NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Use and Safety of Paxlovid Among Patients with Moderate or Severe Hepatic or Renal Impairment
Protocol number	C4671047
Protocol version identifier	Protocol V1.0
Date	16 November 2022
EU Post-Authorisation Study (PAS) register number	Study will be registered before start of data collection
Active substance	Combination of the oral protease inhibitors nirmatrelvir and ritonavir (ATC code J05AE30)
Medicinal product	Paxlovid
Product reference	PF 07321332/ritonavir
Procedure number	Conditional marketing authorisation EMEA/H/C/005973/0000
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 2 research questions are:
	• What is the comparative safety of liver, abdominal, anaphylactic reactions, and other outcomes, in patients with moderate or severe hepatic impairment exposed to Paxlovid?
	• What is the comparative safety of abdominal, anaphylactic reactions, and other outcomes, in patients with moderate or severe renal impairment exposed to Paxlovid?
	For the population of individuals with moderate or severe hepatic impairment the primary objective is:
	• To assess the safety of Paxlovid relative to the comparator populations who used molnupiravir for COVID-19 and to unexposed patients with COVID-19 with respect to hospitalisations or emergency room visits for the following:
	  • Hepatic transaminase elevations, clinical hepatitis, or jaundice
	  • Severe vomiting, nausea, diarrhoea, or abdominal pain
	  • Dysgeusia, headache, or hypertension
	  • Anaphylactic reactions
	For the population of individuals with moderate or severe renal impairment the primary objective is:
	• To assess the safety of Paxlovid relative to the comparator population who used molnupiravir for COVID-19 and to unexposed patients with COVID-19 with respect to hospitalisations or emergency room visits for the following:
	  • Severe vomiting, nausea, diarrhoea, or abdominal pain
	  • Dysgeusia, headache, or hypertension
	  • Anaphylactic reactions

Countries of study	• France • Spain • United Kingdom • Other countries in Europe are under evaluation

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Marketing Authorisation Holder

Marketing Authorisation Holder	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEMPS	Spanish Medicines Agency of Medicines and Medical Devices [Agencia Española de Medicamentos y Productos Sanitario]
AIFA	Italian Medicines Agency [Agenzia Italiana del Farmaco]
ALD	List of chronic conditions registered in France [Affections de Longue Durée]
ALT	alanine aminotransferase
ARS Toscana	Regional Health Agency of Tuscany, Italy [Agenzia Regionale di Sanità della Toscana]
ASSIR	Sexual and Reproductive Health Care Assistance [Assistència a la Salut Sexual i Reproductiva] (Catalonia, Spain)
BIFAP	Pharmacoepidemiological Research Database for Public Health Systems [Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària] (Spain)
ATC	Anatomical therapeutic chemical (classification system)
CDM	Common data model
CESREES	Ethical and Scientific Committee for Research, Studies and Evaluations in the Field of Health [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
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMA	Conditional marketing authorisation
CMU-C	Couverture médicale universelle complémentaire (France)
CNAM	National Health Insurance Fund [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)

Abbreviation	Definition
DRE	Digital Research Environment
eGFR	Estimated glomerular filtration rate
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
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-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
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
KDIGO	Kidney Disease: Improving Global Outcomes
KM	Kaplan-Meier
MAH	Marketing Authorisation Holder
MELD	Model for End-Stage Liver Disease
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
NHS	National Health Service
NI	Non-interventional

Abbreviation	Definition
ONS	Office for National Statistics
PASS	Post-authorisation safety study
PMSI	National hospital discharge summaries database system (France)
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
PY	Person-year
Q*n* yyyy	Quarter of the calendar year
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]
SNOMED CT	Systemized 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 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

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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.

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4. ABSTRACT

Title

Use and Safety of Paxlovid Among Patients with Moderate or Severe Hepatic or Renal Impairment

- Protocol version 1.0, 16 November 2022
- Main author: Manel Pladevall-Vila, RTI Health Solutions, on behalf of the SIGMA Paxlovid 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 and in individuals with hepatic or renal impairment is not known. Assessing the safety 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). Assessing the safety of Paxlovid among individuals with moderate or severe hepatic or renal impairment is a regulatory commitment to the EMA.

This protocol describes a PASS to assess the safety of Paxlovid in individuals with moderate or severe hepatic or renal impairment in European countries with data sources that can capture exposure and where the target populations, outcomes and key covariates can be ascertained.

Research question and objectives

The 2 research questions are:

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

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

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

- Dysgeusia, headache, or hypertension
- Anaphylactic reactions

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

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

Study design

The study will focus on the target populations. Within each 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 for 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 who were at increased risk for progression to severe COVID-19 but had not received Paxlovid or molnupiravir.

This PASS will make secondary use of several data sources from electronic health records and/or claims data in European countries that have the ability to capture Paxlovid exposure and where the target populations, study outcomes, and key covariates can be ascertained. The study period will start on 01 January 2022 (in alignment with regulatory authorisation and launch in Europe) and end as late as possible, with latest data extraction estimated for quarter 1 2025.

Reports to the EMA will include a progress report with a description of project startup and subsequent activities, a description of the evolution of aspects that have been identified as key challenges for this study, and the list of data sources (per an ongoing feasibility assessment of Paxlovid distribution channels in various countries); 2 annual interim reports with the results of a feasibility assessment that will include the number of Paxlovid-exposed individuals overall and in each target study population, selected characteristics of each exposure group, and preliminary outcome counts; a final report; and, if applicable, a paediatric report 6 months after the end of data collection for the final report.

Population

The target study populations will be individuals with COVID-19 who used Paxlovid or comparator drug molnupiravir, and individuals who were at increased risk for progression to severe COVID-19 but had not received Paxlovid or molnupiravir (the *unexposed comparison group*), while they belong to either of the following subgroups: individuals with moderate or severe hepatic impairment or individuals with moderate or severe renal impairment. For

these populations, follow-up will end at the earliest of 6 months after cohort entry, death, disenrollment/migration, or end of data availability; follow-up for each outcome will end at the occurrence of the given outcome.

Variables

The exposures will be Paxlovid and the comparator molnupiravir, both of 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, and others. Planned outcomes for each target population are as follows:

- For the population with hepatic impairment, hospitalisations or emergency room visits for the following:
  - Hepatic transaminase elevations, clinical hepatitis, or jaundice
  - Severe vomiting, nausea, diarrhoea, or abdominal pain
  - Dysgeusia, headache, or hypertension
  - Anaphylactic reaction
- For the population with renal impairment, hospitalisations or emergency room visits for the following:
  - Severe vomiting, nausea, diarrhoea, or abdominal pain
  - Dysgeusia, headache, or hypertension
  - Anaphylactic reactions

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, and others.

Data sources

As of 30 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. 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 appear 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 is proposed for exploration as a supplementary data source. The AIFA patient registry is proposed for exploration as a source for the feasibility component in Italy.

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

In this study, the duration of the observation period is bound by the dates for producing regulatory reports. All individuals meeting eligibility criteria during the study observation period will be included. As the summaries of product characteristics (SmPCs) caution or contraindicate use in severe hepatic or renal impairment, Paxlovid exposure in these populations is anticipated to be small.

Data analysis

The study will have a cohort design; the design is retrospective, and the data were collected prospectively. Focusing on the target populations, the descriptive component 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 (actual; including pregnant population, population with moderate or severe hepatic impairment, and population with moderate or severe renal impairment in a single document)
- Final CHMP/Pharmacovigilance Risk Assessment Committee (PRAC) feedback: 15 September 2022 (actual)
- Protocol C4671047 V1.0 submission: November 2022 (planned; population with moderate or severe hepatic impairment and population with moderate or severe renal impairment)
- Regulatory protocol endorsement anticipated: Quarter 1 or quarter 2 2023
- Registration in the European Union (EU) PAS Register: Study will be registered prior to start of data collection[a]
- Progress report submission: November 2022 (planned)
- Regulatory protocol endorsement anticipated: quarter 1 or quarter 2 of 2023 (planned)
- Start of data collection: quarter 4 2023 (planned)[a]
- Interim report 1: 12 months after protocol endorsement; estimated for quarter 2 2024[b] (planned)
- Interim report 2: 24 months after protocol endorsement; estimated for quarter 2 2025[b] (planned)
- End of data collection: quarter 2 2025[b] (planned)
- Paediatric study report (as applicable if Paxlovid is used by individuals with moderate or severe hepatic or renal impairment younger than 18 years old[4]): 6 months after the end of data collection for the final report [a] (planned)
- Final study report: 28 November 2025[b] (planned)

[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.

[b] Protocol endorsement from EMA is expected in quarter 1 or quarter 2, 2023. Milestones will be updated once protocol endorsement date is known.

5. AMENDMENTS AND UPDATES

The Paxlovid PASS programme includes study "Use and Safety of Paxlovid During Pregnancy" (C4671037) and study "Use and Safety of Paxlovid Among Patients with Moderate or Severe Hepatic or Renal Impairment" (C4671047). This programme was initially described in a single protocol (C4671037 version 1.0). EMA´s feedback in August-September 2022 resulted in the split of the programme into its 2 current studies, each with a separate protocol. This is the first version of protocol C4671047.

