NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Safety of Paxlovid Among Patients with Moderate or Severe Hepatic or Renal Impairment
Protocol number	C4671047
Protocol version identifier	Protocol V3.0
Date	21 June 2023
EU Post-Authorisation Study (PAS) register number	EUPAS50123
Active substance	Combination of the oral protease inhibitors nirmatrelvir and ritonavir (ATC code J05AE30)
Medicinal product	Paxlovid
Product reference	nirmatrelvir/ritonavir
Procedure number	Marketing authorisation EMEA/H/C/005973
Marketing Authorisation Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No

Research question and objectives	The 2 research questions are: • What is the safety profile of Paxlovid in patients with COVID-19 and moderate or severe hepatic impairment? • What is the safety profile of Paxlovid in patients with COVID-19 and moderate or severe renal impairment? **Moderate or severe hepatic impairment population** Primary objectives • To assess the safety of Paxlovid relative to the comparator populations prescribed molnupiravir (or other comparable medications for COVID-19), where available, and to unexposed patients with COVID-19. • To assess side effects resulting from drug overexposure due to impaired liver function and with regard to severity and frequency compared with comparator groups. Safety outcomes for primary objectives are all safety events in outpatient and inpatient settings, as available, including the following safety outcomes of special interest: • Hepatic transaminase elevations, clinical hepatitis, or jaundice • Severe vomiting, nausea, diarrhoea, or abdominal pain • Dysgeusia, headache, or hypertension • Anaphylactic reactions Secondary objective • To assess all safety events included in the primary objective that require hospitalisation or emergency department visits **Moderate or severe renal impairment population** Primary objectives • To assess the safety of Paxlovid relative to the comparator population prescribed molnupiravir (or other comparable medications for COVID-19), where available, and to unexposed patients with COVID-19. • To assess side effects resulting from drug overexposure due to impaired renal function and with

	regard to severity and frequency compared with comparator groups. Safety outcomes for primary objectives are all safety events in outpatient and inpatient settings, as available, including the following safety outcomes of special interest: • Severe vomiting, nausea, diarrhoea, or abdominal pain • Dysgeusia, headache, or hypertension • Anaphylactic reactions Secondary objective • To assess all safety events included in the primary objective that require hospitalisation or emergency department visits
Countries of study	• France • Spain • United Kingdom • Other countries in Europe are under evaluation
Author	Manel Pladevall-Vila, MD, MS, RTI Health Solutions in collaboration with Aarhus University, University Medical Center Utrecht, and ARS Toscana, on behalf of the SIGMA Consortium Paxlovid PASS research team Cynthia de Luise, PhD, MPH, Pfizer, Inc.

Marketing Authorisation Holder

Marketing Authorisation Holder	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEMPS	Agencia Española de Medicamentos y Productos Sanitario [Spanish Agency of Medicines and Medical Devices]
AIFA	Agenzia Italiana del Farmaco [Italian Medicines Agency]
ALD	Affections de Longue Durée [list of chronic conditions registered in France]
ALT	Alanine aminotransferase
ARS Toscana	Agenzia Regionale di Sanità della Toscana [Regional Health Agency of Tuscany, Italy]
BIFAP	Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària [Pharmacoepidemiological Research Database for Public Health Systems] (Spain)
ATC	Anatomical Therapeutic Chemical (classification system)
CDC	US Centers for Disease Control and Prevention
CDM	Common data model
CESREES	Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé [Ethical and Scientific Committee for Research, Studies and Evaluations in the Field of Health] (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	Caisse Nationale de l'Assurance Maladie [National Health Insurance Fund] (France)
CNIL	Commission Nationale de l'Informatique et des Libertés [French Data Protection Commission]
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Datalink (UK)
CPRD GOLD	General Practitioner Online Database (of CPRD)
DAP	Data Access Partner
DRE	Digital Research Environment

Abbreviation	Definition
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPhMRA	European Pharmaceutical Market Research Association
ED	Emergency department
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

Abbreviation	Definition
NI	Non-interventional
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	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [Information System for Research in Primary Care] (Catalonia, Spain)
SmPC	Summary of product characteristics
SNDS	Système National Des Données de Santé [French Administrative Healthcare Database]
SNOMED CT	Systemized Nomenclature of Medicine–Clinical Terms
UACR	Urine albumin-to-creatinine ratio
UCD	Common dispensing unit (France)
UK	United Kingdom
US	United States
VAC4EU	Vaccine Monitoring Collaboration for Europe

3. RESPONSIBLE PARTIES

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

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

Principal Investigator(s) of the Protocol

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Miriam Sturkenboom, PhD, MSc, FISPE	Head of the Department of Datascience & Biostatistics, professor	Department of Datascience & Biostatistics, University Medical Center Utrecht	Heidelberglaan 100, Utrecht, The Netherlands

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

Country coordinating investigators

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

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4. ABSTRACT

Title

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

- Protocol version 3.0, 21 June 2023
- Main author: Manel Pladevall-Vila, RTI Health Solutions, on behalf of the SIGMA Consortium Paxlovid PASS Research Team

Rationale and background

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

The safety of Paxlovid in individuals with hepatic or renal impairment is not known. 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 safety profile of Paxlovid in patients with COVID-19 and moderate or severe hepatic impairment?
- What is the safety profile of Paxlovid in patients with COVID-19 and moderate or severe renal impairment?

For the population of individuals with *moderate or severe hepatic impairment*, the objectives are:

Primary objectives

- To assess the safety of Paxlovid relative to the comparator populations prescribed molnupiravir (or other comparable medications for COVID-19), where available, and to unexposed patients with COVID-19.
- To assess side effects resulting from drug overexposure due to impaired liver function and with regard to severity and frequency compared with comparator groups.

Safety outcomes for primary objectives are all safety events in outpatient and inpatient settings, as available, including the following safety outcomes of special interest:

- Hepatic transaminase elevations, clinical hepatitis, or jaundice
- Severe vomiting, nausea, diarrhoea, or abdominal pain
- Dysgeusia, headache, or hypertension
- Anaphylactic reactions

Secondary objective

- To assess all safety events included in the primary objective that require hospitalisation or emergency department visits

For the population of individuals with *moderate or severe renal impairment*, the objectives are:

Primary objectives

- To assess the safety of Paxlovid relative to the comparator population prescribed molnupiravir (or other comparable medications for COVID-19), where available, and to unexposed patients with COVID-19.
- To assess side effects resulting from drug overexposure due to impaired renal function and with regard to severity and frequency compared with comparator groups.

Safety outcomes for primary objectives are all safety events in outpatient and inpatient settings, as available, including the following safety outcomes of special interest:

- Severe vomiting, nausea, diarrhoea, or abdominal pain
- Dysgeusia, headache, or hypertension
- Anaphylactic reactions

Secondary objective

- To assess all safety events included in the primary objective that require hospitalisation or emergency department visits

Study design

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

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

Molnupiravir, 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 in the target populations with COVID-19 who had not received Paxlovid, molnupiravir or other comparable medications, referred to as "unexposed patients".

The study period will start on 01 January 2022 (in alignment with regulatory authorisation and launch in Europe) and end based on the calendar period coverage at the time of the last data extraction. See Table 6.

Population

The target study populations are individuals with moderate or severe hepatic or renal impairment with COVID-19 exposed to Paxlovid or comparator drug molnupiravir or other comparable medications, and individuals unexposed to Paxlovid, molnupiravir, or other comparable medications (the *unexposed comparison group).*

Time 0 will be the day on which individuals meet all eligibility criteria; they can start treatment with Paxlovid or molnupiravir or comparable medications within 7 days (a grace period; ie, days [0, 6] inclusive of both bounds) after time 0. Unexposed individuals will be matched with individuals starting Paxlovid by time since COVID-19 diagnosis (days) and calendar time (within ± 1 week; ie, days [−6, 6] inclusive of both bounds). Paxlovid and molnupiravir or comparable medication users will be matched on calendar time. Follow-up of individuals will start between day 1 and day 7, depending on which day the matching of exposed/unexposed occurs. Follow-up will end at the earliest of 1 month after starting treatment; death; disenrollment or migration; end of data availability in the data source; occurrence of the outcome being evaluated, or treatment group crossover.

Variables

The exposures will be Paxlovid and molnupiravir (or other comparable medications for COVID-19 that may be added to the comparison group), which will be ascertained from prescription and pharmacy information or from other data sources (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.

For the population with hepatic impairment, primary outcomes are all safety events in outpatient and inpatient settings, as available, including the following safety outcomes of special interest:

- Hepatic transaminase elevations, clinical hepatitis, or jaundice
- Severe vomiting, nausea, diarrhoea, or abdominal pain

- Dysgeusia, headache, or hypertension
- Anaphylactic reactions

For the population with renal impairment, primary outcomes are all safety events in outpatient and inpatient settings, as available, including the following safety outcomes of special interest:

- Severe vomiting, nausea, diarrhoea, or abdominal pain
- Dysgeusia, headache, or hypertension
- Anaphylactic reactions

Safety events resulting in hospitalisation or emergency department (ED) visit will be considered secondary outcomes in both the population with liver impairment and in the population with renal impairment.

