owner" role. Owner roles will be assigned to the project principal investigators, who will be responsible for managing download requests and verification of the privacy aspects.

9.6.5. Data quality checks

For all data sources that will use the ConcePTION CDM and a common R script, the data quality will be verified using 3 different checks (Sections 9.6.5.1 through 9.6.5.3).

9.6.5.1. Level 1 quality checks (completeness of ETL)

Level 1 data checks review the completeness and content of each variable in each table of the CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (eg, data types, variable lengths, formats, acceptable values). Level 1 checks of R code and instructions are independent of any study and publicly available on the IMI-ConcePTION GitHub (https://github.com/IMI-ConcePTION/Level-1-checks). They should be run on each new data instance that undergoes ETL.

Specific objectives of level 1 checks:

- To assess the integrity of the ETL process from the original data to the ConcePTION CDM for each DAP
- To provide feedback on the integrity of the ETL to the DAP iteratively for the refinement of the DAP's ETL procedure
- To produce high-level characterisation of the data that has undergone ETL to the instance of the CDM in terms of presence/absence of CDM tables and columns, missingness in key variables, frequencies of categorical variables, and distribution of dates and continuous variables

The level 1 checks are divided in 5 major steps:

Step 1: Check ConcePTION CDM table formatting

1. Check if all rows of the CDM csv files in the working directory contain the correct number of variables.
2. Check if all variables in the CDM table are present irrespective of their content.
3. Check if variable names in the csv are written in lowercase.

4. Check for presence of all mandatory variables according to the ConcePTION CDM.
5. Check for presence of non-mandatory variables by comparing between the table of interest and the information recorded in the METADATA table.
6. Check presence of vocabularies for specific variables.
7. Assess formats for all values and compare with a list of acceptable formats that has been filled out in the METADATA table.

Step 2: Conduct missing data analysis

1. Tabulate missingness in all variables, overall and by calendar year (in the tables that contain a date variable).
2. Stratify missing data by meaning (in the tables that contain a meaning variable).
3. Display missing data using bar charts for each CDM table and report as counts and percentages.
4. Stratify missing data by meaning or calendar year, display using line charts for each CDM table, and report as counts and percentages.
5. Stratify missing data by meaning and calendar year, display using heat maps for each CDM table, and report as counts and percentages.

Step 3: Check dates

1. Check if dates are in the correct format (8 characters).
2. Check if date variables contain allowable values, for example:
   - Year: 1995 to present (exception for dates that represent end of follow-up where years in the future will be allowed)
   - Month: 01-12
   - Day: 01-31

Step 4: Check conventions and construct frequency tables of other and categorical variables.

1. Check if the table of interest contains any duplicate rows.
2. Check that all conventions for the table of interest have been adhered to.
3. Construct frequency tables of categorical variables, overall and by calendar year (when the table of interest contains a date variable).
4. Stratify all frequency tables by meaning when the table of interest contains a meaning variable.
5. Report results separately for variables with 2 or more categories.
6. Display the results graphically with bar charts or line charts.

Step 5: Check distribution of continuous variables and date variables

1. Report mean, median, interquartile range, skewness and kurtosis for continuous variables.
2. Report distribution of date variables as counts of dates overall and by calendar year.
3. Stratify all results by the meaning variable if the table of interest contains one.
4. Display results graphically with bar charts or line charts.

Level 1 R scripts output an R Markdown report that is submitted to the DRE and is inspected and assessed by the study team and the DAP, according to a structured template format.

9.6.5.2. Level 2 quality checks (internal consistency of data in CDM)

Aims of level 2 quality checks are to assess internal consistency of the data both within and between tables of the ConcePTION CDM instance for each DAP. The R code for level 2 checks is independent of any study and publicly available on the IMI-ConcePTION GitHub (https://github.com/IMI-ConcePTION/Level-2-checks).

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between 2 or more variables within and between tables. Examples of this type of check include observations occurring before a birth date, observations occurring after a recorded death date, a parent aged 12 years or younger, etc.

The level 2 checks are divided into 8 major steps:

- Detect event dates that occur before birth date.
- Detect event dates after date of death.
- Detect event dates outside observation periods.
- Detect subjects included in a CDM table without a corresponding record in the PERSONS table.
- Detect observations associated with a visit_occurrence_id that occurs before the visit_start_date.
- Detect observations associated with a visit_occurrence_id that occurs after the visit_end_date.
- Detect observations associated with a visit_occurrence_id for which the associated person_id differs from that in the VISIT_OCCURRENCE table.
- Detect subjects indicated in PERSON_RELATIONSHIPS as the parent of a child with a birth_date less than 12 years prior to the recorded birth_date of the associated child.

Level 2 check scripts output an R Markdown report that is submitted to the DRE and is inspected and assessed by the study team and the DAP, according to a structured template format.

9.6.5.3. Level 3 quality checks (study variable check)

Level 3 checks focus on key study variables (population, medications, diagnoses, pregnancy algorithm, medical observations, survey observations and vaccines, lifestyle) based on time anchoring of the population, exclusion criteria and semantic harmonisation of outcomes, exposures, and covariates and are divided into different modules that may be included or not depending on the study questions. Level 3 checks allow for benchmarking within a data source over time, between data sources, and with external benchmark data. Level 3 checks are in development to optimise detection of deviations.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Results will be presented overall and in the strata for the paediatric population (pregnant individuals who were dispensed Paxlovid while aged < 18 years) and for the adult population (18 years of age or older).[69]

9.7.1. Descriptive analyses

Description of the baseline characteristics for the exposed (Paxlovid) and comparator cohorts will be reported as means, standard deviations, medians, and other quartiles for continuous variables and as counts and proportions for categorical variables. The missingness of variables will also be described.

To describe the relative imbalance of characteristics between Paxlovid-exposed and comparator groups, absolute standardised differences will be calculated for each baseline characteristic. For categorical variables with more than 2 levels, we will calculate an overall standardised difference across all levels.

For pregnancy and offspring outcomes, prevalence and 95% CIs will be reported at the end of follow-up.

9.7.2. Unadjusted outcome measures

In the population of pregnant women, unadjusted prevalence, prevalence ratio, and prevalence difference for each pregnancy, offspring, and maternal outcome among Paxlovid users versus each of the 2 comparator groups separately (with active comparator molnupiravir where available), will be estimated, along with their 95% CIs. Subgroup

analyses will be conducted by subgroups defined by demographic and clinical characteristics, as well as other covariates of interest, if the target population sizes are adequate.

For major congenital malformations, the live birth and total prevalences per the EUROCAT definition will be calculated.[70]

Risk/prevalence ratios will be calculated only if at least 5 outcomes are present among the individuals that will be included in a given analysis in the study population from a given data source.

9.7.3. Adjustment for baseline imbalances

Individuals in each cohort under study may have different characteristics that may influence their exposure and their risk of outcomes. To account for such potential confounding, we will stratify by COVID-19 severity (of note, per the indication, patients should have mild COVID-19 at treatment start) and estimate the adjusted risk/prevalence ratios and 95% CIs.

For adjustment, taking into consideration that some of the study outcomes will be rare, while exposure will likely be more evenly distributed, propensity score methods are planned, such as inverse probability of treatment weighting. Propensity score matching with matching ratio up to 1 Paxlovid-exposed individual to 5 individuals in either comparison group will also be considered.

Risk/prevalence ratios and risk differences will be calculated only if at least 5 outcomes are present among the individuals that will be included in a given outcome analysis in the study population from a given data source.

More details, including how correlated observations such as offspring from the same mother will be treated, will be provided in the SAP.

9.7.3.1. Sensitivity analyses

Sensitivity analyses will include

- A modification of the outcome definition (Section 9.3.2) such that completed pregnancies with unknown outcome will also be incorporated.

- A modification of the study period (Section 9.9) to ensure that short pregnancies that start late in the study observation period are not selectively incorporated into the study population; this analysis will stop the accrual of pregnancies earlier to allow at least 10 months of data between LMP and the last observed data point.

9.7.3.2. Meta-analysis

Analyses will be conducted separately within each data source. Using the main estimates from each data source, appropriate random-effects meta-analytic methods will be used to

obtain a combined effect estimate. The heterogeneity across data sources will be checked, and a forest plot will be produced with the data sources and the pooled estimate.