None

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)
Final CHMP/PRAC feedback	15 September 2022 (actual)
Protocol C4671047 V1.0 submission	November 2022 (population with moderate or severe hepatic impairment, and population with moderate or severe renal impairment)
Regulatory protocol endorsement anticipated	Quarter 1 or quarter 2 of 2023
Registration in the EU PAS Register	Study will be registered prior to start of data collection
Progress report submission	November 2022
Regulatory protocol endorsement	Quarter 1 or quarter 2 of 2023
Start of data collection[a]	Quarter 4 2023[b]
Interim report 1	12 months after protocol endorsement; estimated for quarter 2 2024[b]
Interim report 2	24 months after protocol endorsement; estimated for quarter 2 2025[b]
End of data collection[a]	Quarter 2 2025[b]
Paediatric study report (as applicable if Paxlovid is used by individuals with moderate or severe hepatic or renal impairment younger than 18 years old[4])	6 months after the end of data collection for the final report[a]
Final study report	28 November 2025[b]

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 1 or quarter 2 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 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.[5]

The safety of Paxlovid in pregnant women and in individuals with hepatic or renal impairment is not known. Assessing the safety of Paxlovid in pregnant women is a regulatory commitment to the EMA and the UK MHRA. Assessing the safety of Paxlovid among individuals with moderate or severe hepatic or renal impairment is a regulatory commitment to the EMA.

This protocol describes a PASS to assess the safety of Paxlovid in individuals with moderate or severe hepatic or renal impairment in European countries with data sources that can capture exposure and where the target populations, outcomes and key covariates can be ascertained. The study will discuss findings in EU populations in the context of the EU SmPC and findings in the UK in the context of the UK SmPC. This non-interventional study is designated as a PASS and is a commitment to EMA.

7.1. Authorisations

On 22 December 2021, the United States Food and Drug Administration (FDA) issued an Emergency Use Authorization for Paxlovid.[6] On 31 December 2021, the UK MHRA issued a conditional marketing authorisation (CMA) for Paxlovid in Great Britain and a temporary Regulation 174 authorisation for Northern Ireland to ensure supply across all the UK.[7] 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.[8] When the EMA granted a CMA for Paxlovid, it applied in Northern Ireland, and the Regulation 174 authorisation is no longer in place.

7.2. EU 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."[9] 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.

Recommendations for special populations include reducing the dose for patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 to < 60 mL/min). Caution should be exercised when administering Paxlovid to patients with preexisting liver disease, liver enzyme abnormalities, or hepatitis; no dose adjustment is

needed for patients with mild or moderate hepatic impairment (Child-Pugh class A or B). Patients with severe hepatic impairment and patients with severe renal impairment (eGFR < 30 mL/min, including patients with end-stage kidney disease undergoing haemodialysis) should not use Paxlovid.

7.3. United Kingdom summary of product characteristics

The indication of Paxlovid in the 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,"*[10] like in the EU.

Recommendations related to dose adjustment in individuals with renal or hepatic impairment are similar to those in the EU; however, in the UK, Paxlovid is contraindicated in individuals with severe hepatic or renal impairment.

7.4. What is known

Fifteen persons on dialysis with COVID-19 received Paxlovid in a modified (lowered) dosing regimen consisting of 300 mg nirmatrelvir + 100 mg ritonavir on day 1, and 150 mg nirmatrelvir + 100 mg ritonavir once daily for the next 4 days, after dialysis.[11] The authors reported rapid symptom resolution with no safety signals.

In a study of Paxlovid pharmacokinetics conducted in 4 patients diagnosed with COVID-19 and end-stage renal disease and on haemodialysis (in 2- to 3-day intervals), use of Paxlovid resulted in high blood concentrations of nirmatrelvir, but still within the known range in patients without renal failure. Nirmatrelvir did not accumulate, and levels declined to 0 a few days after end of treatment.[12]

Elevated liver function test results are common among patients with COVID-19[13,14] and the combination of lopinavir-ritonavir in patients with COVID-19 has been found to be associated with drug-induced liver injury in a disproportionality analysis of the FDA adverse event reporting system[15] and in 1 observational study.[14] Other observational studies on different protease inhibitors have identified worsening of liver function as a serious adverse event among patients with chronic liver disease.[16-18]

8. RESEARCH QUESTION AND OBJECTIVES

The 2 research questions are:

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

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

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

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

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

9. RESEARCH METHODS

9.1. Study design

The study populations are described in Table 1.

Table 1. Study populations

Study population	General description
Individuals with moderate or severe hepatic impairment and have COVID-19	Hepatic impairment will be ascertained from coded diagnoses and procedures, plus laboratory values if available. Included in the study will be users of Paxlovid, users of the comparator medication molnupiravir, and the unexposed individuals who are at increased risk for progression to severe COVID-19.
Individuals with moderate or severe renal impairment and have COVID-19	Renal impairment will be ascertained from coded diagnoses and procedures, plus laboratory values if available. Included in the study will be users of Paxlovid, users of the comparator medication molnupiravir, and the unexposed individuals who are at increased risk for progression to severe COVID-19.

The study will have a cohort design. For both components, the study will make secondary use of multiple sources of data from electronic health records and/or claims data in European countries. Data sources currently selected can 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 populations, separately for Paxlovid users, users of molnupiravir, and the unexposed

comparator group. Relevant patient characteristics will be presented for each exposure group in each 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[19] (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: individuals who were at increased risk for progression to severe COVID-19 and had not received Paxlovid, molnupiravir, or any other antiviral treatment. Challenges are discussed in Section 9.9. Strategies to reduce confounding will be applied. Briefly, individuals in each target population will be described, and safety outcomes will be assessed in comparative analyses. 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 startup 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 interim reports with results of the feasibility component (described previously) and preliminary outcome counts; a final report with the results of the safety component; and, if applicable (i.e., if patients with moderate or severe hepatic or renal impairment younger than 18 years old[4] use Paxlovid) a paediatric report 6 months after the end of data collection for the final report.

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.[19] 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.[19] Some countries in the EU, eg, Italy, have made it available for use,[20] and the Spanish Health Agency included it among available treatment options.[21] Molnupiravir was approved by the MHRA in the UK in November 2021.[22] The approved indication is consistent with the language in EMA's advice described above.[23]

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.[24] Channelling of patients with liver or kidney disease towards molnupiravir treatment will be addressed analytically.

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	Hepatic Impairment	Renal Impairment	Comments
Remdesivir[25]	• 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	Safety in the population with hepatic impairment is not known; use is not discouraged in the SmPC	Should not be used in patients with eGFR < 30 mL/min	• 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[26]	• 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[26] or intravenous[27]	Not anticipated to substantially affect the metabolism of this product	Not anticipated to substantially affect the metabolism of this product	• 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[28]	• 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 progression to severe respiratory failure determined by plasma levels ≥ 6 ng/mL of soluble urokinase plasminogen activator receptor • Subcutaneous injection	No dose adjustment if moderate impairment (Child-Pugh Class B); caution if severe hepatic impairment	• No dose adjustment if mild impairment; caution if moderate impairment • If eGFR < 30 mL/min or end-stage renal disease, including dialysis, consider using every other day	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[29]	• 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	Not mentioned in SmPC	Not anticipated to substantially affect the metabolism of this product	Intravenous medications are expected to be not well captured in the proposed data sources