In both populations of individuals with moderate or severe hepatic or renal impairment, other than safety outcomes of special interest, safety events will be identified from diagnosis codes of events occurring within 1 month after the initiation of Paxlovid, documented in the participating data sources among eligible Paxlovid-exposed individuals (i.e., events that are recorded after exposure to Paxlovid in individuals who are eligible for the study). These events will then be analysed within the planned cohort design along with the other prespecified study outcomes of special interest. See Section 9.3.2.2. Safety outcomes of special interest will be identified using diagnosis codes, procedures, medical product prescriptions or dispensing, and information collected in other data banks in the selected data sources.

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 United Kingdom (UK), initially or continuing under special government contracts, resulting in different distribution and reimbursement channels being used and subsequent challenges capturing its prescription and distribution. Current information is that prescribed/dispensed Paxlovid should be captured in existing electronic population data sources in France, Spain, and the UK. The Italian Medicines Agency (AIFA) established a national registry for Paxlovid and other antivirals to treat COVID-19. At the time of this writing, capture of Paxlovid dispensing/prescriptions in the existing electronic data sources commonly used for pharmacoepidemiological research in Italy is expected to be minimal. As long as the German government continues to cover payments for Paxlovid, it is also expected that Paxlovid prescriptions will not be captured in the German Statutory Health Insurance data sources.

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

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

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

Study size

All individuals meeting eligibility criteria during the study observation period will be included. As the summaries of product characteristics (SmPCs) caution (EU) or contraindicate (UK) use in severe hepatic or renal impairment, Paxlovid exposure in these populations is anticipated to be small.

Data analysis

Study data will be analysed as a cohort. Descriptive baseline characteristics will include tabulations of age, sex, comorbidities, selected concurrent medications, COVID-19 vaccination status, history of COVID-19, current COVID-19 status and setting of Paxlovid use (among Paxlovid users). Comparative analyses will be based on the estimation of risk ratios and risk 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)
- Protocol C4671047 V1.0 submission: 29 November 2022 (population with moderate or severe hepatic impairment and population with moderate or severe renal impairment)
- Registration in the European Union (EU) PAS Register: Study will be registered prior to start of data collection[a]
- Progress report submission: 29 November 2022
- Start of data collection: quarter 4 2023 (planned)[a]

[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.

- Interim report 1: 14 months after protocol endorsement; estimated for quarter 4 2024[b]
- Interim report 2: 26 months after protocol endorsement; estimated for quarter 4 2025[b]
- End of data collection: quarter 4 2025[b] (planned)
- Final report: estimated for 31 March 2026[b] (planned)

[b] Protocol endorsement from EMA is expected in quarter 3 2023. Milestones will be updated once protocol endorsement date is known.

5. AMENDMENTS AND UPDATES

Key changes after submission to the EMA-PRAC of protocol C4671047, titled *Safety of Paxlovid Among Patients with Moderate or Severe Hepatic or Renal Impairment* (V1.0, dated 16 November 2022), are listed below. Minor changes (eg, wording) are not listed.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
2	21 Jun 2023	4 6	Milestones were updated: protocol endorsement is anticipated in quarter 3 2023	Update based on regulatory timeline for this amendment and changes in scope.
		Cover page 4 8	The study objectives have been changed. The primary objectives now include all potential safety events in all settings (outpatient and inpatient) instead of restricting to emergency department and inpatient events. A secondary objective has been added, which includes the primary outcomes but restricted to events occurring as emergency department visits or hospitalisations.	In response to EMA queries on C4671047 Protocol Amendment 1; EMEA/H/C/005973/MEA/009.2, dated 07 June 2023
		Cover page 4 8	Exploratory outcomes as secondary outcomes have been removed. All safety events are included as primary outcomes.	In response to EMA queries on C4671047 Protocol Amendment 1; EMEA/H/C/005973/MEA/009.2, dated 07 June 2023
		9.3.2.1 9.3.2.2	Primary outcomes have been modified. Primary outcomes include any safety events and safety outcomes of special interest. Secondary outcomes include the primary outcomes that require hospitalisation or ED visits.	To reflect the changes in the primary and secondary objectives and in response to EMA queries on C4671047 Protocol Amendment 1; EMEA/H/C/005973/MEA/009.2, dated 07 June 2023
		9.5	Table 11 in the study size section has been modified to reflect the changes in the outcomes composition.	To reflect the changes in the primary and secondary objectives and in response to EMA queries on C4671047 Protocol Amendment 1; EMEA/H/C/005973/MEA/009.2, dated 07 June 2023

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.7.3.1	The sensitivity analysis extending the risk window from 1 month to 3 and 6 months will be performed for all outcomes; before, it was proposed only for the hepatic outcome.	In response to EMA queries on C4671047 Protocol Amendment 1; EMEA/H/C/005973/MEA/009.2, dated 07 June 2023
		9.7.3.2	Meta-analysis of results has been modified and now includes all outcomes.	To reflect the changes in the primary and secondary objectives and in response to EMA queries on C4671047 Protocol Amendment 1; EMEA/H/C/005973/MEA/009.2, dated 07 June 2023
		9.9	Text regarding primary outcomes other than safety outcomes of special interest has been added to describe the potential limitation of not capturing mild safety events among patients with liver impairment and frequent hospitalisations.	To reflect the changes in objectives and outcomes that now include all events in all settings (inpatient and outpatient)
		10.1 10.2	Changes in the text of the protection of human subjects section have been implemented to use the correct terminology according to EU legislation applicable to the protection of human subjects and also to reflect accurately the structure of the data that will be used in the study.	To use the correct terminology to define the structure of the data that will be used in the study.
		9 12	Clarifications of the content of interim report 1, interim report 2, and the final report and to describe specific elements that will be included in those reports.	In response to EMA queries on C4671047 Protocol Amendment 1; EMEA/H/C/005973/MEA/009.2, dated 07 June 2023
1	14 Apr 2023	Cover page 4 Annex 2	Removed “Use and” from title.	Drug utilisation will no longer be included in this study.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Cover page 4 8	The study objectives have been reworded to explicitly mention that additional comparator drugs might be incorporated into the study and to include additional events.	In response to comments 4 and 5 in Final Assessment Report for non-imposed non-interventional PASS protocol, Post-Authorisation Measure 009; EMEA/H/C/005973/MEA/008, dated 23 February 2023 (hereafter in this table, 2023 CHMP/PRAC Final Assessment Report)
		Cover page 4 8 9.1 12	Other treatments for COVID-19 will be considered to identify the study active comparator cohort. This is reflected now in the objectives. Counts of individuals exposed to such drugs will be presented in interim reports.	In response to comment 5 in the 2023 CHMP/PRAC Final Assessment Report
		4 6 9.1 9.7 12	The paediatric study report, which was a deliverable in the protocol version 2.0, was eliminated. A stratified analysis that will explore use in the paediatric population was added.	In response to comment 1 in the 2023 CHMP/PRAC Final Assessment Report
		4 7	Explicit mentions of the companion PASS on pregnant women have been removed.	In response to comment 2 in the 2023 CHMP/PRAC Final Assessment Report
		7	Clarification of how the different SmPCs in the UK and Europe may impact the use of Paxlovid in the UK and EU populations and how the study findings will be interpreted in that context and in the context of potential health status differences if applicable between the UK and EU populations.	In response to comment 3 in the 2023 CHMP/PRAC Final Assessment Report
		None (Section 7.4 in version 1.0)	This section was removed.	The content of this section was considered not informative.
		4 9.2 9.2.1	The text describing the start and end of follow-up has been modified for clarity, including the note to Figure 1.	In response to comment 9 in the 2023 CHMP/PRAC Final Assessment Report

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Cover page 4 8 9.3.2 9.9	Exploratory outcomes (secondary outcomes) have been added to the study.	In response to comments 4 and 14 in the 2023 CHMP/PRAC Final Assessment Report
		9.1 9.2 9.2.1 9.9	The eligibility criteria and their graphic depiction have been modified so that all target populations with COVID-19 are eligible for this study (patients with moderate or severe hepatic or renal impairment are already at increased risk for progression to severe COVID-19). The exposure window for starting treatment was extended from the previous 0-3 days.	In response to several comments in the 2023 CHMP/PRAC Final Assessment Report
		9.2.2	A sentence has been added stating that the latest available data at the time of the data extraction will be used.	Addressing comment 13 in 2022 CHMP/PRAC Final Assessment Report
		9.4.3	It has been clarified that COVID-19 test results are available in CPRD Aurum.	In response to comment 18 in the 2023 CHMP/PRAC Final Assessment Report
		9.2.1	The interval for matching exposed and unexposed has been expanded; the reasons for and advantages of matching in this setting have been restated for clarity and completeness.	In response to comment 10 in the 2023 CHMP/PRAC Final Assessment Report
		9.3 Annex 3	The medical conditions that are risk factors for progression to severe COVID-19 have been updated; code lists to identify them are provided in Annex 3.	Updated list: to align with current knowledge. Addition of code lists: in response to comment 15 in the 2023 CHMP/PRAC Final Assessment Report
		9.2.1	To capture additional patients with moderate or severe hepatic impairment, an additional table of codes of mild liver diseases has been added. Those codes will be combined with code R18 (Ascites) to capture patients with moderate hepatic impairment.	In response to comment 11 in the 2023 CHMP/PRAC Final Assessment Report