Outcomes for meta-analysis will include all outcomes listed except the exploratory outcomes. A minimum of 3 data points will be required (ie, results from at least 3 data sources need to be available to proceed with meta-analysis for a given outcome). Risk ratios obtained from sensitivity analyses may be meta-analysed if numbers are adequate.

9.7.4. Small cell count policy

The small cell count rules specified in Table 10 will be taken into account when presenting results of the study. The cover page, statistical analysis, and results section of study reports will contain the following boxed statement*:

> This report is for regulatory communications only. For any dissemination beyond regulatory authorities, please refer to the data protection rules, and apply the masking rules regarding small cell count restrictions in Section 9.7 and Table 10.

Table 10. Small cell count rules for reporting results

	SNDS (France)	SIDIAP (Catalonia, Spain)	CPRD Aurum (UK)
Numbers to be masked	1-10	1-4	1-4
Text to be used in redactions	$1 \leq n \leq 10$	$1 \leq n < 5$	$1 \leq n < 5$
Possible to share with SIGMA Paxlovid PASS research centres	No	Yes	Yes
Possible to share with regulatory authorities. Note: report is provided to authorities by MAH (Pfizer)	No[71]	Yes	Yes
Comments		Not applicable	A clear statement about cell count suppression is required

9.8. Quality control

All key study documents, such as the analysis plan and study reports, will undergo quality-control review, senior scientific review, and editorial review. At the SIGMA coordinating centre, an independent Office of Quality Assurance can perform audits and assessments that involve various aspects of projects, including education and training documentation, data entry and data-transfer procedures and documentation, and IRB documentation. Such audits

* Note: The boxed text will be included in study reports; the section number and table refer to the report.

are conducted by the centre's Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures.

Again, according to the procedures developed in the IMI-ConcePTION project, level 1 data checks review the completeness and content of each variable in each table of the CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (eg, data types, variable lengths, formats, acceptable values). Level 2 data checks assess the logical relationship and integrity of data values within a variable or between 2 or more variables within and between tables. Level 3 data checks produce incidence and prevalence rates or proportions and trends over time within a data source (by examining output by age and year) for benchmarking between data sources and against external sources. For details, refer to descriptions of the data quality checks in Section 9.6.5.

9.9. Limitations of the research methods

Key limitations of this study, as foreseen at this time, are listed below.

- *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 listed in Section 9.4. However, in other countries, if Paxlovid is mostly distributed from hospital pharmacies, as has happened in Italy in the first months of Paxlovid availability, data sources commonly used for pharmacoepidemiologic research will not be able to access this information; in Italy, this information is available, in aggregated form, from AIFA. If Paxlovid distribution is documented only in a specific registry, linkage to this registry would be needed for the present study. The MAH and the research team are in close communication sharing information about country-specific distribution channels and sales volume as the information becomes available. The same consideration applies to the comparator drug molnupiravir, which appears to use the same distribution channels as Paxlovid in some data sources.

- *Identifying COVID-19 episodes*. Currently, in many countries, individuals can self- test for COVID-19 at home. As a result, positive test results in the outpatient setting may not be documented in the individual's health records. Furthermore, the intensity of screening has decreased. Documented COVID-19 is an inclusion criterion for this study for all exposure groups; individuals with COVID-19 whose diagnosis or positive test result is not documented will not be identified as eligible for inclusion in this study. For reference, in data from the SNDS in France, 41.3% of Paxlovid users did not have documented COVID-19 tests in the 10 days before or after Paxlovid use (58.7%, or 26,464 of 45,086 for whom this is reported, had such a test);[45] in the previous available report, with data until June 2022, only 27% of Paxlovid users did not have COVID-19 tests within 10 days before or after Paxlovid use.[72,63] Pregnant individuals who test positive on a screening test at the time of hospitalisation for delivery will not be eligible for the study because they do not contribute person-time to the study.

- *Ascertaining COVID-19 vaccination status* if Paxlovid use can be captured only in data sources that do not capture vaccination. Paxlovid is indicated for individuals who are at increased risk for progression to severe COVID-19, and unvaccinated individuals can be considered as being at increased risk for progression to severe COVID-19; this will depend on the country-specific use recommendations. If the available data sources do not capture vaccination, any potentially increased risk for progression to severe COVID-19 due to lack of vaccination will not be captured. At this time, the 3 proposed data sources capture COVID-19 vaccination.

- *Size of target populations*. The target population includes individuals who should not receive Paxlovid per the SmPCs. For this reason, it is expected that the number of Paxlovid-exposed individuals in the target population will be small. If the number of individuals is too small to sustain comparative analyses (please see Section 9.7), analyses will be descriptive only.

- *Comparator group*. At the time of preparing this document, no treatments specific to COVID-19 with an approved indication and mode of use similar to Paxlovid are authorised in the EU. As described in Section 9.1.1, molnupiravir has not been authorised in the EU, but the EMA initially supported national authorities that may want to decide on its early use[10]; for example, AIFA has authorised its use in Italy,[11] and use has been documented. Molnupiravir is a reasonable active comparator and has been selected to serve as such. As noted, molnupiravir appears to use the same distribution channels as Paxlovid, at least in some data sources. However, because molnupiravir was not used or not captured in some of the selected data sources (SIDIAP, SNDS) at the time of preparing this protocol, an alternative comparison group is included: unexposed individuals with COVID-19. Other medications to treat COVID-19 will be considered in the future.

- *Channelling and potential for residual confounding.* Using an active comparator with a similar indication mitigates confounding by design. Channelling will be addressed analytically (eg, propensity score weighting). It is anticipated that channelling will be more substantial in the comparison with an unexposed pregnant population drawn from the general population with COVID-19.

- *Pregnancies detected while they are still ongoing.* The date of pregnancy start may be unavailable in pregnancies that end before 20 gestational weeks. In such pregnancies, the start date of pregnancy could be imputed (for example, using predictive models based on pregnancies with observed start date). Some pregnancies identified as ongoing (because they lack information on pregnancy end) cannot plausibly be still ongoing, possibly reflecting that the end of pregnancy was not captured in the data source. In data sources with a well-established birth registry or other reliable sources of information, pregnancies without information on pregnancy end might be assumed to represent foetal losses. Sensitivity analyses will assume that some pregnancies with unknown outcomes are spontaneous abortions. Additionally, to ensure that short pregnancies that start late in the

study observation period are not selectively incorporated in the study population (inflating the observed prevalence of spontaneous abortions and preterm deliveries), a sensitivity analysis will stop the accrual of pregnancies starting at some point in 2024 (date to be determined), allowing at least 10 months of data before the last observed data point.

- *Simultaneous use of medications that are contraindicated or can have substantial interactions with Paxlovid*. This PASS will be able to find prescriptions or dispensings for these medications, but the data sources will not be able to capture whether patients stop taking the medications for a few days around the period of Paxlovid treatment.

- *Evolving uses of Paxlovid*. Paxlovid has a clearly defined indication in the EU and UK SmPCs; however, the press has disseminated various potential uses that are not in alignment with the SmPCs, such as longer treatment course if symptoms rebound after the 5-day course, [73] use as postexposure prophylaxis (noting that the clinical trial did not meet its prespecified endpoint),[73] as treatment for long COVID-19,[74,75] and paediatric use.[76]

- *Characterising the study population in relation to certain aspects of the indications for Paxlovid and molnupiravir.* Some aspects of the indications for Paxlovid and molnupiravir cannot be ascertained in data sources typically used for PASSs. Need for or use of supplemental oxygen will not be well captured in the data sources. Increased risk for progression to severe COVID-19 may involve subjective determinations from healthcare providers not necessarily based on elements contained in medical records or claims data sources. Exact time since symptom onset will not be known.