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

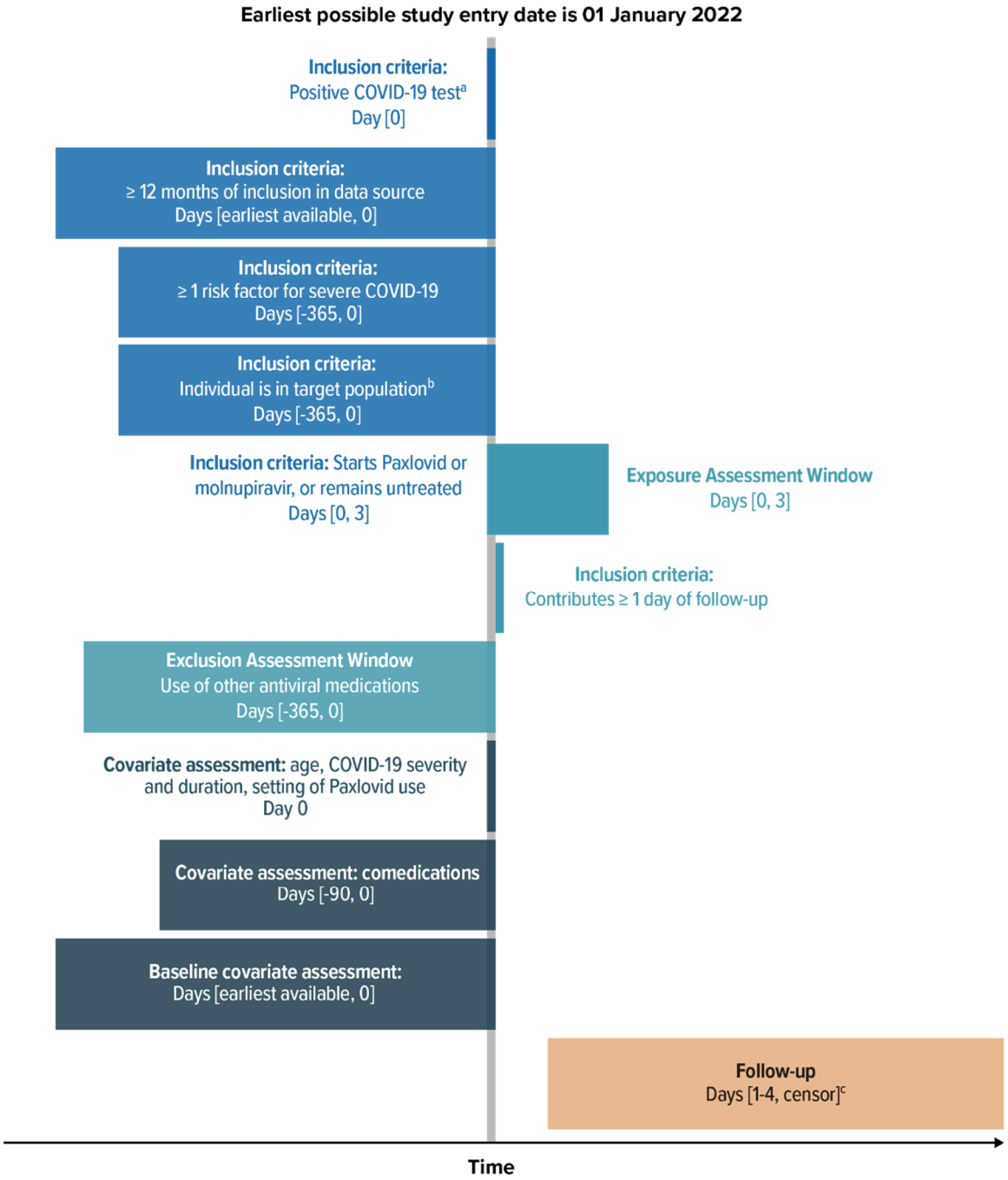
Drug	Indication and mode of administration	Hepatic Impairment	Renal Impairment	Comments
Tocilizumab[30]	• Rheumatoid arthritis, juvenile idiopathic polyarthritis, and other conditions • Treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation • Intravenous infusion	• Dose adjustment needed if liver transaminases are elevated in patients with rheumatoid arthritis • Treatment has been associated with elevation of hepatic transaminases • Serious drug-induced liver injury has been observed.	Mild impairment did not impact pharmacokinetics	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[31]	• 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	Not expected to undergo significant hepatic elimination	Not expected to undergo significant renal elimination	• 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[32]	• 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	No dose adjustment needed	No dose adjustment needed	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/treatments-.vaccines/covid-19-treatments. Accessed 06 October 2022

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. Graphical representation of study design



a. Including positive test, documented diagnosis or documented entry in a COVID-19 registry, reflecting a case of COVID-19 diagnosis.
b. Target populations: (a) moderate or severe hepatic impairment, (b) moderate or severe renal impairment.
c. Follow-up for both populations will start from day 1 (1 day after time 0) through day 4, depending on which day exposure starts, and end at the earliest of 6 months after starting treatment, death, disenrollment or migration, end of data availability, or treatment group crossover. Treatment crossover will occur when unexposed patients start treatment with either Paxlovid or molnupiravir; or when molnupiravir patients start treatment with Paxlovid. Patients on treatment with Paxlovid will not be censored even if they later start another treatment (molnupiravir or any of the drugs listed in Table 2).

Note: The unexposed comparison group will be identified from among the individuals that are at increased risk for progression to severe COVID-19 and also meet the other inclusion criteria.
Figure based on Schneeweiss et al. (2019).[33]

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

9.2.1.1. Individuals with moderate or severe hepatic impairment

Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Having documented COVID-19
2. Having moderate or severe hepatic impairment at the time of COVID-19 diagnosis; the first instance when this happens will be the only possible instance in the study
3. Being at increased risk for severe COVID-19
4. Having at least 12 months of inclusion in the data source at the time of starting the study medications or becoming eligible
5. Having at least 1 day of follow-up
6. Having started treatment with Paxlovid or comparator medication within 3 days of meeting all eligibility criteria or did not start those treatments during that period

Exclusion criterion

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

1. Using any of the medications listed in Table 2 in the previous 365 days and including time 0 (see below for definition of time 0)

After applying the eligibility criteria, the target population will include individuals starting Paxlovid or molnupiravir during the study period, and unexposed individuals.

Time 0 will be the day on which an individual meets all eligibility criteria; they will have 3 days to start the first-time treatment with Paxlovid or molnupiravir (this is often described as a grace period). Unexposed individuals will be matched with individuals starting Paxlovid by time since COVID-19 diagnosis (days) and calendar time (within ± 1 week). Paxlovid and molnupiravir users will be matched on calendar time. Matching at this stage has the objective of increasing comparability of the various treatment groups with regard to time since start of disease and calendar time (calendar time is a proxy for prevalence of circulating variants, preferred therapeutic approaches, etc.).

Follow-up

Follow-up will start from day 1 (1 day after time 0 if they start treatment on day 0) through day 4 (1 day after day 3 if they start treatment on day 3), depending on which day exposure or unexposure (via matching) starts, and end at the earliest of 6 months after starting treatment, death, disenrollment or migration, end of data availability from the data source, or treatment group crossover. *Treatment crossover* is defined in this study as the situation in which individuals who entered the study as unexposed start treatment with Paxlovid or molnupiravir, and when molnupiravir users start treatment with Paxlovid. Patients on treatment with Paxlovid will not be censored even if they start another treatment (molnupiravir or any of the drugs listed in Table 2). Follow-up for each outcome will end at the occurrence of the given outcome.

Identification of hepatic impairment

Hepatic impairment will be ascertained in the 12 months before (and including) time 0.

Taking into consideration that laboratory test results are not available in SNDS (Section 9.4), individuals will be considered to be in this target population if they have a diagnosis code that matches the category of moderate or severe hepatic disease according to the Charlson comorbidity index revised by Glasheen et al.[34], which has shown to correlate with inpatient admissions and mortality rates.[34] The diseases and conditions included in the Charlson category of moderate or severe hepatic disease include the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) or the International Classification of Diseases, Tenth Revision (ICD-10) disease codes listed in Table 3.

Table 3. ICD-10-CM [ICD-10] codes to identify moderate or severe hepatic impairment

ICD-10-CM code [ICD-10 code if different or fifth digit not available in ICD-10]	Description
I85.0x [I85.x] [I98.2] [I98.3]	Oesophageal varices
I86.4	Gastric varices
K70.4x [K70.4]	Alcoholic hepatic failure
K71.1x [K71.1]	Toxic liver disease with hepatic necrosis
K72.1x [K72.1]	Chronic hepatic failure
K72.9x [K72.9]	Hepatic failure, unspecified
K76.5	Hepatic veno-occlusive disease
K76.6	Portal hypertension
K76.7	Hepatorenal syndrome

In data sources where laboratory results are available (SIDIAP and the CPRD have outpatient laboratory test results), severe chronic liver disease could be measured by a Model for End-Stage Liver Disease (MELD) score greater than 24.[35] Although there have been efforts to derive Child-Pugh scores from electronic healthcare data sources with identifiable rich clinical data,[36] that type of data is not available in the data sources proposed for this study. The Child-Pugh score requires data with enough granularity to differentiate clinical levels of severity for ascites and encephalopathy.[37] However, in each data source, the additional use of

procedural codes or treatments for ascites and encephalopathy will be explored to improve the identification of the target population.

9.2.1.2. Individuals with moderate or severe renal impairment

Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Having documented COVID-19
2. Having moderate or severe renal impairment at the time of COVID-19 diagnosis; the first instance when this happens will be the only possible instance in the study
3. Being at increased risk for severe COVID-19
4. Having at least 12 months of inclusion in the data source at the time of starting the study medications or becoming eligible
5. Having at least 1 day of follow-up
6. Having started treatment with Paxlovid or comparator medication within 3 days of the COVID-19 diagnosis or did not start those treatments during that period

Exclusion criterion

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

1. Using any of the medications listed in Table 2 in the previous 365 days and including time 0 (see below for definition of time 0)

After applying the eligibility criteria, the target population will include individuals starting Paxlovid or molnupiravir during the study period, and unexposed individuals.

Time 0 will be the day on which an individual meets all eligibility criteria; they will have 3 days to start the first-time treatment with Paxlovid or molnupiravir (this is often described as a grace period). Unexposed individuals will be matched with individuals starting Paxlovid by time since COVID-19 diagnosis (days) and calendar time (within ± 1 week). Paxlovid and molnupiravir users will be matched on calendar time. Matching at this stage has the objective of increasing comparability of the various treatment groups with regard to time since start of disease and calendar time (calendar time is a proxy for prevalence of circulating variants, preferred therapeutic approaches, etc.).

Follow-up

Follow-up will start from day 1 (1 day after time 0 if they start treatment on day 0) through day 4 (1 day after day 3 if they start treatment on day 3), depending on which day exposure or unexposure (via matching) starts, and end at the earliest of 6 months after starting treatment, death, disenrollment or migration, end of data availability from the data source, or treatment group crossover. *Treatment crossover* is defined in this study as the situation in which individuals who entered the study as unexposed start treatment with Paxlovid or molnupiravir, and when molnupiravir users start treatment with Paxlovid. Patients on treatment with Paxlovid will not be censored even if they start another treatment

(molnupiravir or any of the drugs listed in Table 2). Follow-up for each outcome will end at the occurrence of the given outcome.