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.2.1 9.7.3.1	It has been clarified in the text that both diagnosis codes and laboratory results (where available) will be used to identify the target populations. In order to capture patients with moderate hepatic impairment, the threshold for the MELD score has been modified. Use of Child-Pugh scores has been added to complement the use of MELD scores in data sources with laboratory results (SIDIAP and CPRD). Patients with a Child-Pugh score of 7 or more will be included in a sensitivity analysis in those data sources. The criteria to include patients with moderate or severe renal impairment have been modified. A new criterion has been added: patients with eGFR $\geq$ 60 mL/min/ 1.73 m^2 and severe microalbuminuria (> 300 mg/g or > 30 mg/mmol) are now eligible for inclusion	In response to comment 12 in the 2023 CHMP/PRAC Final Assessment Report
		9.4.2	Details on how information on COVID-19 tests is available for research in SIDIAP have been added.	In response to comment 17 in the 2023 CHMP/PRAC Final Assessment Report
		9.4.4.1	The term “PASS-DUS” has been removed from this section. The AIFA description has been updated.	In response to comment 19 in the 2023 CHMP/PRAC Final Assessment Report
		9.7.4	The text for masking small cell counts was modified to explicitly denote both bounds of the masked range; eg, ”1 $\leq$ n $\leq$ 10” will be used instead of “n $\leq$ 10.”	Further described in response to comment 21 in the 2023 CHMP/PRAC Final Assessment Report

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason

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

6. MILESTONES

Milestone	Planned/actual date
Protocol C4671037 V1.0 submission	31 May 2022 (actual; including pregnant population, population with moderate or severe hepatic impairment, and population with moderate or severe renal impairment in a single protocol)
Protocol C4671047 V1.0 submission	November 2022 (population with moderate or severe hepatic impairment, and population with moderate or severe renal impairment)
Registration in the EU PAS Register	14 December 2022
Progress report submission	29 November 2022
Start of data collection[a]	Quarter 4 2023[b]
Interim report 1	14 months after protocol endorsement; estimated for quarter 4 2024[b]
Interim report 2	26 months after protocol endorsement; estimated for quarter 4 2025[b]
End of data collection[a]	Quarter 4 2025[b]
Final study report	31 March 2026[b] (planned)

CHMP = Committee for Medicinal Products for Human Use (of the European Medicines Agency); EU PAS Register = European Union Electronic Register of Post-authorisation Studies;
PRAC = Pharmacovigilance Risk Assessment Committee (of the European Medicines Agency).

Note: Contracts for study implementation between the sponsor and research organisation(s), data source selection, and approvals by data protection, data custodian, ethics, and scientific review bodies, several of which require a final or endorsed protocol, are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

a. Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts."[3] Simple counts are not part of this definition. End of data collection is "the date from which the analytical data set is completely available."[3]

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

7. RATIONALE AND BACKGROUND

Paxlovid contains nirmatrelvir (formerly PF-07321332) and ritonavir copackaged. Nirmatrelvir is an oral protease inhibitor that blocks the activity of 3-chymotrypsin-like cysteine protease, an enzyme required for the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19). Ritonavir slows the metabolism of nirmatrelvir in a way that allows nirmatrelvir to remain active in the body for longer periods of time and at higher concentrations. Nirmatrelvir is expected to retain activity against the Omicron variant.[4]

The safety of Paxlovid in individuals with hepatic or renal impairment is not known. Assessing the safety of Paxlovid among individuals with moderate or severe hepatic or renal impairment is a regulatory commitment to the European Medicines Agency (EMA).

This protocol describes a post-authorisation safety study (PASS) to assess the safety of Paxlovid in individuals with moderate or severe hepatic or renal impairment in European countries with data sources that have the ability to capture exposure and where the target populations, outcomes, and key covariates can be ascertained. The European Union (EU) summary of product characteristics (SmPC) and the United Kingdom (UK) SmPC are slightly different. The UK SmPC is more restrictive than the EU SmPC regarding the use of Paxlovid among patients with hepatic or renal impairment (see Section 7.3), which may impact the use of Paxlovid among the target population in the UK. Therefore, 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 and will also consider possible differences (if applicable) in health status between the studied populations in the EU and the UK. This non-interventional study is designated as a PASS and is a commitment to the EMA.

7.1. Authorisations

On 22 December 2021, the United States (US) Food and Drug Administration (FDA) issued an Emergency Use Authorization for Paxlovid.[5] On 31 December 2021, the UK MHRA issued a conditional marketing authorisation (CMA) for Paxlovid in Great Britain.[6] Paxlovid was authorised for use in the EU for the treatment of COVID-19 following the granting of a CMA by the European Commission on 28 January 2022.[7] The CMA was converted to full MA on 24 February 2023.

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."*[8] The recommended dosage is 300 mg of nirmatrelvir (two 150-mg tablets) and 100 mg ritonavir (one 100-mg tablet) taken together orally every 12 hours for 5 days. Paxlovid should be started as early as possible after the COVID-19 diagnosis and within 5 days of symptom onset. The 5-day treatment should be completed even if the patient requires hospitalisation due to COVID-19 progression after starting Paxlovid treatment.

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 pre-existing 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. UK 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,"*[9] 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.

8. RESEARCH QUESTION AND OBJECTIVES

The 2 research questions are:

- What is the safety profile of Paxlovid in patients with COVID-19 and moderate or severe hepatic impairment?
- What is the safety profile of Paxlovid in patients with COVID-19 and moderate or severe renal impairment?

For the population of individuals with *moderate or severe hepatic impairment*, the objectives are:

Primary objectives

- To assess the safety of Paxlovid relative to the comparator populations prescribed molnupiravir (or other comparable medications for COVID-19), where available, and to unexposed patients with COVID-19.
- To assess side effects resulting from drug overexposure due to impaired liver function with regard to severity and frequency compared with comparator groups.

Safety outcomes for primary objectives are all safety events in outpatient and inpatient settings, as available, including the following safety outcomes of special interest:

- Hepatic transaminase elevations, clinical hepatitis, or jaundice
- Severe vomiting, nausea, diarrhoea, or abdominal pain
- Dysgeusia, headache, or hypertension
- Anaphylactic reactions

Secondary objective

- To assess all safety events included in the primary objective that require hospitalisation or emergency department visits

For the population of individuals with *moderate or severe renal impairment*, the objectives are:

Primary objectives

- To assess the safety of Paxlovid relative to the comparator population prescribed molnupiravir (or other comparable medications for COVID-19), where available, and to unexposed patients with COVID-19.
- To assess side effects resulting from drug overexposure due to impaired renal function with regard to severity and frequency compared with comparator groups.

Safety outcomes for primary objectives are all safety events in outpatient and inpatient settings, as available, including the following safety outcomes of special interest:

- Severe vomiting, nausea, diarrhoea, or abdominal pain
- Dysgeusia, headache, or hypertension
- Anaphylactic reactions

Secondary objective

- To assess all safety events included in the primary objective that require hospitalisation or emergency department visits

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 (or other comparable medications), and the unexposed individuals, all with 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 (or other comparable medications), and the unexposed individuals, all with 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 (interim report 1 and interim report 2) will provide counts of the target populations, separately for Paxlovid users, users of

molnupiravir, users of other comparable medications (Section 9.1.2, Table 2), and the unexposed comparator group. Relevant patient characteristics will be presented for each exposure group in 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[10] (see additional discussion in Section 9.1.1). At the time of preparing this protocol, molnupiravir was not utilised in the populations covered by some selected data sources or its use was not captured by the data sources (eg, France and Information System for Research in Primary Care [SIDIAP] in Catalonia, Spain). Therefore, a second comparator group is included in the study: individuals in the target populations with COVID-19 who 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, if feasible. Pooling of results using meta-analytic techniques is planned for the primary and secondary outcomes. 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 annual interim reports with results of the feasibility component (described previously) and preliminary outcome counts; and a final report with the results of the safety component.

The ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) study protocol checklist to confirm that all key methods elements for pharmacoepidemiology research are addressed explicitly in this protocol is included in Annex 2.