- *Exploratory outcomes.* Limitations of identifying all safety events after exposure include that some of those events will be related to the condition and not necessarily to Paxlovid's safety profile. The proposed approach identifies safety events based on diagnosis codes only, and those events will be prevalent or incident. Given that some data sources use unique coding systems, exploratory outcomes may not be equivalent across all data sources, preventing meta-analysis. However, this approach will facilitate the identification of other health outcomes that may potentially be related to the safety profile of Paxlovid in pregnant individuals.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study using secondary data collection and does not pose any risks for individuals. Each DAP will apply for an independent ethics committee (IEC) review according to local regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

10.1. Patient information

This study involves data that exist in pseudonymised or anonymised format held by the data holders and to which the DAPs have protocol-based access. The proposed study is a non-interventional study reusing healthcare data (secondary data collection). The DAPs will process the pseudonymised data to which they have access and provide aggregated (anonymised) data to RTI. CPRD will provide anonymised data to RTI for analysis. Data protection and privacy regulations will be respected in collecting, forwarding, processing, and storing data from study participants.

10.2. Patient consent

The DAPs and CPRD will follow the applicable country-specific laws for accessing and processing personal data with respect to the need for notice to or consent from the study subjects.

10.3. Institutional review board/independent ethics committee

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs or other relevant authorities. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigour, and follow generally accepted research practices described in the following paragraphs.

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[77] and has been designed in line with the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology*[78] and the UK MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions.[79] The *ENCePP Checklist for Study Protocols*[80] has been completed for the protocol (see Annex 2).

The study is a PASS and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E*[81] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies*[3] and with the 2012 EU pharmacovigilance legislation, adopted 19 June 2012.[82] The study will comply with the study reporting requirements specified in Module VIII Section VIII.B.6.3.1., "Progress Reports," and Section VIII.B.6.3.2., "Final Study Report" of the *Guideline of Good Pharmacovigilance Practices*.[3]

In alignment with EMA GVP Module VIII Section VIII.B.2., "Study Registration," the study and its protocol will be registered in the European Union Electronic Register of Post-

authorisation Studies (EU PAS Register)[83] prior to the start of data collection. At completion, the final report or its summary will be posted.

The SIGMA research team and study sponsor adhere to the general principles of transparency and independence in the *ENCePP Code of Conduct*.[84]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, progress report, and interim and final study reports will be submitted to the EMA Pharmacovigilance Risk Assessment Committee (PRAC) as agreed on in the risk management plan and included in other regulatory communications as relevant.

Study reports will be prepared using a template following the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII, Section B.4.3.[3] Reports will include a progress report with a description of project start-up and subsequent activities, the evolution of the identified challenges for this study, and the list of anticipated data sources (per an ongoing feasibility assessment on Paxlovid distribution channels in various countries); 2 annual interim reports with the number of Paxlovid-exposed individuals, individuals exposed to the medications listed in Table 2, and preliminary primary and exploratory outcome counts; and a final report. The reports will include/consider the following elements:

- In the analysis and interpretation of study results, that maternal outcomes may influence pregnancy and infant outcomes (interim reports and the final report).
- If matching criteria require further revision in case of insufficient matching, a description of the modified analysis. In this scenario, a sensitivity analysis with the original matching specifications will be considered (final report).
- Modification(s) to the algorithms to identify pregnancies if the algorithms used differ from the cited publications (final report).
- Limitation of missing/incomplete information on termination of pregnancy due to foetal anomaly (final report).

- The final list of risk factors for severe COVID-19 used for this study (final report).

- Any new relevant information on data linkage of SNDS to the SI-DEP (interim reports 1 and 2) and implications of the lack of linkage, if applicable, for the study in the second interim report.

As noted in Section 10.4, in alignment with EMA GVP Module VIII Section VIII.B.2, the study and its protocol will be registered in the EU PAS Register[83] prior to the start of data collection. At completion, the final report or its summary will be posted.

Study results will be submitted for publication following recommendations of the International Committee of Medical Journal Editors,[85] and communication in appropriate scientific venues (eg, International Conference on Pharmacoepidemiology & Therapeutic Risk Management [ICPE]) will be considered. In its *Guidelines for Good Pharmacoepidemiology Practices (GPP)*, the International Society for Pharmacoepidemiology (ISPE) contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance."[77] In alignment with EMA *GVP Module VIII: Post-Authorisation Safety Studies*,[3] Section VIII.B.5, and the *ENCePP Code of Conduct*,[86] the MAH and investigators will agree upon a publication policy allowing the members of the research team to independently prepare publications based on the study results, irrespective of data ownership. The MAH will be entitled to view the results and interpretations included in the manuscript and provide comments before submission of the manuscript for publication. The MAH and research team are aware that the MAH should communicate to the regulatory agency(ies) the final manuscript of the article within 2 weeks after first acceptance for publication.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the responsible parties are aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

1. SIGMA. SIGMA Consortium website. 2022. Available from: https://sigmaconsortium.eu. Accessed on: 07 April 2022.
2. VAC4EU. VAccine monitoring Collaboration for Europe. 2019. Available from: https://vac4eu.org/. Accessed on: 15 March 2022.
3. EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (EMA/813938/2011 Rev 3). 13 October 2017. Available from: 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 on: 30 July 2021.
4. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med. 2022;386(15):1397-408.
5. FDA. Emergency use authorization 105 (Paxlovid). 22 December 2021. Available from: https://www.fda.gov/media/155049/download. Accessed on: 14 March 2022.
6. MHRA. Regulatory approval of Paxlovid. 09 February 2022. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid. Accessed on: 14 March 2022.
7. EMA. COVID-19: EMA recommends conditional marketing authorisation for Paxlovid. 27 January 2022. Available from: https://www.ema.europa.eu/en/news/covid-19-ema-recommends-conditional-marketing-authorisation-paxlovid. Accessed on: 14 March 2022.
8. EMA. Paxlovid summary of product characteristics. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf. Accessed on: 14 March 2022.
9. MHRA. Paxlovid summary of product characteristics. January 2022. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045762/Reg_SPC_PX_2_0_GB.pdf. Accessed on: 05 September 2022.
10. EMA. EMA issues advice on use of Lagevrio (molnupiravir) for the treatment of COVID-19. 19 November 2021. Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19 Accessed on: 14 March 2022.
11. AIFA. Molnupiravir and remdesivir available for the treatment of non-hospitalized COVID-19 patients at high risk of progressing to severe disease. 30 December 2021. Available from: https://www.aifa.gov.it/en/-/disponibilit%C3%A0-molnupiravir-e-remdesivir-trattamento-pazienti-non-ospedalizzati-covid-19-1. Accessed on: 7 March 2023.
12. AEMPS. Criterios para valorar la administración de las nuevas alternativas terapéuticas antivirales frente a la infección por SARS-CoV-2 (version 3) [Spanish]. 04 April 2022. Available from: https://www.aemps.gob.es/medicamentos-de-uso-humano/acceso-a-medicamentos-en-situaciones-especiales/criterios-para-valorar-la-administracion-de-las-nuevas-alternativas-terapeuticas-antivirales-frente-a-la-infeccion-por-sars-cov-2/?lang=en. Accessed on: 28 April 2022.

13. CHMP. Lagevrio. 24 February 2023. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/lagevrio. Accessed on: 06 March 2023.
14. MHRA. First oral antiviral for COVID-19, Lagevrio (molnupiravir), approved by MHRA. 04 November 2021. Available from: https://www.gov.uk/government/news/first-oral-antiviral-for-covid-19-lagevrio-molnupiravir-approved-by-mhra#:~:text=Dr%20June%20Raine%2C%20MHRA%20Chief,and%20have%20granted%20its%20approval. Accessed on: 07 April 2022.
15. MHRA. Lagevrio summary of product characteristics. 04 November 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1030930/Legavrio_SMPC_4Nov21.pdf. Accessed on: 7 April 2022.
16. OpenSAFELY. Coverage and uptake of antivirals and neutralising monoclonal antibodies for the treatment of non-hospitalised patients with COVID-19. 30 January 2023. Available from: https://reports.opensafely.org/reports/antivirals-and-nmabs-for-non-hospitalised-covid-19-patients-coverage-report/. Accessed on: 06 April 2023.
17. EMA. Veklury summary of product characteristics. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/veklury-epar-product-information_en.pdf. Accessed on: 23 September 2022.
18. EMA. Evusheld summary of product characteristics. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/evusheld-epar-product-information_en.pdf. Accessed on: 26 September 2022.
19. ANSM. Evusheld (Tixagevimab / Cilgavimab) [French]. 2022. Available from: https://ansm.sante.fr/tableau-acces-derogatoire/tixagevimab-150-mg-cilgavimab-150-mg-solution-injectable-evusheld. Accessed on: 09 January 2022.
20. EMA. Kineret summary of product characteristics. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/kineret-epar-product-information_en.pdf. Accessed on: 22 July 2022.
21. EMA. Regkirona summary of product characteristics. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/regkirona-epar-product-information_en.pdf. Accessed on: 29 July 2022.
22. EMA. RoActemra summary of product characteristics. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf. Accessed on: 26 April 2022.
23. EMA. Ronapreve summary of product characteristics. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/ronapreve-epar-product-information_en.pdf. Accessed on: 18 March 2022.
24. EMA. Xevudy summary of product characteristics. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/xevudy-epar-product-information_en.pdf. Accessed on: 28 July 2022.
25. Schneeweiss S, Rassen JA, Brown JS, et al. Graphical depiction of longitudinal study designs in health care databases. Ann Intern Med. 2019;170(6):398-406.