Identification of renal impairment

Renal impairment will be ascertained in the 12 months before (and including) time 0.

Because laboratory results are not available in SNDS and are available only for outpatient visits in CPRD and SIDIAP (Section 9.4), diagnosis codes will also be used to identify patients with moderate or severe renal impairment. The ICD-10 codes listed in Table 4 will be used and have been proposed to identify severe and moderate renal disease as part of the Charlson Comorbidity Index by Ludvigsson et al.[38] Patients will be selected into the cohort if they have 2 different occurrences of those codes separated by at least 90 days. The ICD-10 codes will be adapted to the specific disease coding system used in each data source. There is evidence in the literature that algorithms based on diagnosis codes that are used to identify patients with moderate or severe renal impairment are not sensitive.[39,40] Therefore, in the data sources without laboratory results, it is likely that a large proportion of patients will not be captured (see Section 9.9, Limitations of the research methods).

Table 4. ICD-10 codes to identify moderate or severe renal impairment

ICD-10- code	Description
I12.0	Hypertensive renal disease with renal failure
I13.1	Hypertensive heart and renal disease with renal failure
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
N03.2 – N03.7	Chronic nephritic syndrome
N05.2-N05.7	Unspecified nephritic syndrome
N11	Chronic tubulo-interstitial nephritis
N18.3	Chronic kidney disease, Stage 3 (moderate)
N18.4	Chronic kidney disease, Stage 4 (severe)
N18.5	Chronic kidney disease, Stage 5 (end-stage renal disease)
N18.9	Chronic kidney disease, unspecified
N19.x	Unspecified kidney failure
N25.0	Renal osteodystrophy
Q61.1-Q61.3	Polycystic kidney disease
Z94.0	Kidney transplant status
Z49.x	Care involving dialysis
Z99.2	Dependence on renal dialysis

In data sources where laboratory results are available (SIDIAP and CPRD), individuals will also be considered to be in this target population if they have 2 eGFR test results < 60 mL/min/1.73 m^2—taken from Levey et al.[41]—separated by at least 90 days (with no normal values in between) but not more than 540 days.

The eGFR will be defined using eGFR as recorded in the data source either by diagnosis codes or laboratory results. If eGFR is not recorded in the data source, it will be derived from creatinine levels using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,[42] which removes the race-related coefficient, following recommendations from recent evidence and guideline statements:[43-46]

$eGFR = 142 \times \min(Scr/\kappa, 1)^{a1} \times \max(Scr/\kappa, 1)^{a2} \times c^{Age} \times d$ [if female]

Where:

- Scr is serum creatinine concentration
- $a_1 = -0.241$ for females and -0.302 for males
- $a_2 = -1.200$
- $c = 0.9938$
- $d = 1.012$
- κ is 0.7 for female participants and 0.9 for male participants; min indicates the minimum of Scr/κ and 1, and max indicates the maximum of Scr/κ and 1
- The exponent a_1 is used for levels of creatinine $\leq$ 0.9 mg/dL for male participants and $\leq$ 0.7 mg/dL for female participants
- The exponent a_2 is used for levels of creatinine > 0.9 mg/dL for male participants and > 0.7 mg/dL for female participants

Definitions for CKD stages are based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[41,47] Currently, albuminuria levels are also used to stratify levels of renal impairment,[47] but clinicians often use dipstick measurements, which are not captured in most data sources. For that reason, we propose using only eGFR for staging in this study.

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, with final data extraction estimated for quarter 1 2025.

Table 5 shows the anticipated dates during which data will be observed for each study report.

Table 5. 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	Q4 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

a In CPRD Aurum, HES linkage is required. As of August 2022, 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
Note: Interim report 1 has an anticipated data cut in Q4 2023; interim report 2, in Q4 2024; final report, in Q1 2025.

9.2.3. Outcome risk window of interest

For Paxlovid, molnupiravir, and unexposed patients, the main risk window for outcome ascertainment will be the first month after the start of follow-up. As mentioned in Section 8,

there is concern that the safety outcomes may be related to overexposure to Paxlovid due to the underlying liver and/or hepatic impairment in the target population. Treatment duration is short (5 days) and it is assumed that the risk of overexposure will not go beyond 1 month after starting the treatment. However, risk windows of 3 and 6 months will also be considered for outcomes that may have longer or unknown risk windows (eg, acute liver injury).

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. There will be 2 comparison groups: active comparator molnupiravir and no treatment with either Paxlovid or molnupiravir (unexposed).

9.3.2. Outcomes

The outcomes will be those listed in Table 6. They will be ascertained using coded diagnoses, procedures, medical product prescriptions or dispensing, and information collected in other data banks in the selected data sources. 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, i.e., the electronic information ordered chronologically, could be reviewed. To ascertain sensitivity, and in particular differential sensitivity, random samples of 'possible' cases might be reviewed.

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. For example, after use of the study drug or comparator, the first hospitalisation for a hepatic event will be a study outcome and will determine the end of follow-up for this outcome; later hospitalisations for hepatic events will not be included. For combined endpoints (eg, hospitalisations or emergency room visits for dysgeusia, headache, or hypertension), only the first occurrence of any of the components of the outcome will be ascertained. However, the frequency of the different components of the combined endpoint that determine the first event will be described.

Table 6. Study outcomes in each target population

Study population	Study outcomes
Hepatic impairment population	Hospitalisation or emergency room visit for • Hepatic transaminase elevations, clinical hepatitis, or jaundice • Severe vomiting, nausea, diarrhoea, or abdominal pain • Dysgeusia, headache, or hypertension • Anaphylactic reactions
Renal impairment population	Hospitalisation or emergency room visit for: • Severe vomiting, nausea, diarrhoea, or abdominal pain • Dysgeusia, headache, or hypertension • Anaphylactic reactions

9.3.3. Other variables

In addition, the following study variables will be included:

- Demographics
- Comorbidities and characteristics that will be quantified to identify increased risk for progression to severe COVID-19, including cancer diagnoses or treatments, CKD, chronic liver disease, chronic respiratory disease, cardiovascular or cerebrovascular disease, obesity, Down syndrome, mental health conditions, sickle-cell disease, diabetes, human immunodeficiency virus (HIV) infection and use of immunosuppressants.[48] Increased risk for severe COVID-19 will be ascertained in the 12 months before and including time 0.
- 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 bullet point (acknowledging that prescribing physicians may not base their assessment on exactly these variables).
- Comedications, including medications listed as contraindicated or with potentially significant interactions with Paxlovid in the EU SmPC,[9] Section 7.3 and Table 1, or the UK SmPC,[10] 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 30 September 2022, the MAH confirmed that Paxlovid has been supplied to France, Germany, Italy, Spain, Slovenia, Sweden, and the UK, initially or continuing under special government contracts, resulting in different distribution and reimbursement channels being used and subsequent challenges capturing its prescription and distribution. Current information is that prescribed/dispensed Paxlovid should be captured in existing electronic population data sources in France, Spain, and the UK. Currently, the proposed data sources are SNDS (France), SIDIAP (Catalonia, Spain), and CPRD Aurum (UK). Exposure counts are presented in Table 7.

Table 7. Study feasibility: Paxlovid distribution in Europe

Country	Capture in data sources
France	Medic'AM: 12,634 dispensed boxes in February-June 2022 EPI-PHARE report: 12,179 individuals received Paxlovid between 04 February and 29 June 2022[49]
Germany	Not available
Italy	AIFA: 81,709 treatments as of 2 November 2022
Slovenia	Not available
Spain	SIDIAP (includes only region of Catalonia in Spain): 353 Paxlovid prescriptions for 339 individuals from 07 April to 30 June 2022
Sweden	Not available at this point
United Kingdom	CPRD Aurum: 400 prescriptions as of 13 September 2022 OpenSAFELY: 10,850 individuals as of 07 October 2022[24]

In France, Paxlovid received early access authorisation on 20 January 2022 and has been made available for prescription since 03 February 2022[50] 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 dispensing 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. 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 will be captured. The Spanish Medicines Agency (AEMPS) informs that novel antivirals are distributed through the normal channels.[21] 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. 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. The Pharmacoepidemiological Research Database for Public Health Systems [Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària] (BIFAP), which collects longitudinal medical records from various regions in Spain and is administered by AEMPS (Spanish medicines agency), is not available for studies funded by pharmaceutical companies.

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.

Slovenia had a very small supply (about 1000 packs), leading to a very 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. The AIFA national registry for antivirals for COVID-19 is proposed for exploration as a source for the feasibility information in Italy.

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.

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.[51] 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 CMU-C (*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.[51]

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 National Health Insurance Fund in France [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.[52]

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.[53] 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, i.e., assembling a chronological listing of diagnoses, procedures, and medications recorded for a patient, can be conducted.[54]

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 Ethical and Scientific Committee for Research, Studies and Evaluations in the Field of Health [Comiteś thèque et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé] (CESREES) and from the French Data Protection Commission [Commission Nationale de l'Informatique et des Libertés] (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 278 primary care centres that are part of the Catalan Health Institute in Catalonia (northeast Spain), which has 3414 participating general practitioners. SIDIAP has pseudonymised records for 5.7 million people (80% of the Catalan population) and is representative of the Catalan population.