9.1.1. Discussion of molnupiravir as an active comparator

Molnupiravir was not authorised in the EU at the time of writing this protocol. However, EMA issued advice indicating that it could be used, like Paxlovid, to treat adult patients with COVID-19 who do not need supplemental oxygen and who are at increased risk for progression to severe COVID-19.[10] Like Paxlovid, molnupiravir is to be administered within 5 days of symptom onset and taken for 5 days. Molnupiravir should not be administered in pregnancy or to individuals who can become pregnant and are not using contraception.[10] Some countries in the EU, eg, Italy, have made it available for use,[11] and the Spanish Health Agency included it among available treatment options.[12] On 23 February 2023, EMA's Committee for Medicinal Products for Human Use (CHMP) issued a negative opinion on the marketing authorisation filing for molnupiravir for the treatment of COVID-19 in adults because "the clinical benefit of Lagevrio in the treatment of adults with COVID-19 who are not receiving supplemental oxygen and who are at increased risk of developing severe COVID-19 could not be demonstrated."[13]

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

Because of the similar indication and mode of use, molnupiravir users are anticipated to be comparable to Paxlovid users in terms of COVID-19 severity at treatment start and risk for progression to severe COVID-19. Molnupiravir can be used in patients with hepatic or renal impairment, which can result in channelling of patients with these problems to molnupiravir and away from Paxlovid. This was confirmed in OpenSAFELY data: 0.7% of Paxlovid users had liver disease and less than 0.5% had kidney disease, while 4.9% of molnupiravir users had liver disease and 11.2% had kidney disease.[16] 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[17]	• Adults and children with pneumonia requiring supplemental oxygen • Adults and children who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intravenous	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[18]	• COVID-19 preexposure prophylaxis in adults and adolescents • Treatment of adults and adolescents with COVID-19 who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intramuscular[18] or intravenous[19]	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[20]	• Rheumatoid arthritis, periodic fever syndromes, familial Mediterranean fever, and other conditions • COVID-19 treatment in adults with pneumonia requiring supplemental oxygen who are at risk for 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

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

Drug	Indication and mode of administration	Hepatic Impairment	Renal Impairment	Comments
Regdanvimab[21]	• Treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intravenous infusion	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
Tocilizumab[22]	• Rheumatoid arthritis, juvenile idiopathic polyarthritis, and other conditions • Treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation • Intravenous infusion	• 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[23]	• COVID-19 postexposure prophylaxis • Treatment of COVID-19 in adults and adolescents who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intravenous infusion or subcutaneous injection	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

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

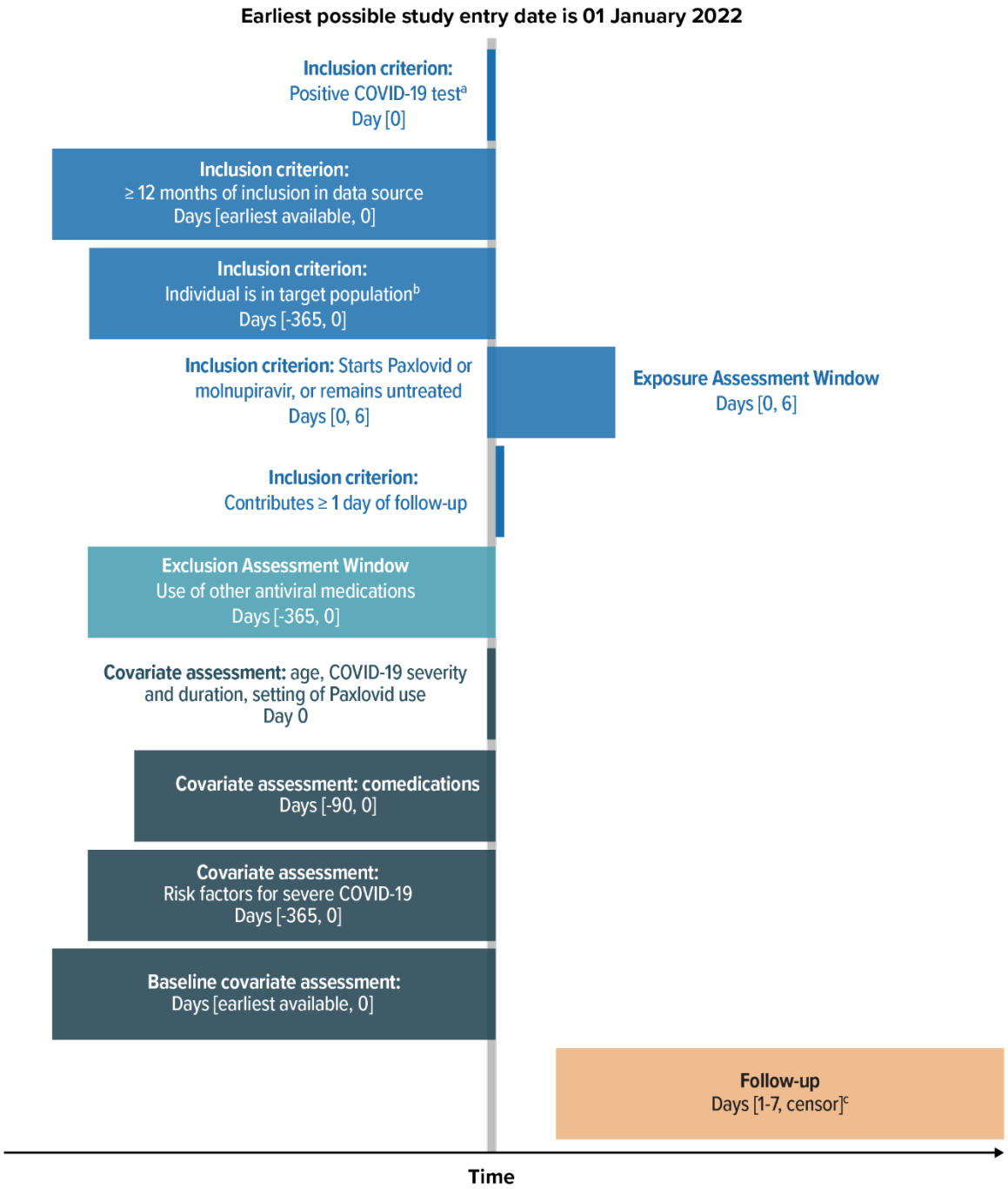
Drug	Indication and mode of administration	Hepatic Impairment	Renal Impairment	Comments
Sotrovimab[24]	• Treatment of adults and adolescents with COVID-19 who do not require oxygen supplementation and are at increased risk for progression to severe COVID-19 • Intravenous infusion	No dose adjustment needed	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/covid-19-medicines. Accessed 12 June 2023.

9.2. Setting

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

Figure 1. Graphical representation of study design



Note: The unexposed comparison group will be identified from individuals in the target population who have not received any antiviral COVID-19 treatment and who also meet the other inclusion criteria. Figure based on Schneeweiss et al[25]

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 7 (1 day after day 6 if they start treatment on day 6), depending on which day exposure or unexposure (via matching) starts, and end at the earliest of 1 month after starting treatment, death, disenrollment or migration, occurrence of the outcome being evaluated, end of data availability from the data source, or treatment group crossover. Treatment crossover will occur when unexposed patients start treatment with either Paxlovid or molnupiravir or other comparable medications, or when patients taking molnupiravir or other comparable medications 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).

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 the following inclusion criteria to be eligible for inclusion in the study:

1. Individual has documented COVID-19
2. Individual had moderate or severe hepatic impairment at the time of COVID-19 diagnosis
3. Individual has at least 12 months of inclusion in the data source at the time of starting the study medications or becoming eligible
4. Individual has at least 1 day of follow-up
5. Individual started treatment with Paxlovid or comparator medication within 7 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. Individual used 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 (or other comparable medications) during the study period, and unexposed individuals.

Time 0 will be the day on which an individual meets all eligibility criteria (Figure 1); they will have 7 days to start the first-time treatment with Paxlovid or molnupiravir or other comparable medication (this is often described as a grace period; ie, days [0, 6] inclusive of both bounds). Unexposed individuals will be matched with individuals starting Paxlovid by time since COVID-19 diagnosis (days) and calendar time (within ± 1 week; ie, days [−6, 6]

inclusive of both bounds). Paxlovid and molnupiravir users (or other comparable medications users) will be matched on calendar time. Matching at this stage intends to (1) increase comparability of treatment groups regarding time since start of disease, including potential changes in severity over time, (2) balance immortal time by imposing the observed immortal time before treatment among the treated onto the untreated patients,[26] and (3) ensure that treated and untreated are contemporary (calendar time is a proxy for prevalence of circulating variants, preferred therapeutic approaches, etc). If insufficient matches are found because of the restriction imposed by the period of 1 week around the diagnosis for matching, the period will be extended. This change, if applicable, will be described in the final report together with sensitivity analyses of the impact of extending the period.