26. Karim ME, Gustafson P, Petkau J, et al. Comparison of statistical approaches for dealing with immortal time bias in drug effectiveness studies. Am J Epidemiol. 2016;184(4):325-35.
27. Innovative Medicines Initiative. ConcePTION pregnancy algorithms. 2022. Available from: https://github.com/ARS-toscana/ConcePTIONAlgorithmPregnancies. Accessed on: 15 March 2022.
28. Campbell J, Bhaskaran K, Thomas S, et al. Investigating the optimal handling of uncertain pregnancy episodes in the CPRD GOLD Pregnancy Register: a methodological study using UK primary care data. BMJ Open. 2022;12(2):e055773.
29. Margulis AV, Huybrechts KF. Identification of pregnancies in healthcare data: a changing landscape. Pharmacoepidemiol Drug Saf. 2023;32(1):84-86.
30. Bérard A, Abbas-Chorfa F, Kassai B, et al. The French Pregnancy Cohort: medication use during pregnancy in the French population. PLoS One. 2019;14(7):e0219095.
31. Blotière PO, Weill A, Dalichampt M, et al. Development of an algorithm to identify pregnancy episodes and related outcomes in health care claims databases: an application to antiepileptic drug use in 4.9 million pregnant women in France. Pharmacoepidemiol Drug Saf. 2018;27(7):763-70.
32. Giner Soriano M, Gómez Lumbreras A, Lestón Vázquez M, et al. Exposure to drugs used in acute conditions during pregnancy: population-based cohort study with electronic health records [abstract 73]. BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY. 2022;10.1111/bcpt.13724.
33. Gómez Lumbreras A, Giner Soriano M, Lestón Vázquez M, et al. Implementation of preventing activities during pregnancy: population-based cohort study with electronic health records [abstract 79]. BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY. 2022;10.1111/bcpt.13724.
34. Thurin NH, Pajouheshnia R, Roberto G, et al. From inception to ConcePTION: genesis of a network to support better monitoring and communication of medication safety during pregnancy and breastfeeding. Clin Pharmacol Ther. 2022;111(1):321-31.
35. Lestón Vázquez M, Giner Soriano M, Prat Vallverdú O, et al. Development of an algorithm to identify pregnancy episodes in a primary care database [abstract 75]. BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY. 2022;10.1111/bcpt.13724.
36. MHRA. CPRD Aurum Pregnancy Register, version 1.0. 23 May 2022. Available from: https://cprd.com/sites/default/files/2022-05/CPRD%20Aurum%20PregnancyRegister_Documentation_v1.pdf. Accessed on: 06 April 2023.
37. Minassian C, Williams R, Meeraus WH, et al. Methods to generate and validate a pregnancy register in the UK Clinical Practice Research Datalink primary care database. Pharmacoepidemiol Drug Saf. 2019;28(7):923-33.
38. Campbell J, Shepherd H, Welburn S, et al. Methods to refine and extend a pregnancy register in the UK Clinical Practice Research Datalink primary care databases. Pharmacoepidemiol Drug Saf. 2022;10.1002/pds.5584.

39. MHRA. CPRD Mother Baby Link documentation, version 1.2. 3 May 2017. Available from: https://cprd.com/sites/default/files/2022-02/MotherBabyLink_Documentation_v1.2.pdf. Accessed on: 01 February 2023.
40. MHRA. CPRD Aurum Mother-Baby Link documentation, version 0.2. 06 December 2022. Available from: https://cprd.com/sites/default/files/2022-12/CPRD_Aurum_MotherBabyLink_Documentation_v0.2.pdf. Accessed on: 06 April 2023.
41. EUROCAT. EUROCAT Guide 1.5, Chapter 3.2, Minor anomalies for exclusion 31 May 2022. Available from: https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Guide_1.5_Chapter_3.2.pdf Accessed on: 21 March 2023.
42. EUROCAT. EUROCAT Guide 1.5, Chapter 3.3, Subgroups of congenital anomalies. 17 November 2022. Available from: https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Guide_1.5_Chapter_3.3.pdf Accessed on: 21 March 2023.
43. CDC. COVID-19. Underlying medical conditions associated with higher risk for severe COVID-19: information for healthcare professionals. 09 February 2023. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Accessed on: 6 April 2023.
44. Bateman BT, Mhyre JM, Hernandez-Diaz S, et al. Development of a comorbidity index for use in obstetric patients. Obstet Gynecol. 2013;122(5):957-65.
45. Bouillon K, Bertrand M, Baricault B, et al. Utilisation de l'antiviral oral Paxlovid® (nirmatrelvir/ritonavir) délivré dans les pharmacies de ville du 4 février au 27 octobre 2022 - etude nationale réalisée à partir des données [French]. 24 November 2022. Available from: https://www.epi-phare.fr/app/uploads/2022/11/epi-phare_utilisation_paxlovid_20221124.pdf. Accessed on: 4 April 2023.
46. AIFA. Archivio registri 2023 [Italian]. 2023. Available from: https://www.aifa.gov.it/en/1159. Accessed on: 4 April 2023.
47. CORRUSS. Mise à disposition l'antiviral du laboratoire PFIZER: PAXLOVID® (association de PF-07321332 150 mg et ritonavir 100 mg, comprimés pelliculés) [French]. 02 February 2022. Available from: https://solidarites-sante.gouv.fr/IMG/pdf/dgs-urgent__2022_22_paxlovid.pdf. Accessed on: 28 April 2022.
48. French Ministry of Health and Prevention. Evolution de la prise en charge face aux sous-variants BA.4 et BA.5 - DGS-Urgent N°2022_66 [French]. 11 July 2022. Available from: https://sante.gouv.fr/IMG/pdf/dgs-urgent_n_2022_66_-_evolution_prise_en_charge_ba.4_ba_5.pdf. Accessed on: 01 March 2023.
49. Generalitat de Catalunya. Coronavirus SARS-CoV-2: Infomació per a professionals [Catalan]. 03 August 2022. Available from: https://canalsalut.gencat.cat/web/.content/_A-Z/C/coronavirus-2019-ncov/professionals/recomanacions-inici-seguiment-tractament-paxlovid.pdf. Accessed on: 07 March 2023.

50. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017;26(8):954-62.
51. SNDS. Patients vaccinés contre le COVID-19 [French]. 07 July 2021. Available from: https://documentation-snds.health-data-hub.fr/fiches/ir_vac_f.html. Accessed on: 02 May 2022.
52. Commission Nationale de l'Informatique et des Libertés (France). Délibération n°2021-077du 1er juillet 2021 portant avis sur un projet de décret modifiant le décret n° 2020-551 du 12 mai 2020 relatif aux systèmes d'information mentionnés à l'article 11 de la loi n° 2020-546 du 11 mai 2020 prorogeant l'état d'urgence sanitaire et complétant ses dispositions et le décret n° 2020-1690 du 25 décembre 2020 autorisant la création d'un traitement de données à caractère personnel relatif aux vaccinations contre la covid-19 (demande d'avis n° 21010901) [French]. 08 July 2021. Available from: https://www.legifrance.gouv.fr/cnil/id/CNILTEXT000043765544. Accessed on: 02 May 2022.
53. Thurin NH, Bosco-Levy P, Blin P, et al. Intra-database validation of case-identifying algorithms using reconstituted electronic health records from healthcare claims data. BMC Med Res Methodol. 2021;21(1):95.
54. Recalde M, Rodriguez C, Burn E, et al. Data resource profile: the Information System for Research in Primary Care (SIDIAP). Int J Epidemiol. 2022;51(6):e324-e36.
55. SIDIAP. Available information. SIDIAP dynamics. 2022. Available from: https://www.sidiap.org/index.php/en/dades-en/informacio-disponible-en. Accessed on: 06 April 2023.
56. MHRA. Release notes: CPRD Aurum November 2022. November 2022. Available from: https://cprd.com/sites/default/files/2022-11/2022-11%20CPRD%20Aurum%20Release%20Notes.pdf. Accessed on: 02 February 2023.
57. MHRA. Feasibility counts for SARS-CoV-2–related codes in CPRD primary care data. May 2022. Available from: https://cprd.com/sites/default/files/2022-05/SARS-CoV-2%20counts%20May2022.pdf. Accessed on: 06 April 2023.
58. OpenSAFELY. About OpenSAFELY. 2022. Available from: https://www.opensafely.org/about/. Accessed on: 07 April 2022.
59. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-36.
60. EUROSTAT. Population on 1 January. 05 November 2021. Available from: https://ec.europa.eu/eurostat/databrowser/view/tps00001/default/table?lang=en. Accessed on: 07 March 2023.
61. Green ACA, Curtis HJ, Higgins R, et al. Trends, variation, and clinical characteristics of recipients of antiviral drugs and neutralising monoclonal antibodies for covid-19 in community settings: retrospective, descriptive cohort study of 23.4 million people in OpenSAFELY. BMJ Medicine. 2023;2(1):e000276.
62. Ventura SJ, Abma JC, Mosher WD, et al. Estimated pregnancy rates for the United States, 1990-2005: an update. Natl Vital Stat Rep. 2009;58(4):1-14.
63. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

64. CDC. Update on overall prevalence of major birth defects—Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep. 2008;57(1):1-5.
65. MacDorman MF, Gregory EC. Fetal and perinatal mortality: United States, 2013. Natl Vital Stat Rep. 2015;64(8):1-24.
66. Rothman KJ. Episheet—spreadsheets for the analysis of epidemiologic data. 15 November 2021. Available from: https://www.rtihs.org/sites/default/files/2022-04/Episheet.xls. Accessed on: 07 October 2022.
67. Innovative Medicines Initiative. Report on existing common data models and proposals for ConcePTION. 04 August 2020. Available from: https://www.imi-conception.eu/wp-content/uploads/2020/10/ConcePTION-D7.5-Report-on-existing-common-data-models-and-proposals-for-ConcePTION.pdf. Accessed on: 11 April 2022.
68. Becker BFH, Avillach P, Romio S, et al. CodeMapper: semiautomatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiol Drug Saf. 2017;26(8):998-1005.
69. EMA. Guideline on good pharmacovigilance practices (GVP). Product- or population-specific considerations IV: paediatric population. 25 October 2018. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-iv_en-0.pdf. Accessed on: 24 October 2022.
70. EUROCAT. Calculation of prevalence and their 95% confidence intervals. 2022. Available from: https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/Calculations%20of%20Prevalence%20and%20CIs.pdf. Accessed on: 07 October 2022.
71. CNAM. SNDS and SNDS OMOP: guide for permanent access [Documentation du SNDS & SNDS OMOP: guide accès permanents; in French]. 6 February 2022. Available from: https://documentation-snds.health-data-hub.fr/snds/formation_snds/documents_cnam/guides_pedagogiques_snds/guide_pedagogique_acces_permanents.html#quelles-donnees-du-snds-peuvent-etre-exportees-et-importeesSNDS. Accessed on: 20 June 2023.
72. Bouillon K, Bertrand M, Baricault B, et al. Étude d'utilisation de l'antiviral oral Paxlovid du 4 février au 29 juin 2022 [French]. 13 September 2022. Available from: https://www.epi-phare.fr/app/uploads/2022/09/epi-phare_utilisation_paxlovid_20220913.pdf. Accessed on: 11 October 2022.
73. Larkin C. Pfizer's COVID drug fails to show benefit as preventive therapy. 29 April 2022. Available from: https://news.bloomberglaw.com/coronavirus/pfizers-covid-drug-fails-to-show-benefit-as-preventive-therapy. Accessed on: 13 May 2022.
74. Ledford H. Can drugs reduce the risk of long COVID? What scientists know so far. Nature. 2022;604(7904):20-21.
75. Wu K. The promising treatment for long COVID we're not even trying. 10 May 2022. Available from: https://www.theatlantic.com/health/archive/2022/05/long-covid-treatment-pfizer-paxlovid/629810/. Accessed on: 13 May 2022.
76. Reuters. Pfizer begins COVID pill study in high-risk children aged 6-17. 09 March 2022. Available from: https://www.reuters.com/business/healthcare-

pharmaceuticals/pfizer-begins-covid-pill-study-high-risk-children-aged-6-17-2022-03-09/. Accessed on: 18 May 2022.
77. ISPE. Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. June 2015. Available from: https://www.pharmacoepi.org/resources/policies/guidelines-08027/. Accessed on: 03 August 2021.
78. ENCePP. Guide on methodological standards in pharmacoepidemiology (revision 9). July 2021. Available from: http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml. Accessed on: 30 July 2021.
79. MHRA. MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions. 16 December 2021. Available from: https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions. Accessed on: 14 March 2022.
80. ENCePP. ENCePP checklist for study protocols (revision 4). 15 October 2018. Available from: http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml. Accessed on: 30 July 2021.
81. ICH. Pharmacovigilance planning. E2E. 2004. Available from: https://database.ich.org/sites/default/files/E2E_Guideline.pdf. Accessed on: 03 August 2021.
82. European Commission. Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council. 20 June 2012. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF. Accessed on: 02 August 2021.
83. ENCePP. The European Union electronic Register of Post-Authorisation Studies (EU PAS Register). 2022. Available from: http://www.encepp.eu/encepp_studies/indexRegister.shtml. Accessed on: 14 March 2022.
84. ENCePP. The ENCePP seal. 28 July 2021. Available from: http://www.encepp.eu/encepp_studies/index.shtml. Accessed on: 02 August 2021.
85. ICMJE. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. May 2022. Available from: https://www.icmje.org/recommendations/. Accessed on: 9 March 2023.
86. ENCePP. The ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies (Revision 4). 15 March 2018. Available from: http://www.encepp.eu/code_of_conduct/. Accessed on: 02 August 2021.
87. Margulis AV, Kawai AT, Anthony MS, et al. Perinatal pharmacoepidemiology: how often are key methodological elements reported in publications? Pharmacoepidemiol Drug Saf. 2022;31(1):61-71.

88. AIFA. COVID-19 antiviral registration form. 2022. Available from: https://www.aifa.gov.it/documents/20142/1658003/Scheda_Registro_antivirali_COVID19_25.02.2022.zip. Accessed on: 06 April 2022.