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, in January and July.

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=48126).

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

Clinical Practice Research Datalink (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 99% English practices (https://cprd.com/Data). Most of the data are coded using SNOMED codes. As of March 2022, CPRD Aurum contained data on 13,400,000 current acceptable patients (i.e., active patients available for research) and 41,000,000 patients, including deceased and transferred-out patients.[55] 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. 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, PASS-DUS (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 3. 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 for the PASS-DUS, including specific questions on pregnancy and renal and hepatic impairment.

AIFA issues periodic reports on use of COVID-19 oral antiviral treatments in aggregated form (i.e., no individual-level data are available); these reports are publicly available.[56] As of 04 May 2022 (10th report), 12,424 Paxlovid treatment courses had been administered in

Italy, as well as 24,779 molnupiravir treatment courses. Therefore, the information in this patient registry is of great interest to the Paxlovid 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 a new (pending to finalise) agreement 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 Regional Health Agency of Tuscany (ARS Toscana) and the province of Caserta in Campania.

- Tuscany is an Italian region, with approximately 3.6 million inhabitants. The Regional Health Agency of Tuscany (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 pseudonymous identifier. The ARS Toscana database routinely collects primary care and secondary care drug prescriptions for outpatient use and can 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 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[57,58] 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 people 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 8 describes the main features of OpenSAFELY and CPRD Aurum.

Table 8. Main features of OpenSAFELY and CPRD Aurum

Feature	OpenSAFELY	CPRD Aurum
UK population[a]	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)
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)

Table 8. Main features of OpenSAFELY and CPRD Aurum

Feature	OpenSAFELY	CPRD Aurum
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 programs also run centrally. Analysis programs 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
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)

a. UK population as of 01 January 2019 (estimated; this is the last available estimate).[59]

9.5. Study size

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

At the time of writing this protocol, the number of treatments supplied to various countries was known and is presented in Section 9.4. Numbers by safety population and exposure group in each data source will be obtained in interim analyses.

The sizes of the populations with hepatic or renal impairment are anticipated to be small. In a study of 31,000 adults with COVID-19 identified in the ambulatory or hospital setting in the United States in 2020, 0.4% had previous moderate or severe liver disease and 8.7% had previous kidney disease.[60] Among 16,347 adult patients hospitalised with COVID-19 in Spain, 1.9% had previous chronic liver disease and 13.1% had previous renal impairment.[61]

As the SmPCs recommend caution or directly contraindicate use in severe hepatic or renal impairment, exposure in these populations is anticipated to be small.

For orientation regarding the study size, we used to OpenSAFELY publicly available data.[24] OpenSAFELY's public reports indicated that 3060 individuals aged 12 years or older had received Paxlovid and 4500 had received molnupiravir as of 28th April 2022, among approximately 23 million individuals registered in general practices in England using the TPP SystmOne primary care records system.[24] As of 28th April 2022, 40 Paxlovid users had liver disease (1.3 % of Paxlovid users at the time), and fewer than 8 had kidney disease (Table 9).[24] Percentages were higher in molnupiravir users and in patients eligible for treatment with drugs for COVID-19.

Table 9. Proportions of individuals with liver or kidney disease in OpenSAFELY among individuals eligible for treatment or treated with medications for COVID-19

	Eligible	Treated	Treated with Paxlovid	Treated with molnupiravir
All	102,170	16,930	3060	4500
Liver disease	6240 (6.1%)	750 (4.4%)	40 (1.3 %)	240 (5,3%)
Kidney disease	6660 (6.5%)	1930 (11.4%)	< 8 (< 0.3%)	520 (11.6%)

Note: Counts in this table are a subset of counts in the OpenSAFELY report dated 06 April 2022, Table 1[24] and include drug use up to 23 February 2022. Eligibility for treatment is based on having a positive test for COVID-19 or receiving a COVID-19-specific treatment, and an immune-mediated inflammatory disorders, primary immune deficiencies, solid cancers, selected rare neurological conditions, haematological diseases, stem cell transplant, solid organ transplant, kidney disease, liver disease, Down´s syndrome and immunosuppression due to HIV or AIDS.[62] COVID-19-specific treatments were Paxlovid, sotrovimab, remdesivir, molnupiravir and casirivimab.[62] Percentages shown in this table are column percentages.

We also used data available in the SNDS, 12,179 persons 16 years old or older used Paxlovid between 04 February and 29 June 2022; use increased each month. [49] The mean age of users was 66.2 years and 54% were female. Of Paxlovid users, 321 had liver conditions, 5 were on chronic dialysis and 182 had had a kidney transplant; 27% of Paxlovid users did not have documented COVID-19 tests in the 10 days before or after receiving Paxlovid.

Combining the information available in OpenSAFELY and SNDS, between 0.3% and 1.5% of the patients treated with Paxlovid had renal disease and between 1.3% and 2.6% had liver disease.

Table 10 displays the incidence rates assumed for the outcomes proposed among patients with moderate or severe renal impairment together with the literature source used. Incidence rates for the outcomes as defined in the current protocol were not available for the combined outcomes of abdominal pain and the dysgeusia and had to be extrapolated or assumed.

Table 10. Incidence rates assumed for study outcomes

Outcome	Incidence rate or range	Reference
Hospitalisation or ER visit for anaphylactic reactions	2-13 per 100,000 PYs	Avillach et al.[63]
Hospitalisation or ER visit for hepatic transaminase elevations, clinical hepatitis, or jaundice (equivalent to acute liver injury)	4% of patients with COVID-19 had abnormal ALT results (between 2-5 times the upper limit of normality); an incidence of 40 per 1000 PYs has been assumed.	Phipps et al. [13]
Hospitalisation or ER visits for severe vomiting, nausea, diarrhoea, or abdominal pain	6% of all emergency room visits; 17% of the patients were admitted to the hospital (93,367 visits ER visits in 2014); an incidence of 100 per 1000 PYs has been assumed.	Cervellin et al.[64]
Hospitalisation or ER visit for dysgeusia, headache, or hypertension	Up to 68.3%-74.6% of patients with COVID-19 reported headache; an incidence of 600 per 1000 PYs has been assumed.	Sekiguchi et al.[65]

For the study size calculations in Table 11, we have assumed that combining all Paxlovid users across all data sources there would be between 10,000 and 30,000 users of Paxlovid and that 1% of the users will have moderate or severe renal disease and that 2% will have moderate or severe liver disease. Table 11 contains the probability that the upper bound of the 95% CI around the observed risk ratio (RR) will be below 1.5, 2.0, 2.5, and 3.0 for various study sizes of exposed patients and the incidence rates estimated for the different outcomes and with some assumptions. These calculations assume a 1-to-10 ratio between exposed and unexposed patients and that the true RR between those exposed and comparators is 1.0. Table 11 shows the precision of the relative risk estimates will be low for anaphylactic reactions and the hepatic outcome, while it will be larger for the other outcomes. It is likely that only relatively common events will be observed with high certainty, given that the anticipated size of the study population is small.

Table 11. Probability that the upper 95% confidence limit of the observed risk ratio will be below 1.5, 2, 2.5, and 3 for various study sizes of exposed patients, assuming that the true RR is 1 and the ratio of exposed to unexposed (or of exposed to treated with molnupiravir) patients is 1 to 10

Outcome and cumulative incidence rate	Patients exposed	Upper confidence limit of RR			
		1.5	2.0	2.5	3.0
Anaphylactic reactions					
13/100,000 PYs	100	0,028	0,030	0,031	0,033
	150	0,028	0,031	0,033	0,035
	200	0,029	0,032	0,034	0,037
	250	0,029	0,033	0,036	0,038
	300	0,030	0,034	0,037	0,040
Hepatic outcomes					

Table 11. Probability that the upper 95% confidence limit of the observed risk ratio will be below 1.5, 2, 2.5, and 3 for various study sizes of exposed patients, assuming that the true RR is 1 and the ratio of exposed to unexposed (or of exposed to treated with molnupiravir) patients is 1 to 10

Outcome and cumulative incidence rate	Patients exposed	Upper confidence limit of RR			
		1.5	2.0	2.5	3.0
40/1000 PYs	100	0,121	0,271	0,430	0,571
	150	0,160	0,379	0,589	0,745
	200	0,199	0,479	0,713	0,856
	250	0,238	0,569	0,805	0,922
	300	0,277	0,647	0,871	0,959
Hospitalizations for abdominal pain					
100/1000 PYs	100	0,251	0,596	0,830	0,937
	150	0,351	0,770	0,946	0,990
	200	0,445	0,876	0,985	0,999
	250	0,531	0,936	0,996	1,000
	300	0,607	0,968	0,999	1,000

Note: Background incidence rates were obtained from references in Table 10 and for some outcomes had to be extrapolated or assumed from prevalence rates or other rates

9.6. Data management

This study will be conducted in a distributed manner, using a common protocol, CDM, and common analytics programs 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:

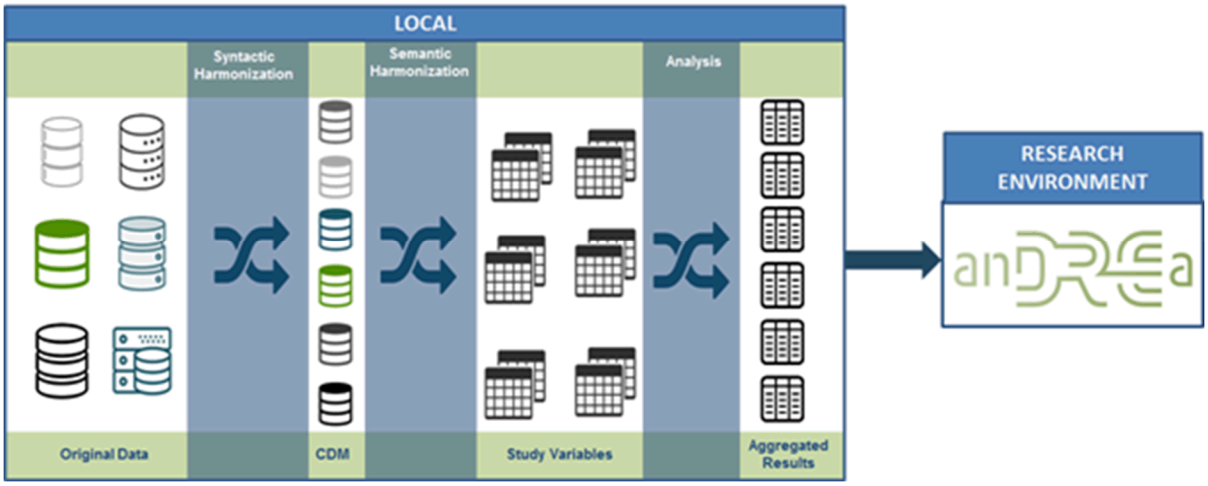
1. Extraction, transformation, and loading (ETL) of data to a CDM. To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation will be used. The CDM that will be used has been developed during the IMI-ConcePTION project.[66] In this CDM, data 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 Classification of Diseases, Ninth Revision), SNOMED, READ, or International Classification of Primary Care (ICPC) terminologies starting with a modified version of the ADVANCE Codemapper in VAC4EU.[67] 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 programs 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 programs, 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, renal and hepatic populations algorithms, 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.

The study will focus on the target populations shown in Table 1; analyses will be conducted separately in each target population.

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.

Outcomes for the target populations will be described in each of the cohorts based on cumulative incidence (1 − Kaplan-Meier [KM] estimator) with 95% CIs at the end of each risk window (eg, 1 month, 3 months, and 6 months).

9.7.2. Unadjusted outcome measures

The cumulative incidence of each corresponding safety outcome in the 2 target populations will be computed as 1 − KM estimator at different time intervals (eg, 1 month, 3 months and 6 months) (1 – KM curves by cohort will be displayed). Time to outcome will be defined as the time from day after the treatment start (time 0, see Section 9.2.1) until the occurrence of the outcome or censoring. Risk (1 − KM) differences and risk ratios and 95% CI will be

estimated at different time intervals, which can be adapted to the specific nature of each outcome. Measures of frequency and association and their 95% CIs will be estimated at the end of follow-up for each outcome.

Unadjusted comparative analyses will compare risk in Paxlovid users with risk in molnupiravir users (in data sources where molnupiravir is available) and, separately, with risk in the unexposed comparator group (in all data sources).

Risk 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.

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.

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 degree of hepatic or renal impairment (in those target populations, to the extent possible) and estimate the adjusted risk 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 exposed to 10 unexposed persons will also be considered. The matching ratio between Paxlovid users and patients not exposed to Paxlovid or molnupiravir will be up to 1:10. In the comparison between Paxlovid users and molnupiravir users the matching ratio will be determined based on future exposure counts, likely to be 1:1 or 1:2.

Risk ratios 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.

9.7.3.1. Sensitivity analyses

Sensitivity analyses will include the following:

- In the data sources that have laboratory results available (CPRD and SIDIAP), the positive and negative predictive values of the diagnosis code–based algorithms to identify the populations with moderate or severe renal or hepatic impairment will be estimated in a sample of 200 patients identified by the algorithm and in a sample of 200 patients not identified as having hepatic or renal impairment. The laboratory-based algorithms will be considered the gold standard. The results will inform the magnitude of the potential under ascertainment of the target populations in France.
- The potential effect of unmeasured confounding will be evaluated using quantitative bias analysis methods described by VanderWeele and Ding [68]. This analysis will evaluate how strong unmeasured confounding would have to be to explain away the association reported in the analysis of the risk of the outcomes in the 2 target populations. The

analysis will use a bias factor to obtain the maximum degree to which a given set of unmeasured confounders could alter the observed RR in the main analysis.

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. A minimum of 3 data points will be required (i.e., 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 12 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 12.

Table 12. 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	≤ 10	< 5	< 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	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. Documented COVID-19 is an inclusion criterion for this study; the undercapture of positive at-home tests will likely result in individuals with COVID-19 not being identified as eligible for inclusion in this study. For reference, in data from the SNDS in France, 27% of Paxlovid users did not have documented COVID-19 tests in the 10 days before or after Paxlovid use.[49] Identifying unexposed individuals who were at increased risk for severe COVID-19 and did not receive any COVID-19–specific treatment requires a positive test result or a diagnosis code to be documented.
- *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 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. Currently, the 3 proposed data sources capture COVID-19 vaccination.

- *Size of target populations*. The target populations include 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 populations will be small. This is already reflected in the small number of individuals with liver or kidney disease identified in OpenSAFELY as of February 2022 (Section 9.5). 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 supports national authorities that may want to decide on its early use[19]; for example, AIFA has recently authorised its use in Italy,[20] 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. 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 who were at increased risk for progression to severe COVID-19.
- *Channelling and potential for residual confounding.* Using an active comparator with a similar indication mitigates confounding by design. However, as expected, we observed potential channelling of patients with hepatic or renal impairment away from Paxlovid, reflecting that prescribers adhere to the precautions listed in the SmPCs. Channelling will be addressed analytically (eg, propensity score weighting). It is anticipated that channelling would also be observed if using an unexposed comparator group (see Table 9 in Section 9.5).
- *Identifying populations with hepatic or renal impairment and related safety endpoints*. In clinical practice, these populations and endpoints are identified based on signs, symptoms, and laboratory test results that will be incompletely captured in electronic health records or healthcare claims. In this study, we will identify these populations and endpoints through diagnostic and procedure proxies.
- *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,[69] use as postexposure prophylaxis (noting that the clinical trial

did not meet its prespecified endpoint),[70] as treatment for long COVID-19,[71,72] and paediatric use.[73]

- *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.

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 anonymized structured format and contain no patient personal information. Furthermore, the proposed study is a non-interventional study reusing healthcare data (secondary data collection). All data collected in the study will be deidentified with no breach of confidentiality regarding personal identifiers or health information. Data protection and privacy regulations will be respected in collecting, forwarding, processing, and storing data from study participants.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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 rigor and follow generally accepted research practices described in the following paragraphs.

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[74] and has been designed in line with the *ENCePP Guide on Methodological Standards in*

Pharmacoepidemiology[75] and the UK MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions.[76] The *ENCePP Checklist for Study Protocols*[77] 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*[78] 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.[79] 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)[80] 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*.[81]

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 (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., 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 startup 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 overall and in each target study population and exposure group and preliminary outcome counts; a final report; and, if applicable, a paediatric report 6 months after the end of data collection for the final 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[80] prior to the start of data collection. At completion, the final report or its summary will be posted.

Study results will be published following recommendations of the International Committee of Medical Journal Editors,[82] 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."[74] In alignment with EMA *GVP Module VIII: Post-Authorisation Safety Studies*,[3] Section VIII.B.5, and the *ENCePP Code of Conduct*,[83] 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 agencies 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. 2022. https://sigmaconsortium.eu. Accessed 7 April 2022.

2. VAC4EU. VAccine monitoring Collaboration for Europe. 2019. https://vac4eu.org/. Accessed 15 Mar 2022.

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

4. EMA. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Product- or population-specific considerations IV: paediatric population. 25 October 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-iv_en-0.pdf. Accessed 24 October 2022.

5. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med. 2022 Feb 16;386(15):1397-408. doi:http://dx.doi.org/10.1056/NEJMoa2118542.

6. FDA. US Food and Drug Administration. Paxlovid emergency use authorization 105. 22 Dec 2021. https://www.fda.gov/media/155049/download. Accessed 14 Mar 2022.

7. MHRA. Medicines and Healthcare products Regulatory Agency. Regulatory approval of Paxlovid. 9 Feb 2022. https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid. Accessed 14 Mar 2022.

8. EMA. European Medicines Agency. COVID-19: EMA recommends conditional marketing authorisation for Paxlovid. 27 Jan 2022. https://www.ema.europa.eu/en/news/covid-19-ema-recommends-conditional-marketing-authorisation-paxlovid. Accessed 14 Mar 2022.

9. EMA. European Medicines Agency. Paxlovid summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf. Accessed 14 Mar 2022.

10. MHRA. Medicines and Healthcare products Regulatory Agency. Paxlovid summary of product characteristics. January 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045762/Reg_SPC_PX_2_0_GB.pdf. Accessed 5 Sep 2022.