Follow-up

Follow-up will start from day 1 (1 day after time 0 if an individual starts treatment on day 0) through day 7 (1 day after day 6 if they start treatment on day 6), depending on which day exposure or unexposure (via matching) starts, and end at the earliest of 1 month after starting treatment, death, disenrollment or migration, occurrence of the outcome being evaluated, 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 (or other comparable medications), and when molnupiravir users (or users of other comparable medications) 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).

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[27], which has shown to correlate with inpatient admissions and mortality rates.[27] 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. In addition, and to maximise the inclusion of individuals with moderate or severe hepatic impairment, codes included in the adaptation of the Charlson Comorbidity Index for mild liver disease by Ludvigsson et al[28] will be included as moderate or severe hepatic impairment if they coexist with an ascites code (R18). This complementary list of codes is included in Table 4.

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, I85.1 [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

Table 4. ICD-10-CM [ICD-10] codes to identify mild severe hepatic impairment. The codes listed will identify moderate or severe hepatic impairment when coexisting with Ascites code R18

ICD-10-CM code [ICD-10 code if different or fifth digit not available in ICD-10]	Description
B15-B19	Viral hepatitis
K70.31 [K70.3]	Alcoholic cirrhosis of liver with ascites [Alcoholic cirrhosis of liver]
K73*	Chronic hepatitis, not elsewhere classified
K74.60/K74.69 [K74.6]	Other and unspecified cirrhosis of liver
K75.4	Autoimmune hepatitis
K70.9	Alcoholic liver disease unspecified

Source: Ludvigsson et al[28]

In data sources where laboratory results are available (SIDIAP and CPRD have outpatient laboratory test results), severe chronic liver disease can be measured by a Model for End-Stage Liver Disease (MELD) score greater than 24.[29] There is no exact correspondence between Child-Pugh stages and the MELD scores. However, patients with MELD scores equal to or greater than 10 have similar mortality than do patients with a Child-Pugh score of less than 10.[30] Moreover patients with COVID-19 with those scores have poorer prognosis than patients with lower MELD scores.[31] The same score threshold combined with elastography has clear prognosis implications for patients.[32] Thus, we propose to include in the study individuals with MELD scores equal to or greater than 10 to identify via laboratory results additional individuals with moderate or severe hepatic impairment. Although there have been efforts to derive Child-Pugh scores from electronic healthcare data sources with identifiable rich clinical data,[33] those types of data are 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.[34] 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. Individuals with diagnosis or procedural codes indicating ascites or encephalopathy will be

assigned 2 Child-Pugh score points for each clinical sign present (or 4 if they have both signs). The absence of each of the clinical signs will be assigned 1 point each (or 2 points if neither of the 2 signs are present). Thus, only the presence or absence of ascites and encephalopathy will be evaluated. It will not be possible to evaluate the severity of ascites and encephalopathy; thus, no individuals will be assigned 3 points. However, individuals with a Child-Pugh score of 7 or more will be included in a sensitivity analysis in those data sources with available laboratory results, thereby ensuring that individuals with at least Child-Pugh stage B are included. To summarise, in data sources with available laboratory results, the Child-Pugh and MELD scores will be calculated on top of the codes displayed in Table 3 and Table 4 to identify additional individuals with moderate or severe hepatic impairment.

9.2.1.2. Individuals with moderate or severe renal impairment

Inclusion criteria

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

1. Individual has documented COVID-19
2. Individual has 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. Individual has at least 12 months of inclusion in the data source at the time of starting the study medications or becoming eligible
4. Individual has at least 1 day of follow-up
5. Individual started treatment with Paxlovid or comparator medication within 7 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. Individual used 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 7 days to start the first-time treatment with Paxlovid or molnupiravir or other comparable medications (this is often described as a grace period; ie, days [0, 6] inclusive of both bounds). Unexposed individuals will be matched with individuals starting Paxlovid by time since COVID-19 diagnosis (days) and calendar time (within ± 1 week; ie, days [−6, 6] inclusive of both bounds). Paxlovid and molnupiravir users (or other comparable medications) will be matched on calendar time. Matching at this stage intends to (1) increase comparability of treatment groups regarding time since start of disease, including potential

changes in severity over time, (2) balance immortal time by imposing the observed immortal time before treatment among the treated onto the untreated patients,[26] and (3) ensure that treated and untreated are contemporary (calendar time is a proxy for prevalence of circulating variants, preferred therapeutic approaches, etc). If insufficient matches are found because of the restriction imposed by the period of 1 week around the diagnosis for matching, the period will be extended. This change, if applicable, will be described in the final report together with sensitivity analyses of the impact of extending the period.

Follow-up

Follow-up will start from day 1 (1 day after time 0 if they start treatment on day 0) through day 7 (1 day after day 6 if they start treatment on day 6), depending on which day exposure or unexposure (via matching) starts, and end at the earliest of 1 month after starting treatment, death, disenrollment or migration, occurrence of the outcome being evaluated, 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 (or other comparable medications), and when molnupiravir users (or users of other comparable medications) 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).

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 5 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[28] 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.[35,36] 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).

Table 5. 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)

Table 5. ICD-10 codes to identify moderate or severe renal impairment

ICD-10- code	Description
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 in this target population if:

- They have 2 eGFR test results < 60 mL/min/1.73 m^2—taken from Levey et al[37]—separated by at least 90 days (with no normal values in between) but not more than 540 days

OR

- They have 2 urine albumin-to-creatinine ratio (UACR) results ≥ 30 mg/g separated by at least 90 days (with no normal values in between) and no more than 540 days (severe albuminuria).

Definitions for CKD stages are based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[37,38] Currently, albuminuria levels are also used to stratify levels of renal impairment.[38] The 3 microalbuminuria categories add prognosis information on renal and cardiovascular complications to the eGFR categories. However, patients in eGFR categories 1 and 2 (eGFR ≥ 60 mL/min/1.73 m^2) and moderate albuminuria have a different clinical profile and normal to moderately increased risk of complications. Therefore, among patients with eGFR ≥ 60 mL/min/1.73 m^2, only the patients with severe albuminuria will be considered. A potential limitation using UACR test results is that clinicians often use dipstick measurements, which are not captured in most data sources.

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,[39] which removes the race-related coefficient, following recommendations from recent evidence and guideline statements:[40-43]

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

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 ≤ 0.9 mg/dL for male participants and ≤ 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

9.2.2. Study period

The study period will start on 01 January 2022 (in alignment with regulatory authorisation in Europe) and end based on the calendar period coverage at the time of the last data extraction. Table 6 shows the anticipated dates during which data will be observed for each study report. The latest available data at the time of the data extraction will be used.

Table 6. Dates for start of study period and end of data availability for each study report in each data source

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

CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics; Q*n* = quarter of a year; SIDIAP = Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) Catalonia, Spain; SNDS = French Administrative Healthcare Database [System National De Données de Santé].

a. In CPRD Aurum, HES linkage is required. As of June 2023, the latest release of HES data covers the period April 1997 to March 2021. This lag time of coverage may delay the start of the analysis or limit the availability of data for the analysis

Note: Interim report 1 has an anticipated data cut in Q4 2023; interim report 2 and final report in Q4 2024.

9.2.3. Outcome risk window of interest

For Paxlovid, molnupiravir, other comparable treatments, if applicable, and unexposed patients, the risk window for outcome ascertainment will be the first month after the start of follow-up. Treatment duration is short (5 days) and it is assumed that the risk of overexposure or the safety outcomes will not go beyond 1 month after starting the treatment.

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 (or other alternative comparable medications) and no treatment with either Paxlovid or molnupiravir (unexposed).

9.3.2. Outcomes

9.3.2.1. Primary outcomes

The primary outcomes will be the safety outcomes listed in Table 7 occurring in any setting (outpatient or inpatient), as available.

Table 7. Primary study outcomes in each target population

Study population	Study outcomes
Hepatic impairment population	Any safety event Safety outcomes of special interest: • Hepatic transaminase elevations, clinical hepatitis, or jaundice • Severe vomiting, nausea, diarrhoea, or abdominal pain • Dysgeusia, headache, or hypertension • Anaphylactic reactions
Renal impairment population	Any safety event Safety outcomes of special interest: • Severe vomiting, nausea, diarrhoea, or abdominal pain • Dysgeusia, headache, or hypertension • Anaphylactic reactions

Identification of safety events will be derived from evaluation of events following Paxlovid initiation (see Section 9.3.2.1.2.).

9.3.2.1.1. Safety outcomes of special interest

Safety outcomes of special interest listed in Table 7 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, ie, 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 hepatic event will be a study outcome and will determine the end of follow-up for this outcome; later hepatic events will not be included. However, later hepatic events resulting in hospitalisation or ED visit will be included as secondary outcomes when the first hepatic event identified did not result in hospitalisation or ED visit. For combined endpoints (eg, 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.