14. LIST OF TABLES

Table 1. Study population 26
Table 2. Other EMA-approved drugs to treat COVID-19 29
Table 3. Dates for start of study period and end of data availability for each study report in each data source 36
Table 4. Study outcomes in the target population 37
Table 5. Identification of pregnancy-related outcomes and outcome-specific exposure windows 38
Table 6. Study feasibility: Paxlovid in European data sources/registries 42
Table 7. Main features of OpenSAFELY and CPRD Aurum 50
Table 8. Precision (95% confidence intervals) expected for proportions of Paxlovid users in the target population 53
Table 9. Study sizes needed for the upper limit of the risk ratio 95% confidence intervals to be below selected thresholds with a probability of 0.8 among pregnant women 54
Table 10. Small cell count rules for reporting results 63
Table 4-1. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19 89
Table 4-2. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19: conditions listed as disabilities 95

15. LIST OF FIGURES

Figure 1. Overview of the timing for covariate ascertainment 31
Figure 2. Data management plan 56

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Safety of Paxlovid During Pregnancy

EU PAS Register® number: EUPAS50117 **Study reference number (if applicable):** protocol number C4671037

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection*	☒	☐	☐	6
1.1.2 End of data collection†	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	4, 6
1.1.4 Interim report(s)	☒	☐	☐	4, 6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	4, 6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	Cover, 4, 7, 8
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9.1, 9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	4, 9.1, 9.2, 9.7
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	4, 9.1, 9.4
3.3 Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	4, 9.7

* Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

† Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section number**
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	4, 9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	4, 9.2.2
	4.2.2 Age and sex	☒	☐	☐	4, 9.1, 9.2.1
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	4, 9.1, 9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.1
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 9.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section number**
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	4, 9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	4, 9.1.1, 9.3.1

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4, 9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQOL, QALYs, DALYs, healthcare services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section number**
7.1	Does the protocol address ways to measure confounding? (eg, confounding by indication)	☒	☐	☐	4, 9.7
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	4, 9.1 9.2.1
7.3	Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3.2

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section number**
8.1	Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3, 9.4, Annex 4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section number**
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3, 9.4, Annex 4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3, 9.4, Annex 4
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3, 9.4
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.3, 9.4, Annex 4
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3, 9.4, Annex 4
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3, 9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3, 9.4, Annex 4
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4, 9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	4, 9.7
10.4 Are stratified analyses included?	☒	☐	☐	4, 9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	4, 9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6.5, 9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.3.2, 9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6, 9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	3, 9.1, 9.4, 9.5, Annex 4

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	0
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	4, 6, 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	4, 6, 12

Comments:

Main author of the protocol:	Andrea Margulis
Signature & date:	Andrea Margulis 21 June 2023

ANNEX 3. PERINATAL PHARMACOEPIDEMIOLOGY RESEARCH CHECKLIST

This checklist lists methods-related elements that are key in perinatal pharmacoepidemiology research. The columns for yes, no, or not applicable (N/A) reflect whether each element is specified in the present document. The column for section number reflects where in the document the element is specified (if applicable).

#	Element	Yes	No	N/A	Section number
Source of information on beginning and end of pregnancy					
1	Source of information for start of pregnancy (eg, electronic algorithm, ultrasound)	X			9.2.1
2	Source of information for pregnancy outcome date (eg, recorded codes for spontaneous abortion, date estimated using an algorithm)	X			9.2.1
Composition of the study population					
3	Multifoetal pregnancies included in study population?	X			9.2.1
4	More than 1 pregnancy per woman included in study population?	X			9.2.1
5	Foetuses with chromosomal abnormalities included in study population?	X			9.2.1
6	Foetuses with major malformations included in study population?	X			9.2.1
7	Foetuses with minor malformations included in study population?	X			9.2.1
8	Non-live births included in denominator?	X			9.7
Mother-infant and father-infant linkages					
9	If mother-infant linkage was implemented, was the process described?	X			9.2.1 9.4
10	If mother-infant linkage was implemented, was the success rate reported?			X	
11	If mother-infant linkage was implemented, was the information taken from maternal versus infant files?			X	
12	If father-infant linkage was implemented, was the process described?			X	
13	If father-infant linkage was implemented, was the success rate reported?			X	
Analytical aspects					
14	Unit of analysis for pregnancy outcomes		X		
15	Unit of analysis for foetal or infant outcomes		X		
16	Gestational age at start of follow-up		X		
17	Was intrafamily correlation considered?		X		
Comments: Mother-infant linkage was not yet implemented. The process has not been described in detail in this document. Father-infant linkage not needed in this study. Analytical aspects will be developed in the statistical analysis plan.					

N/A = not applicable.
Source: Margulis et al (87)

ANNEX 4. PRELIMINARY CODE LISTS TO IDENTIFY RISK FACTORS FOR PROGRESSION TO SEVERE COVID-19

This annex presents the risk factors for progression to severe COVID-19 as listed by the US Centers for Disease Control and Prevention (CDC (43)) under the titles "higher risk (conclusive)" and "suggestive higher risk". Preliminary ICD-10 and ATC code lists to identify these risk factors have been identified and listed in Table 4-1 and Table 4-2.

Identification of these risk factors will be based primarily on diagnosis codes; some drugs that are used specifically to treat the corresponding conditions will be used as proxies. Conditions that appear indented will be combined in the variable under which they are indented (eg, bronchiectasis, chronic obstructive pulmonary disease, and others will be combined as chronic lung disease). All conditions listed as disabilities in the source will be combined in a single variable denoting disabilities. When a code in Table 4-1 or Table 4-2 has 3 or 4 digits, all codes nested within the noted code will be included; eg, asthma includes ICD-10 code J45, so J45.1, J45.2, and J45.3 will also be used to identify asthma.

Table 4-1. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Asthma	J45 J46	Asthma Status asthmaticus	None	
Cancer	C00-C97	Malignant neoplasms	L01A L01B L01C L01X L01FB L01FC L01FD L01FE L01FF	Alkylating agents Antimetabolites Plant alkaloids and other natural products Other antineoplastic agents CD22 (Clusters of Differentiation 22) inhibitors CD38 (Clusters of Differentiation 38) inhibitors HER2 (Human Epidermal Growth Factor Receptor 2) inhibitors EGFR (Epidermal Growth Factor Receptor) inhibitors PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors
Cerebrovascular disease	G45 I61 I63 I64 I65 I66 I67.8 I67.9	Transient cerebral ischaemic attacks and related syndrome Intracerebral haemorrhage Cerebral infarction Stroke, not specified as haemorrhage or infarction Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction Other specified cerebrovascular diseases Cerebrovascular disease, unspecified	None	
Chronic kidney disease	N18.2 N18.3 N18.4 N18.5 N18.9	Chronic kidney disease, stage 2 Chronic kidney disease, stage 3 Chronic kidney disease, stage 4 Chronic kidney disease, stage 5 Chronic kidney disease, unspecified	None	
Chronic lung disease				
Bronchiectasis	J47 Q33.4	Bronchiectasis Congenital bronchiectasis	None	

Table 4-1. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)
COPD (chronic obstructive pulmonary disease)	J40	Bronchitis, not specified as acute or chronic	None
	J41	Simple and mucopurulent chronic bronchitis	
	J42	Unspecified chronic bronchitis	
	J43	Emphysema	
	J44	Other chronic obstructive pulmonary disease	
Interstitial lung disease	J84	Other interstitial pulmonary diseases	None
	J99.0	Rheumatoid lung disease	
	M05.1	Rheumatoid lung disease	
Pulmonary embolism	I26	Pulmonary embolism	None
Pulmonary hypertension	I27.0	Primary pulmonary hypertension	B01AC09 epoprostenol B01AC21 treprostinil C02KX01 bosentan C02KX02 ambrisentan C02KX03 sitaxentan C02KX04 macitentan C02KX05 riociguat C02KX52 ambrisentan and tadalafil C02KX54 macitentan and tadalafil
	I27.2	Other secondary pulmonary hypertension	
Chronic liver diseases			
Cirrhosis	I85	Oesophageal varices	None
	I98.2	Oesophageal varices without bleeding in diseases classified elsewhere	
	I98.3	Oesophageal varices with bleeding in diseases classified elsewhere	
	I86.4	Gastric varices	
	K71.1	Toxic liver disease with hepatic necrosis	
	K72.1	Chronic hepatic failure	
	K72.9	Hepatic failure, unspecified	
	K76.5	Hepatic veno-occlusive disease	
	K76.6	Portal hypertension	
	K76.7	Hepatorenal syndrome	
	K74.6	Other and unspecified cirrhosis of liver	
	K73	Chronic hepatitis, not elsewhere classified	
Non-alcoholic fatty liver disease	K76.0	Non-alcoholic fatty liver disease	None
Alcoholic liver disease	K70.9	Alcoholic liver disease unspecified	None
	K70.4	Alcoholic hepatic failure	
	K70.3	Alcoholic cirrhosis of liver	
Autoimmune hepatitis	K75.4	Autoimmune hepatitis	None