11. Hiremath S, McGuinty M, Argyropoulos C, Brimble KS, Brown PA, Chagla Z, et al. Prescribing Nirmatrelvir/Ritonavir for COVID-19 in Advanced CKD. Clin J Am Soc Nephrol. 2022 Aug;17(8):1247-50. doi:http://dx.doi.org/10.2215/CJN.05270522.

12. Lingscheid T, Kinzig M, Krüger A, Müller N, Bölke G, Tober-Lau P, et al. Pharmacokinetics of nirmatrelvir and ritonavir in COVID-19 patients with end stage renal disease on intermittent haemodialysis. medRxiv. 2022:2022.08.19.22277959. doi:http://dx.doi.org/10.1101/2022.08.19.22277959.

13. Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. Hepatology. 2020 Sep;72(3):807-17. doi:http://dx.doi.org/10.1002/hep.31404.

14. Song JE, Kang MK, Lee YR, Lee CH, Park JG, Kweon YO, et al. Multicenter Analysis of Clinical Features and Prognosis of COVID-19 Patients with Hepatic Impairment. Gut Liver. 2021 Jul 15;15(4):606-15. doi:http://dx.doi.org/10.5009/gnl20267.

15. Tang H, Zhou L, Li X, Kinlaw AC, Yang JY, Moon AM, et al. Drug-induced liver injury associated with lopinavir-ritonavir in patients with COVID-19: a disproportionality analysis of U.S. food and drug administration adverse event reporting system (FAERS) data. Int J Clin Pharm. 2021 Aug;43(4):1116-22. doi:http://dx.doi.org/10.1007/s11096-021-01311-5.

16. Gheorghe L, Iacob S, Curescu M, Brisc C, Cijevschi C, Caruntu F, et al. Real-Life Use of 3 Direct-Acting Antiviral Regimen in a Large Cohort of Patients with Genotype-1b HCV Compensated Cirrhosis. J Gastrointestin Liver Dis. 2017 Sep;26(3):275-81. doi:http://dx.doi.org/10.15403/jgld.2014.1121.263.iac.

17. Petta S, Marzioni M, Russo P, Aghemo A, Alberti A, Ascione A, et al. Ombitasvir, paritaprevir, and ritonavir, with or without dasabuvir, plus ribavirin for patients with hepatitis C virus genotype 1 or 4 infection with cirrhosis (ABACUS): a prospective observational study. Lancet Gastroenterol Hepatol. 2017 Jun;2(6):427-34. doi:http://dx.doi.org/10.1016/s2468-1253(17)30048-1.

18. Calleja JL, Crespo J, Rincón D, Ruiz-Antorán B, Fernandez I, Perelló C, et al. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort. J Hepatol. 2017 Jun;66(6):1138-48. doi:http://dx.doi.org/10.1016/j.jhep.2017.01.028.

19. EMA. European Medicines Agency. EMA issues advice on use of Lagevrio (molnupiravir) for the treatment of COVID-19. 19 Nov 2021. https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19 Accessed 14 Mar 2022.

20. AIFA. Italian Medicines Agency. Molnupiravir and remdesivir available for the treatment of non-hospitalized COVID-19 patients at high risk of progressing to severe disease. 30 Dec 2021. https://www.aifa.gov.it/en/-/disponibilit%C3%A0-molnupiravir-e-remdesivir-trattamento-pazienti-non-ospedalizzati-covid-19-1. Accessed 14 Mar 2022.

21. AEMPS. Agencia Española de Medicamentos y Productos Sanitarios. Criterios para valorar la administración de las nuevas alternativas terapéuticas antivirales frente a la infección por SARS-CoV-2 (version 3). 4 April 2022. 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 28 April 2022.

22. MHRA. Medicines and Healthcare products Regulatory Agency. First oral antiviral for COVID-19, Lagevrio (molnupiravir), approved by MHRA. 4 November 2021. 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 7 April 2022.

23. MHRA. Medicines and Healthcare products Regulatory Agency. Molnupiravir summary of product characteristics. 4 November 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1030930/Legavrio_SMPC_4Nov21.pdf. Accessed 7 April 2022.

24. OpenSAFELY. Coverage and uptake of antivirals and neutralising monoclonal antibodies for the treatment of non-hospitalised patients with COVID-19. 2022. https://reports.opensafely.org/reports/antivirals-and-nmabs-for-non-hospitalised-covid-19-patients-coverage-report/. Accessed 10 April 2022.

25. EMA. European Medicines Agency. Veklury summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/veklury-epar-product-information_en.pdf. Accessed 23 September 2022.

26. EMA. European Medicines Agency. Evusheld summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/evusheld-epar-product-information_en.pdf. Accessed 26 September 2022.

27. ANSM. L'Agence Nationale de Sécurité du Médicament et des Produits de Santé Evusheld (Tixagevimab / Cilgavimab). 2022. https://ansm.sante.fr/tableau-acces-derogatoire/tixagevimab-150-mg-cilgavimab-150-mg-solution-injectable-evusheld. Accessed 9 January 2022.

28. EMA. European Medicines Agency. Kineret summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/kineret-epar-product-information_en.pdf. Accessed 22 July 2022.

29. EMA. European Medicines Agency. Regkirona summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/regkirona-epar-product-information_en.pdf. Accessed 29 July 2022.

30. EMA. European Medicines Agency. RoActemra summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf. Accessed 26 April 2022.

31. EMA. European Medicines Agency. Ronapreve summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/ronapreve-epar-product-information_en.pdf. Accessed 18 March 2022.

32. EMA. European Medicines Agency. Xevudy summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/xevudy-epar-product-information_en.pdf. Accessed 28 July 2022.

33. Schneeweiss S, Rassen JA, Brown JS, Rothman KJ, Happe L, Arlett P, et al. Graphical depiction of longitudinal study designs in health care databases. Ann Intern Med. 2019 Mar 19;170(6):398-406. doi:http://dx.doi.org/10.7326/M18-3079.

34. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson Comorbidity Index: ICD-9 update and ICD-10 translation. Am Health Drug Benefits. 2019 Jun-Jul;12(4):188-97.

35. Kim WR, Mannalithara A, Heimbach JK, Kamath PS, Asrani SK, Biggins SW, et al. MELD 3.0: the Model for End-Stage Liver Disease updated for the modern era. Gastroenterology. 2021 Dec;161(6):1887-95 e4. doi:http://dx.doi.org/10.1053/j.gastro.2021.08.050.

36. Kaplan DE, Dai F, Aytaman A, Baytarian M, Fox R, Hunt K, et al. Development and Performance of an Algorithm to Estimate the Child-Turcotte-Pugh Score From a National Electronic Healthcare Database. Clin Gastroenterol Hepatol. 2015 Dec;13(13):2333-41 e1-6. doi:http://dx.doi.org/10.1016/j.cgh.2015.07.010.

37. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006 Jan;44(1):217-31. doi:http://dx.doi.org/10.1016/j.jhep.2005.10.013.

38. Ludvigsson JF, Appelros P, Askling J, Byberg L, Carrero JJ, Ekström AM, et al. Adaptation of the Charlson Comorbidity Index for register-based research in Sweden. Clin Epidemiol. 2021;13:21-41. doi:http://dx.doi.org/10.2147/clep.S282475.

39. Cole NI, Liyanage H, Suckling RJ, Swift PA, Gallagher H, Byford R, et al. An ontological approach to identifying cases of chronic kidney disease from routine primary care data: a cross-sectional study. BMC Nephrol. 2018 Apr 10;19(1):85. doi:http://dx.doi.org/10.1186/s12882-018-0882-9.

40. Jalal K, Anand EJ, Venuto R, Eberle J, Arora P. Can billing codes accurately identify rapidly progressing stage 3 and stage 4 chronic kidney disease patients: a diagnostic test study. BMC Nephrol. 2019 Jul 12;20(1):260. doi:http://dx.doi.org/10.1186/s12882-019-1429-4.

41. Levey AS, Eckardt KU, Dorman NM, Christiansen SL, Cheung M, Jadoul M, et al. Nomenclature for kidney function and disease: executive summary and glossary from a Kidney Disease: Improving Global Outcomes (KDIGO) consensus conference. Kidney Int Rep. 2020 Jul;5(7):965-72. doi:http://dx.doi.org/10.1016/j.ekir.2020.03.027.

42. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021 Nov 4;385(19):1737-49. doi:http://dx.doi.org/10.1056/NEJMoa2102953.

43. Duggal V, Thomas IC, Montez-Rath ME, Chertow GM, Kurella Tamura M. National estimates of CKD prevalence and potential impact of estimating glomerular filtration rate without race. J Am Soc Nephrol. 2021 Jun 1;32(6):1454-63. doi:http://dx.doi.org/10.1681/asn.2020121780.

44. Tsai JW, Cerdeña JP, Goedel WC, Asch WS, Grubbs V, Mendu ML, et al. Evaluating the impact and rationale of race-specific estimations of kidney function: estimations from U.S. NHANES, 2015-2018. EClinicalMedicine. 2021 Dec;42:101197. doi:http://dx.doi.org/10.1016/j.eclinm.2021.101197.