9.3.2.1.2. Other primary safety outcomes

These outcomes will be identified from diagnosis codes from outpatient diagnoses (as available in each data source), hospitalisation discharge diagnoses and ED diagnoses documented in the participating data sources among eligible Paxlovid-exposed individuals. These will be events that are recorded up to 1 month after the Paxlovid dispensing date in individuals who are eligible for the study. Events that are included among the primary outcomes will be removed from the preliminary list. The resulting list will be reviewed by the research team to determine whether any item does not merit assessment.

These outcomes will be analysed within the planned cohort design. Events selected from data sources using the same coding system will be included in all data sources using the same coding system if they are found in more than 1 data source. Events identified using SNOMED CT will be assessed in CPRD Aurum only, and the same approach will be followed in other data sources using unique coding systems.

Analyses will be conducted only if a minimum number of cases are observed in the study population. The events will be identified during analyses for interim reports; the list and counts of the selected outcomes for outcomes other than outcomes of special interest will be presented in the first and second interim reports; safety analyses on these outcomes will be presented in the final study report.

9.3.2.2. Secondary outcomes

The outcomes listed in Table 7 resulting in ED visits or hospitalisations will be identified and considered as secondary outcomes.

9.3.3. Other variables

In addition, the following study variables will be included:

- Demographics
- Conditions that will be ascertained to identify increased risk for progression to severe COVID-19:[44] asthma, cancer, cerebrovascular disease, chronic kidney disease, chronic lung diseases (only bronchiectasis, chronic obstructive pulmonary disease [COPD], interstitial lung disease, pulmonary embolism, pulmonary hypertension), chronic liver diseases (only cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis), cystic fibrosis, type-1 diabetes, type-2 diabetes, disabilities (see list in Annex 3), heart conditions (including heart failure, coronary artery disease and cardiomyopathies), human immunodeficiency virus (HIV) infection, mental health conditions (only mood disorders [including depression] and schizophrenia spectrum disorders), neurologic conditions (only dementia), obesity (body mass index ≥ 30 kg/m^2), primary immunodeficiencies, smoking (current or former), solid organ or blood stem cell transplantation, tuberculosis, and use of immunosuppressive medications including corticosteroids. Conditions associated with suggestive higher risk will also be ascertained:[44] overweight (body mass index ≥ 25 kg/m^2 but < 30 kg/m^2), sickle cell

disease, and substance use disorders. Increased risk for progression to severe COVID-19 will be ascertained in the 12 months before time 0. From the noted reference,[44] not incorporated will be physical inactivity (because it is not ascertainable in the selected data sources). Codes to identify these variables are presented in Annex 3.

For the purpose of this PASS, individuals at increased risk for progression to severe COVID-19 will be those with a 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 these exact variables).

- Comedications, including medications listed as contraindicated or with potentially significant interactions with Paxlovid in the EU SmPC,[8] Section 4.3 and Table 1, or the UK SmPC,[9] Table 1 and Table 2. Use of these medications will be quantified in the 3 months before Paxlovid use to provide information on the number of patients who may be at risk for simultaneous use of Paxlovid and these medications; please see caveats in Section 9.9.
- COVID-19 diagnoses, days since current infection, COVID-19 severity at start of treatment.
- COVID-19 vaccination status, as available.

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

9.4. Data sources

As of 20 March 2023, the MAH confirmed that Paxlovid has been supplied to Denmark, France, Germany, Italy, the Netherlands, Norway, Slovenia, Spain, Sweden, and the UK, initially or continuing under special government contracts, resulting in different distribution and reimbursement channels being used and subsequent challenges capturing its prescription and distribution. Current information is that prescribed/dispensed Paxlovid should be captured in existing electronic population data sources in Denmark, France, Spain, and the UK. Currently, the proposed data sources are SNDS (France), SIDIAP (Catalonia, Spain), and CPRD Aurum (UK). Exposure counts are presented in Table 8.

Table 8. Study feasibility: Paxlovid in European data sources/registries

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

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

In France, Paxlovid received early access authorisation on 20 January 2022 and has been made available for prescription since 03 February 2022[47] in outpatient settings (a specific procedure needs to be completed by general practitioners and community pharmacists) and inpatient settings (including emergency care). To date, only dispensing from the outpatient setting (community pharmacies) are captured in SNDS; for inpatients and ED visits, the drug is directly provided to the hospital by health authorities, and patient exposure is not captured. In July 2022, access to Paxlovid was extended to the following groups: individuals who are immunocompromised (regardless of age or vaccination status), those at high risk of severe disease due to comorbidities when they have an incomplete vaccination status (ie, when they are unvaccinated at any age, have not received a booster at any age, or have not received a second booster in individuals aged > 60 years); patients aged > 60 years with or without comorbidities when their vaccination schedule is incomplete (absence of second booster in particular).[48] Note that 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.[12] For Paxlovid (authorised), due to the interactions and special warnings for use, a special validation is required. Each autonomous region (eg, Catalonia) establishes its own validation, and the validation process should be shorter than 24 hours. 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 MAH will share additional information about Paxlovid supply and forecast for other European countries as it becomes available, and the research team will evaluate whether this allows capture of Paxlovid in additional electronic data sources in these countries.

- In Denmark, Paxlovid has been supplied. Distribution started in 2022; data for 2022 indicate that 400 courses of treatment had been sold in 2022 (Table 8).
- The Italian Medicines Agency (AIFA) established a national registry for Paxlovid and other antivirals for COVID-19. At this time, and while direct Italian government funding rather than funding through individual region occurs, capture of Paxlovid dispensing/prescriptions in the established electronic data sources that are commonly used for PASSs in Italy (eg, regional or local health unit data sources) is expected to be minimal. Initially, Paxlovid could only be prescribed and dispensed in selected centres in each Italian region (modality 1). As of April 2022, Paxlovid can be dispensed in pharmacies with a prescription also by general practitioners (modality 2). The counts, but not the clinical characteristics of the patients receiving Paxlovid under modality 2 are

captured in the AIFA registry (D Striano, Pfizer Italy, email communication, 13 May 2022).

- As long as the German government continues to cover Paxlovid payments, it is expected that Paxlovid prescriptions will not appear in the German Statutory Health Insurance data sources, which is based on prescriptions reimbursed by the insurers.
- The Netherlands had a supply (about 15,000 packs), leading to a small study size.
- Norway had a supply (about 25,000 packs), leading to a small study size.
- Slovenia had a supply (19,000 packs as of March 2023), leading to a small study size.
- In Sweden, Paxlovid will be prescribed and distributed in hospitals, and therefore will not be captured in the Swedish registers typically used for pharmacoepidemiology research.
- The UK OpenSAFELY data source is proposed for exploration as a supplementary data source for the PASS.

9.4.1. France: French Administrative Healthcare Database (SNDS)

SNDS contains individual-level pseudonymised information on all outpatient reimbursed claims from all main French healthcare insurance schemes linked to the national hospital discharge summaries database and the national death register. It currently covers the overall French population—about 67 million individuals—from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires, capturing data from 2011.[49] 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.[49]

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.[50]

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.[51] While the linkage of the SI-DEP to the SNDS has been anticipated by the French law, issues related to the linkage are being addressed. The SNDS data holder is currently working on improving the linkage process, but the release date has not been communicated yet. The fact that a test has been performed is well captured by the database even in the absence of this linkage. Outpatient diagnoses are not captured in the SNDS.

By law, it is not possible to go back to the patient to collect additional information. Most outcomes are identified with hospital diagnosis codes. For some studies, independent expert validation using reconstituted electronic health records using all information in the database, ie, assembling a chronological listing of diagnoses, procedures, and medications recorded for a patient, can be conducted.[52]

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 328 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 5.8 million people (75% of the Catalan population) and is representative of the Catalan population.[53]

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.[53]

Recent reports have shown SIDIAP data to be useful for epidemiological research. SIDIAP is listed under the ENCePP resources database (https://www.encepp.eu/encepp/viewResource.htm?id=48126).

To facilitate research on COVID-19, SIDIAP has included within the data available for research information on COVID-19 tests conducted within the Catalan public primary care system, including test type (eg, antigen test), date, and result.[54] No additional linkages are needed.

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

9.4.3. UK: Clinical Practice Research Datalink Aurum and Hospital Episode Statistics

The 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 only English practices.[55] Most of the data are coded using SNOMED codes. As of November 2022, CPRD Aurum contained data on 15,713,221 current acceptable patients (ie, active patients available for research) and 46,761,868 patients, including deceased and transferred-out patients.[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.

COVID-19 tests results are available in CPRD Aurum without additional linkages, including results from PCR tests.[56] Other COVID-19–related data sets could be explored. Study applications need to be submitted to and approved by the CPRD Research Data Governance. RTI Health Solutions also needs to complete an institutional review board (IRB) application for non-human research status determination.