Table 4-1. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Cystic fibrosis	E84	Cystic fibrosis	R07AX02 R07AX30 R07AX31 R07AX32	ivacaftor ivacaftor and lumacaftor ivacaftor and tezacaftor ivacaftor, tezacaftor and elexacaftor
Type 1 or 2 diabetes	E10 E11 E12 E13 E14 O24.0 O24.1 O24.2 O24.3 G63.2 H36.0 N08.3	Type 1 diabetes mellitus Type 2 diabetes mellitus Malnutrition-related diabetes mellitus Other specified diabetes mellitus Unspecified diabetes mellitus Pre-existing type 1 diabetes mellitus Pre-existing type 2 diabetes mellitus Pre-existing malnutrition-related diabetes mellitus Pre-existing diabetes mellitus, unspecified Diabetic polyneuropathy Diabetic retinopathy Glomerular disorders in diabetes mellitus	A10	Drugs used in diabetes
Disabilities	Individual disabilities are listed separately in the table below			
Heart conditions				
Heart failure	I11.0 I13.0 I13.2 I50	Hypertensive heart disease with (congestive) heart failure Hypertensive heart and renal disease with (congestive) heart failure Hypertensive heart and renal disease with both (congestive) heart failure and renal failure Heart failure	C01A C01D B01A	Cardiac glycosides Vasodilators used in cardiac diseases Antithrombotic agents
Coronary artery disease	I20 I21 I22 I23 I24 I25 T82.2 Z95.1 Z95.5	Angina pectoris Acute myocardial infarction Subsequent myocardial infarction Certain current complications following acute myocardial infarction Other acute ischaemic heart diseases Chronic ischaemic heart disease Mechanical complication of coronary artery bypass and valve grafts Presence of aortocoronary bypass graft Presence of coronary angioplasty implant and graft		

Table 4-1. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Cardiomyopathies	I25.5	Ischaemic cardiomyopathy		
	I42	Cardiomyopathy		
	I43	Cardiomyopathy in diseases classified elsewhere		
	O90.3	Cardiomyopathy in the puerperium		
HIV infection	B20	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases	J05AE01	saquinavir
			J05AE02	indinavir
			J05AE03	ritonavir
	B21	Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms	J05AE04	nelfinavir
			J05AE05	amprenavir
			J05AE07	fosamprenavir
	B22	Human immunodeficiency virus [HIV] disease resulting in other specified diseases	J05AE08	atazanavir
			J05AE09	tipranavir
			J05AE10	darunavir
	B23	Human immunodeficiency virus [HIV] disease resulting in other conditions	J05AF01	zidovudine
			J05AF02	didanosine
			J05AF03	zalcitabine
	B24	Unspecified human immunodeficiency virus [HIV] disease	J05AF04	stavudine
			J05AF06	abacavir
			J05AG01	nevirapine
	O98.7	Human immunodeficiency virus [HIV] disease complicating pregnancy, childbirth and the puerperium	J05AG02	delavirdine
			J05AG03	efavirenz
			J05AG04	etravirine
			J05AG05	rilpivirine
			J05AG06	doravirine
			J05AR	all in chapter
Mental health conditions				
Mood disorders (including depression)	F30-F39	Mood [affective] disorders	None	
	F92.0	Depressive conduct disorder		
	F41.2	Mixed anxiety and depressive disorder		
Schizophrenia spectrum disorders	F20	Schizophrenia	None	
	F21	Schizotypal disorder		
	F22	Persistent delusional disorders		
	F23.1	Acute polymorphic psychotic disorder with symptoms of schizophrenia		
	F23.2	Acute schizophrenia-like psychotic disorder		
	F25	Schizoaffective disorders		
Neurological conditions: dementia	F00	Dementia in Alzheimer disease	None	
	F01	Vascular dementia		
	F02	Dementia in other diseases classified elsewhere		
	F03	Unspecified dementia		
	G31.0	Circumscribed brain atrophy, which includes frontotemporal dementia		
	G31.8	Other specified degenerative diseases of nervous system, which includes Lewy body(ies) (dementia) (disease)		

Table 4-1. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Obesity (BMI > 30)	E66	Obesity	A08AB A08AA	Peripherally acting anti-obesity products Centrally acting anti-obesity products
Physical inactivity	Will not be identified as a separate entity			
Pregnancy (current or recent)	Will not be identified as a separate entity			
Primary immunodeficiencies	D80 D81 D82 D83 D84	Immunodeficiency with predominantly antibody defects Combined immunodeficiencies Immunodeficiency associated with other major defects Common variable immunodeficiency Other immunodeficiencies	None	
Smoking (current or former)	F17 Z72.0	Mental and behavioral disorders due to use of tobacco Tobacco use	N07BA01 N07BA03 N07BA04	Nicotine Varenicline Cytisinicline
Solid organ or blood stem cell transplantation	Z94.0 Z94.1 Z94.2 Z94.3 Z94.4 T86.0 T86.1 T86.2 T86.3 T86.4 Y83.0	Kidney transplant status Heart transplant status Lung transplant status Heart and lungs transplant status Liver transplant status Bone-marrow transplant rejection Kidney transplant failure and rejection Heart transplant failure and rejection Heart-lung transplant failure and rejection Liver transplant failure and rejection Surgical operation with transplant of whole organ	None	

Table 4-1. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Tuberculosis	A15	Respiratory tuberculosis, bacteriologically and histologically confirmed	J04AC01	isoniazid
			J04AC51	isoniazid, combinations
			J04AD02	tiocarlide
	A16	Respiratory tuberculosis, not confirmed bacteriologically or histologically	J04AD03	ethionamide
			J04AK01	pyrazinamide
			J04AK02	ethambutol
	A17	Tuberculosis of nervous system	J04AK03	terizidone
	A18	Tuberculosis of other organs	J04AK04	morinamide
	A19	Miliary tuberculosis	J04AK05	bedaquiline
	B20.0	HIV disease resulting in mycobacterial infection	J04AK06	delamanid
			J04AK07	thioacetazone
	B90	Sequelae of tuberculosis	J04AK08	pretomanid
	J65	Pneumoconiosis associated with tuberculosis	J04AM01	streptomycin and isoniazid
			J04AM02	rifampicin and isoniazid
	K23.0	Tuberculous oesophagitis	J04AM03	ethambutol and isoniazid
	K67.3	Tuberculous peritonitis	J04AM04	thioacetazone and isoniazid
	K93.0	Tuberculous disorders of intestines, peritoneum and mesenteric glands	J04AM05	rifampicin, pyrazinamide and isoniazid
	M01.1	Tuberculous arthritis	J04AM06	rifampicin, pyrazinamide, ethambutol and isoniazid
	M49.0	Tuberculosis of spine		
	M90.0	Tuberculosis of bone	J04AM07	rifampicin, ethambutol and isoniazid
	N33.0	Tuberculous cystitis		
	N74.0	Tuberculous infection of cervix uteri	J04AM08	isoniazid, sulfamethoxazole, trimethoprim and pyridoxine
	N74.1	Female tuberculous pelvic inflammatory disease		
	P37.0	Congenital tuberculosis		
Use of immunosuppressive medications including corticosteroids	None		H02	Corticosteroids
			L04A	Immunosuppressants
Overweight (BMI > 25 but < 30)	Will not be identified as a separate entity		None	
Sickle cell disease	D57	Sickle-cell disorders	B06AX01	crizanlizumab
			B06AX03	voxelotor

Table 4-1. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Substance use disorders	F10	Mental and behavioural disorders due to use of alcohol	N07BB01	disulfiram
	F11	Mental and behavioural disorders due to use of opioids	N07BB02	calcium carbimide
	F12	Mental and behavioural disorders due to use of cannabinoids	N07BB03	acamprosate
	F13	Mental and behavioural disorders due to use of sedatives or hypnotics	N07BB05	nalmefene
	F14	Mental and behavioural disorders due to use of cocaine		
	F15	Mental and behavioural disorders due to use of other stimulants, including caffeine		
	F16	Mental and behavioural disorders due to use of hallucinogens		
	F18	Mental and behavioural disorders due to use of volatile solvents		
	F19	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances		

BMI = body mass index; HIV = human immunodeficiency virus; ICD-10 = *International Classification of Diseases, 10th Revision*.
Source of risk factors: CDC (43)