45. Bundy JD, Mills KT, Anderson AH, Yang W, Chen J, He J. Prediction of end-stage kidney disease using estimated glomerular filtration rate with and without race: a prospective cohort study. Ann Intern Med. 2022 Jan 11;175(3):305-13. doi:http://dx.doi.org/10.7326/m21-2928.

46. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. J Am Soc Nephrol. 2021 Sep 23. doi:http://dx.doi.org/10.1681/ASN.2021070988.

47. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013 Jan;3(1):1-150.

48. CDC. Centers for Disease Control and Prevention. COVID-19. People with certain medical conditions. 2022. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed 13 April 2022.

49. Bouillon K, Bertrand M, Baricault B, Botton J, Jabagi M, Le Vu S, et al. Étude d'utilisation de l'antiviral oral Paxlovid du 4 février au 29 juin 2022 [French]. 13 September 2022. https://www.epi-phare.fr/app/uploads/2022/09/epi-phare_utilisation_paxlovid_20220913.pdf. Accessed 11 October 2022.

50. CORRUSS. Centre opérationnel de régulation et de réponse aux urgences sanitaires et sociales. Mise à disposition l'antiviral du laboratoire PFIZER: PAXLOVID® (association de PF-07321332 150 mg et ritonavir 100 mg, comprimés pelliculés). 2 February 2022. https://solidarites-sante.gouv.fr/IMG/pdf/dgs-urgent__2022_22_paxlovid.pdf. Accessed 28 April 2022.

51. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):954-62. doi:http://dx.doi.org/10.1002/pds.4233.

52. SNDS. Patients vaccinés contre le COVID-19. 7 July 2021. https://documentation-snds.health-data-hub.fr/fiches/ir_vac_f.html. Accessed 2 May 2022.

53. 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). 8 July 2021. https://www.legifrance.gouv.fr/cnil/id/CNILTEXT000043765544. Accessed 2 May 2022.

54. Thurin NH, Bosco-Levy P, Blin P, Rouyer M, Jove J, Lamarque S, et al. Intra-database validation of case-identifying algorithms using reconstituted electronic health records from healthcare claims data. BMC Med Res Methodol. 2021 May 1;21(1):95. doi:http://dx.doi.org/10.1186/s12874-021-01285-y.

55. MHRA. Medicines and Healthcare products Regulatory Agency. Release notes: CPRD Aurum March 2022. March 2022. https://cprd.com/sites/default/files/2022-03/2022-03%20CPRD%20Aurum%20Release%20Notes.pdf. Accessed 13 April 2022.

56. AIFA. Italian Medicines Agency. Archivio registri 2022. 2022. https://www.aifa.gov.it/en/archivio-registri-2022. Accessed 6 April 2022.

57. OpenSAFELY. About OpenSAFELY. 2022. https://www.opensafely.org/about/. Accessed 07 April 2022.

58. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug;584(7821):430-6. doi:http://dx.doi.org/10.1038/s41586-020-2521-4.

59. EUROSTAT. Usually resident population on 1 January. 5 November 2021. http://appsso.eurostat.ec.europa.eu/nui/show.do. Accessed 28 April 2022.

60. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: a federated electronic medical record analysis. PLoS Med. 2020 Sep;17(9):e1003321. doi:http://dx.doi.org/10.1371/journal.pmed.1003321.

61. Burn E, You SC, Sena AG, Kostka K, Abedtash H, Abrahao MTF, et al. Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study. Nat Commun. 2020 Oct 6;11(1):5009. doi:http://dx.doi.org/10.1038/s41467-020-18849-z.

62. The OpenSAFELY Collaborative, Green A, Curtis HJ, Higgins R, Smith R, Mehrkar A, et al. Trends, regional variation and clinical characteristics of recipients of antivirals and neutralising monoclonal antibodies for non-hospitalised COVID-19: a descriptive cohort study of 23.4 million people in OpenSAFELY [preprint]. medRxiv. 2022:2022.03.07.22272026. doi:http://dx.doi.org/10.1101/2022.03.07.22272026.

63. Avillach P, Coloma PM, Gini R, Schuemie M, Mougin F, Dufour JC, et al. Harmonization process for the identification of medical events in eight European healthcare databases: the experience from the EU-ADR project. J Am Med Inform Assoc. 2013 Jan 1;20(1):184-92. doi:http://dx.doi.org/10.1136/amiajnl-2012-000933.

64. Cervellin G, Mora R, Ticinesi A, Meschi T, Comelli I, Catena F, et al. Epidemiology and outcomes of acute abdominal pain in a large urban Emergency Department: retrospective analysis of 5,340 cases. Ann Transl Med. 2016 Oct;4(19):362. doi:http://dx.doi.org/10.21037/atm.2016.09.10.

65. Sekiguchi K, Watanabe N, Miyazaki N, Ishizuchi K, Iba C, Tagashira Y, et al. Incidence of headache after COVID-19 vaccination in patients with history of headache: A cross-sectional study. Cephalalgia. 2022 Mar;42(3):266-72. doi:http://dx.doi.org/10.1177/03331024211038654.

66. Innovative Medicines Initiative. Report on existing common data models and proposals for ConcePTION. 4 August 2020. 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 11 April 2022.

67. Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom M, et al. CodeMapper: semiautomatic coding of case definitions. A contribution from the

ADVANCE project. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):998-1005. doi:http://dx.doi.org/10.1002/pds.4245.

68. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017 Jul 11. doi:http://dx.doi.org/10.7326/m16-2607.

69. Sheikh K. Can COVID symptoms rebound after taking Paxlovid? 5 May 2022. https://www.nytimes.com/2022/05/05/well/live/can-covid-symptoms-rebound-after-taking-paxlovid.html. Accessed 13 May 2022.

70. Larkin C. Pfizer's COVID drug fails to show benefit as preventive therapy. 29 April 2022. https://www.bloomberg.com/news/articles/2022-04-29/pfizer-s-covid-drug-fails-to-show-benefit-as-preventive-therapy. Accessed 13 May 2022.

71. Ledford H. Can drugs reduce the risk of long COVID? What scientists know so far. Nature. 2022 Apr;604(7904):20-1. doi:http://dx.doi.org/10.1038/d41586-022-00823-y.

72. Wu K. The promising treatment for long COVID we're not even trying. 10 May 2022. https://www.theatlantic.com/health/archive/2022/05/long-covid-treatment-pfizer-paxlovid/629810/. Accessed 13 May 2022.

73. Reuters. Pfizer begins COVID pill study in high-risk children aged 6-17. 9 March 2022. https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-begins-covid-pill-study-high-risk-children-aged-6-17-2022-03-09/. Accessed 18 May 2022.

74. ISPE. International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. June 2015. https://www.pharmacoepi.org/resources/policies/guidelines-08027/. Accessed 3 August 2021.

75. ENCePP. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Guide on methodological standards in pharmacoepidemiology (revision 9). July 2021. http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml. Accessed 30 July 2021.

76. MHRA. Medicines and Healthcare products Regulatory Agency. MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions. 16 Dec 2021. https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions. Accessed 14 Mar 2022.

77. ENCePP. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ENCePP checklist for study protocols (revision 4). 15 October 2018. http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml. Accessed 30 July 2021.

78. ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Pharmacovigilance planning. E2E. 2004. https://database.ich.org/sites/default/files/E2E_Guideline.pdf. Accessed 3 August 2021.

79. 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. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF. Accessed 2 August 2021.

80. ENCePP. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. The European Union Electronic Register of Post-Authorisation Studies (EU PAS Register). 2022. http://www.encepp.eu/encepp_studies/indexRegister.shtml. Accessed 14 Mar 2022.

81. ENCePP. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. The ENCePP seal. 28 July 2021. http://www.encepp.eu/encepp_studies/index.shtml. Accessed 2 August 2021.

82. ICMJE. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. December 2019. http://www.icmje.org/recommendations/. Accessed 30 July 2021.

83. ENCePP. The ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies (Revision 4). 15 March 2018. http://www.encepp.eu/code_of_conduct/. Accessed 2 August 2021.

84. AIFA. Italian Medicines Agency. COVID-19 antiviral registration form. 2022. https://www.aifa.gov.it/documents/20142/1658003/Scheda_Registro_antivirali_COVID19_25.02.2022.zip. Accessed 6 April 2022.

14. LIST OF TABLES

15. LIST OF FIGURES

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: Use and Safety of Paxlovid Among Patients with Moderate or Severe Hepatic or Renal Impairment

EU PAS Register® number: not registered yet **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

† 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 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
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? (i.e., 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
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, 9.2.1.1, 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)	☐	☒	☐	

Section 6: Outcome definition and measurement	Yes	No	N/A	Section number
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 3
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 3
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 3
9.2.2 Outcomes? (eg, date of occurrence, multiple events, severity measures related to event)	☒	☐	☐	9.3, 9.4

Section 9: Data sources	Yes	No	N/A	Section number
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.3, 9.4, Annex 3
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 3
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 3
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?	☒	☐	☐	9.7

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?	☒	☐	☐	9.8
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)	☒	☐	☐	9.1, 9.4, 9.5 Annex 3

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?	☒	☐	☐	10.3
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: Manel Pladevall	
Signature & date:	

ANNEX 3. 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 9.4.4.1), 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 several 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,[84] at the end of this annex, 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

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