9.4.4. Additional exploration of data sources

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

Paxlovid users in Italy are being registered in a national registry mandated by AIFA. More details about the AIFA registry for patients receiving COVID-19 oral antiviral agents and its data collection form are provided in Annex 4. The form covers information to be collected at enrolment and 1 section that needs to be completed via telephone follow-up 1 month later. The baseline form collects demographic and comorbidity information appropriate to identify the patients of interest to describe drug utilisation, including specific questions on pregnancy and renal and hepatic impairment. AIFA does not collect data to support the safety analyses that are described in this protocol; at this point, individual-level data are not available to external researchers.

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

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

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

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

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

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

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

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

hospitals or hospital-like facilities. Pathways to identify eligible patients and facilitate access to Paxlovid are determined by each region.

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

- Tuscany is an Italian region, with approximately 3.6 million inhabitants. The ARS Toscana is a research institute in the Tuscany region. The ARS Toscana data source comprises all information collected by the Tuscany region to account for the healthcare delivered to its inhabitants. Moreover, ARS Toscana collects data from regional initiatives. All data in the ARS Toscana data source can be linked at the individual level through a 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. UK: 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 9 describes the main features of OpenSAFELY and CPRD Aurum.

Table 9. 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

Table 9. Main features of OpenSAFELY and CPRD Aurum

Feature	OpenSAFELY	CPRD Aurum
Access	• Only approved users • Project approval required from NHS England	• Through paid CPRD licence • Subject to protocol approval via CPRD's Research Data Governance Process
In-hospital treatments for COVID-19	Yes	No (plan to reach out to explore whether these linkages would be possible)
Laboratory test results	Yes, from primary care health records	Yes, from primary care health records
Data Security	OpenSAFELY does not allow moving patient data outside the secure environments where they already reside. Data reside centrally, and analysis programmes also run centrally. Analysis programmes are written by researchers.	Data are downloaded locally, and researchers have access to pseudonymised patient data in electronic repositories protected by each institution under the requirements of a licence and/or data use agreement with CPRD.
Can analytical files be downloaded locally?	No, only dummy data sets that can support the programming of analytical code	Yes
Software required to run analysis	Stata, R, or Python	Any
Knowledge and implementation of other IT systems required?	Git/GitHub	None
Open access policy	• All platform activity is publicly logged. All code for data management and analysis is shared centrally, under open licences and by default, for scientific review and efficient re-use.	All scripts and codes lists are kept by the investigators running the different studies according to their institution's policies.
Transparency	• All projects started within OpenSAFELY are visible to the public. • OpenSAFELY requires all researchers to archive and publish their analytic code, changes are shared publicly.	• A list of approved projects using CPRD data is publicly available from CPRD's site (https://cprd.com/approved-studies-using-cprd-data). • A list of publications using CPRD data is publicly available from CPRD's site (https://cprd.com/bibliography).

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

a. UK population as of 01 January 2019 (estimated; this is the last available estimate).[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 US 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, information from 2 data sources is provided. OpenSAFELY[62] reports that of 93,860 individuals aged 12 years or older who were eligible for COVID-19 treatment, 4680 individuals aged 12 years or older had received Paxlovid and 4620 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 (Note: the publication states a total of 93,870 potentially eligible patients, but the addition of age-specific counts in Table 3 of the referenced paper results in the number that we report here).[62] As of 28th April 2022, 40 Paxlovid users had liver disease (0.9 % of Paxlovid users at the time), and fewer than 8 had kidney disease (Table 10). Percentages were higher in molnupiravir users and in patients eligible for treatment with drugs for COVID-19.[62]

Table 10. 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	93,860	19,040	4680	4620
Liver disease	5110 (5.4%)	800 (4.2%)	40 (0.9 %)	250 (5,4%)
Kidney disease	5860 (6.2%)	2020 (10.6%)	< 8 (< 0.2%)	540 (11.7%)

COVID-19 = coronavirus disease 2019.

Note: Eligibility for treatment is based on having a positive test for COVID-19 or receiving a COVID-19–specific treatment, and having an immune-mediated inflammatory disorder, primary immune deficiencies, solid cancers, selected rare neurological conditions, haematological diseases, stem cell transplant, solid organ transplant, kidney disease, liver disease, Down's syndrome, or immunosuppression due to HIV or AIDS.[63] COVID-19–specific treatments were Paxlovid, sotrovimab, remdesivir, molnupiravir, and casirivimab.[63] Percentages shown in this table are column percentages. Patient counts of eligible patients reported in the referenced publication[62] are somewhat lower than in the previous report,[16] despite the observation periods being practically identical.

We also used data available in SNDS: 50,818 individuals aged 18 years or older used Paxlovid between 04 February and 27 October 2022, and use increased each month.[45] The mean age of users was 67 years, and 55% were female. Of these Paxlovid users, 1227 had liver conditions, 49 were on chronic dialysis, and 556 had received a kidney transplant; 41%

of Paxlovid users did not have a documented COVID-19 test 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 11 displays the incidence rates assumed for the safety outcomes of special interest proposed among patients with moderate or severe liver or 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 dysgeusia and had to be extrapolated or assumed.

Table 11. Incidence rates assumed for safety outcomes of special interest

Outcome	Incidence rate or range	Reference
Anaphylactic reactions	2-13 per 100,000 PYs	Avillach et al[64]
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[65]
Severe vomiting, nausea, diarrhoea, or abdominal pain	6% of all emergency department visits; 17% of the patients were admitted to the hospital (93,367 ED visits in 2014); an incidence of 100 per 1000 PYs has been assumed.	Cervellin et al[66]
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[67]

For the study size calculations in Table 12, we have assumed that by combining all Paxlovid users across all data sources, there would be between 10,000 and 30,000 users of Paxlovid, that 1% of the users will have moderate or severe renal disease, and that 2% of the users will have moderate or severe liver disease. Table 12 shows 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 exposed individuals and comparators is 1.0. Table 12 shows that the precision of the relative risk estimates will be low for anaphylactic reactions and the hepatic outcome, whereas 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 12. 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 per 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					
40 per 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
Severe abdominal pain					
100 per 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

PY = person-year; RR = risk ratio.
Note: Background incidence rates were obtained from references in Table 11, 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, common data model (CDM), and common analytics programmes based on existing health data, to the extent 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.[68] 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

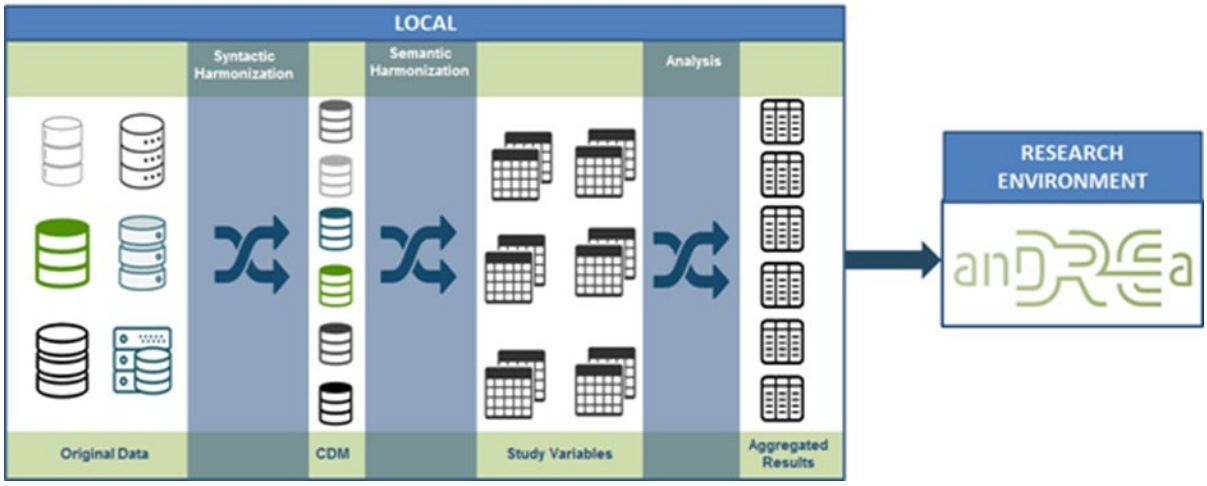
conducted to measure the integrity of the ETL, as well as internal consistency within the context of the CDM (see Section 9.8).

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

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

Figure 2. Data management plan



9.6.1. Record retention

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

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

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

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

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

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

9.6.2. Data extraction

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

9.6.3. Data processing and transformation

Data processing and transformation will be conducted using R (and SAS quality-control code) against the syntactically harmonised CDM. The scripts will first transform the data in the syntactically harmonised CDM to semantically harmonised study variables (see

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

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

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

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

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

9.6.4. Data access

Within the DRE, each project-specific area consists of a separate secure folder called a "workspace." Each workspace is secured behind a firewall. Each workspace can be accessed only by users specific to its respective data source. Access to this workspace is possible only with double authentication using an identification code and password together with the user's mobile phone for authentication. Upload of files is possible for all researchers with access to the workspace within the DRE. The DRE offers tools to control and monitor which activities take place within projects, in compliance with General Data Protection Regulations and Good Clinical Research Practices.