Table 4-2. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19: conditions listed as disabilities

At-risk medical conditions identified by diagnosis codes: disabilities	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)
Attention-deficit/hyperactivity disorder (ADHD)	Included in neurodevelopmental disorders		None
Autism	Included in neurodevelopmental disorders		None
Cerebral palsy	G80	Cerebral palsy	None
Charcot foot	M14.6	Neuropathic arthropathy	None
Chromosomal disorders	Q90-Q99		None
Chromosome 17 and 19 deletion	Included among chromosomal disorders		None
Chromosome 18q deletion	Included among chromosomal disorders		None
Cognitive impairment	None		None
Congenital hydrocephalus	Q03	Congenital hydrocephalus	None

Table 4-2. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19: conditions listed as disabilities

Congenital malformations	Major congenital malformations, will be defined as the study outcome major congenital malformations	None
Deafness/hearing loss	Z45.3 Adjustment and management of implanted hearing device H90 Conductive and sensorineural hearing loss Z46.1 Fitting and adjustment of hearing aid H91 Other hearing loss Z97.4 Presence of external hearing-aid	None
Disability indicated by Barthel Index	None	None
Down syndrome	Included among chromosomal disorders	None
Fahr's syndrome	G23.8 Other specified degenerative diseases of basal ganglia	None
Fragile X syndrome	Included among chromosomal disorders	None
Gaucher disease	E75.2 Other sphingolipidosis	A16AX10 eliglustat A16AX06 miglustat A16AB01 alglucerase A16AB02 imiglucerase A16AB11 taliglucerase alfa A16AB10 velaglucerase alfa
Hand and foot disorders	Will not be identified as a separate entity	None
Learning disabilities	Will not be identified as a separate entity	None
Leber's hereditary optic neuropathy (LHON) or autosomal dominant optic atrophy (ADOA)	H35.5 Hereditary retinal dystrophy H47.2 Optic atrophy	None
Leigh syndrome	G31.8 Other specified degenerative diseases of nervous system	None
Limitations with self-care or activities of daily living	Z73.6 Limitation of activities due to disability	None
Maternal inherited diabetes and deafness (MIDD)	Will not be identified as a separate entity	None
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and risk markers	Included in neuromuscular disorders Risk markers: not included	None
Mobility disability	Included in limitations with self-case	None
Movement disorders	R25 Abnormal involuntary movements R26 Abnormalities of gait and mobility R27 Other lack of coordination G20-26 Extrapyramidal and movement disorders F44.4 Dissociative motor disorders F98.4 Stereotyped movement disorders	None
Multiple disability (referred to in research papers as "bedridden disability")	Included in limitations with self-case	None

Table 4-2. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19: conditions listed as disabilities

Multisystem disease	Will not be identified as a separate entity	
Myoclonic epilepsy with ragged red fibres (MERRF)	Included in neuromuscular disorders	None
Myotonic dystrophy	Included in neuromuscular disorders	None
Neurodevelopmental disorders	F84 Pervasive developmental disorders F90 Hyperkinetic disorders	N06BA11 dexmethylphenidate N06BA15 dexmethylphenidate and serdexmethylphenidate N06BA04 methylphenidate N06BA02 dexamfetamine N06BA12 lisdexamfetamine N06BA09 atomoxetine C02AC02 guanfacine
Neuromuscular disorders	A05.1 Botulism G12 Spinal muscular atrophy and related syndromes G61 Inflammatory polyneuropathy G62 Other polyneuropathies G63 Polyneuropathy in diseases classified elsewhere G70 Myasthenia gravis and other myoneural disorders G71 Primary disorders of muscles G72 Other myopathies G73 Disorders of myoneural junction and muscle in diseases classified elsewhereG12 Spinal muscular atrophy and related syndromes M33.2 Polymyositis	N07XX02 riluzole N07XX14 edaravone N07AA02 pyridostigmine N07AA30 ambenonium M09AX07 nusinersen M09AX10 risdiplam M09AX03 ataluren M09AX08 golodirsen M09AX12 viltolarsen M09AX13 casimersen M09AX04 drisapersen M09AX06 eteplirsen
Neuromyelitis optica spectrum disorder (NMOSD)	G36.0 Neuromyelitis optica [Devic]	None
Neuropathy, ataxia, and retinitis pigmentosa (NARP)	None	None
Perinatal spastic hemiparesis	None	None
Primary mitochondrial myopathy (PMM)	Included in neuromuscular disorders	None
Progressive supranuclear palsy	G23.1 Progressive supranuclear ophthalmoplegia [Steele-Richardson-Olszewski]	None
Senior-Loken syndrome	Q61.5 Medullary cystic kidney	None
Severe and complex disability (referred to in research papers as “polyhandicap disability”)	Will not be identified as a separate entity	None
Spina bifida and other nervous system anomalies	Included in major congenital malformations	None

Table 4-2. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19: conditions listed as disabilities

Spinal cord injury	S14	Injury of nerves and spinal cord at neck level	None
	T09.3	Injury of spinal cord, level unspecified	
	S24	Injury of nerves and spinal cord at thorax level	
	S34	Injury of nerves and lumbar spinal cord at abdomen, lower back and pelvis level	
	P11.5	Birth injury to spine and spinal cord	
	T91.3	Sequelae of injury of spinal cord	
Tourette syndrome	F95.2	Combined vocal and multiple motor tic disorder [de la Tourette]	None
Traumatic brain injury	S02.0	Fracture of vault of skull	None
	S02.1	Fracture of base of skull	
	S02.7	Multiple fractures involving skull and facial bones	
	S02.8	Fractures of other skull and facial bones	
	S02.9	Fracture of skull and facial bones part unspecified	
	S04	Injury of cranial nerves	
	S06	Intracranial injury	
	S07.1	Crushing injury of skull	
	S07.8	Crushing injury of other parts of head	
	S07.9	Crushing injury of head part unspecified	
	S09.7	Multiple injuries of head	
	S09.8	Other specified injuries of head	
	S09.9	Unspecified injury of head	
	T02.0	Fractures involving head with neck	
	T04.0	Crushing injuries involving head with neck	
	T06.0	Injuries of brain and cranial nerves with injuries of nerves and spinal cord at neck level	
Visual impairment/ blindness	H54	Visual impairment including blindness (binocular or monocular)	None
Wheelchair use	Z99.3	Dependence on wheelchair	None
	Z46.8	Fitting and adjustment of other specified devices	

ICD-10 = *International Classification of Diseases, 10th Revision*.
Source of risk factors: CDC (43)

ANNEX 5. ADDITIONAL INFORMATION

Italian Medicines Agency (AIFA) registry for patients receiving COVID-19 oral antiviral agents, Italy

Based on the AIFA Determination published on O.J. n. 31 of 07 February 2022 (Paxlovid modality 1 in Section 9.4), selection of the patients who are eligible for treatment is entrusted to general practitioners and to any physicians in contact with the patient (including local home-caring units). Such physicians are only in charge of selecting and referring patients to a number of specified centres identified by the local administrative districts in each of the 20 regions. Prescription of the product is limited to the physicians working within these centres (any specialty) where the product can also be dispensed to the patient.

A registry monitoring form[88] should be completed for each patient, as per AIFA requirement. The eligibility criteria in the registry are the same for COVID-19 oral antiviral agents (Paxlovid and molnupiravir [Merck]). The patient needs to present with at least 1 of the following risk factors associated with possible progression to severe disease:

- Active oncologic/onco-haematologic disease
- Chronic kidney failure
- Severe bronchopneumopathy
- Primary or acquired immunodeficiency
- Obesity (body mass index ≥ 30)
- Severe cardiovascular disease (heart failure, coronary disease, cardiomyopathy)
- Decompensated diabetes mellitus

Document Approval Record

Document Name:	C4671037_PROTOCOL AMENDMENT 3_V4_21JUN2023
Document Title:	C4671037_PROTOCOL AMENDMENT 3_V4_21JUN2023

Signed By:	Date(GMT)	Signing Capacity
Younus, Muhammad	23-Jun-2023 13:35:40	Final Approval
De Bernardi, Barbara	23-Jun-2023 21:14:45	EUQPPV Approval