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

9.6.5. Data quality checks

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

9.6.5.1. Level 1 quality checks (completeness of ETL)

Level 1 data checks review the completeness and content of each variable in each table of the CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (eg, data types, variable lengths, formats, acceptable values).

Level 1 checks of R code and instructions are independent of any study and publicly available on the IMI-ConcePTION GitHub (https://github.com/IMI-ConcePTION/Level-1-checks). They should be run on each new data instance that undergoes ETL.

Specific objectives of level 1 checks:

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

The level 1 checks are divided in 5 major steps:

Step 1: Check ConcePTION CDM table formatting

1. Check if all rows of the CDM csv files in the working directory contain the correct number of variables.
2. Check if all variables in the CDM table are present irrespective of their content.
3. Check if variable names in the csv are written in lowercase.
4. Check for presence of all mandatory variables according to the ConcePTION CDM.
5. Check for presence of non-mandatory variables by comparing between the table of interest and the information recorded in the METADATA table.
6. Check presence of vocabularies for specific variables.
7. Assess formats for all values and compare with a list of acceptable formats that has been filled out in the METADATA table.

Step 2: Conduct missing data analysis

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

Step 3: Check dates

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

- Day: 01-31

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

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

Step 5: Check distribution of continuous variables and date variables

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

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

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

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

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

The level 2 checks are divided into 8 major steps:

- Detect event dates that occur before birth date.
- Detect event dates after date of death.
- Detect event dates outside observation periods.
- Detect subjects included in a CDM table without a corresponding record in the PERSONS table.
- Detect observations associated with a visit_occurrence_id that occurs before the visit_start_date.
- Detect observations associated with a visit_occurrence_id that occurs after the visit_end_date.

- Detect observations associated with a visit_occurrence_id for which the associated person_id differs from that in the VISIT_OCCURRENCE table.
- Detect subjects indicated in PERSON_RELATIONSHIPS as the parent of a child with a birth_date less than 12 years prior to the recorded birth_date of the associated child.

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

9.6.5.3. Level 3 quality checks (study variable check)

Level 3 checks focus on key study variables (population, medications, diagnoses, 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. Within each target population, and if sufficient numbers of patients allow for it, results will be presented overall and in the strata of the paediatric population (ie, individuals who are dispensed Paxlovid while aged < 18 years) and the adult population (18 years of age or older).[70]

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 the risk window (ie, 1 month after starting follow-up).

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 1 month after starting follow-up (1 – KM curves by cohort will be displayed). Time to outcome will be defined as the time from start of follow-up (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. The propensity score 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 and risk differences will be calculated only if at least 5 outcomes are present among the individuals that will be included in a given outcome analysis in the study population from a given data source.

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.

- In the data sources that have laboratory results available (CPRD and SIDIAP), a sensitivity analysis will also include patients with a calculated Child-Pugh score of 7 or higher in the target population of individuals with moderate or severe hepatic impairment.
- The risk window will be extended to 3 and 6 months to detect potential cases that may appear a long time after having stopped Paxlovid or comparable medications.[71]
- The potential effect of unmeasured confounding will be evaluated using quantitative bias analysis methods described by VanderWeele and Ding.[72] 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. A minimum of 3 data points will be required (ie, results from at least 3 data sources need to be available to proceed with meta-analysis for a given outcome). Risk ratios obtained from sensitivity analyses may be meta-analysed if numbers are adequate.

9.7.4. Small cell count policy

The small cell count rules specified in Table 13 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 13.

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

Table 13. Small cell count rules for reporting results

	SNDS (France)	SIDIAP (Catalonia, Spain)	CPRD Aurum (UK)
Numbers to be masked	1-10	1-4	1-4
Text to be used in redactions	$1 \leq n \leq 10$	$1 \leq n < 5$	$1 \leq n < 5$
Possible to share with SIGMA Paxlovid PASS research centres	No	Yes	Yes
Possible to share with regulatory authorities. Note: report is provided to authorities by MAH (Pfizer)	No[73]	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 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, 41.3% of Paxlovid users did not have documented COVID-19 tests in the 10 days before or after Paxlovid use (58.7%, or 26,464 of 45,086 for whom this is reported, had such a test)[45]; in the previous available report, with data until June 2022, only 27% of Paxlovid users did not have COVID-19 tests within 10 days before or after Paxlovid use.[74] Identifying unexposed individuals that 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 (see Section 9.5). If the number of individuals is too small to sustain comparative analyses (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;[10] for example, AIFA has recently authorised its use in Italy,[11] and use has been documented. Molnupiravir is a reasonable active comparator and has been selected to serve as such. As noted, molnupiravir appears to use the same distribution channels as Paxlovid, at least in some data sources. Because molnupiravir was not used or not captured in some of the selected data sources (SIDIAP, SNDS) at the time of preparing this protocol, an alternative comparison group is included: unexposed individuals with COVID-19.

- *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 (see Table 9 in Section 9.5). Channelling will be addressed analytically (eg, propensity score weighting). It is anticipated that channelling will be more substantial in the unexposed comparator group.
- *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, use as postexposure prophylaxis (noting that the clinical trial did not meet its prespecified endpoint),[75] as treatment for long COVID-19,[76,77] and paediatric use.[78]
- *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.
- *Primary outcomes other than safety outcomes of special interest.* Limitations of identifying all safety events after exposure include that some of those events will be related to the condition and not necessarily to Paxlovid's safety profile. The proposed approach identifies safety events based on diagnosis codes only, and those events may be prevalent or incident events. Given that some data sources use unique coding systems, those events may not be equivalent across all data sources, and meta-analysis may not be feasible. However, this approach will facilitate the identification of other health outcomes that may potentially be related to the safety profile of Paxlovid in patients with moderate or severe hepatic or renal impairment. Finally, especially among patients with impaired liver function that are severally ill and require frequent hospital admissions, mild outpatient outcomes will be missed among patients hospitalised because of a competing risk setting (hospitalisation prevents the identification of mild outcomes while the patient is hospitalised).

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

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

10.1. Patient information

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

10.2. Patient consent

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

10.3. Institutional review board/independent ethics committee

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

10.4. Ethical conduct of the study

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

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[79] and has been designed in line with the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology*[80] and the UK MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions.[81] The *ENCePP Checklist for Study Protocols*[82] 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*[83] 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.[84] 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)[85] 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*.[86]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

Study reports will be prepared using a template following the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII, Section B.4.3.[3] Reports will include a progress report with a description of project 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, individuals exposed to the medications listed in Table 2, individuals exposed to other new comparable medications that may be authorised, and preliminary outcome counts; and a final report. Interim reports will also provide any new relevant information on data linkage of SNDS to the SI-DEP and implications of the lack of linkage, if applicable, for the study in the second interim report. Interim reports 1 and 2 will provide updated information on the feasibility of using the 2 other potential data sources, AIFA in Italy, and OpenSAFELY in the UK, and on any other potential data source that may be relevant for the study. The final report will describe finally selected propensity score matching ratios between Paxlovid, comparator medications, and unexposed individuals, and the corresponding modified analysis, if necessary. The final report will also include the final list of risk factors for severe COVID-19 used for the study.

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[85] prior to the start of data collection. At completion, the final report or its summary will be posted.

Study results will be submitted for publication following recommendations of the International Committee of Medical Journal Editors,[87] 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."[79] In alignment with EMA *GVP Module VIII: Post-Authorisation Safety Studies*,[3] Section VIII.B.5, and the *ENCePP Code of Conduct*,[88] 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

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

EU PAS Register® number: EUPAS50123 **Study reference number (if applicable):** protocol number C4671047

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

[†] Date from which information on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts.

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

Comments:

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

Comments:

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

‡ Date from which the analytical data set is completely available.

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

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section number**
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQOL, QALYs, DALYS, healthcare services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

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

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section number**
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
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?	☒	☐	☐	9.2.1 9.7

Comments:

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

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section number**
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	3, 9.1, 9.4, 9.5, Annex 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:	Manel Pladevall 21 June 2023

ANNEX 3. PRELIMINARY CODE LISTS TO IDENTIFY RISK FACTORS FOR PROGRESSION TO SEVERE COVID-19

This annex presents the risk factors for progression to severe COVID-19 as listed by the US Centers for Disease Control and Prevention (CDC[44]) under the titles "higher risk (conclusive)" and "suggestive higher risk". Preliminary ICD-10 and ATC code lists to identify these risk factors have been identified and listed in Table 4-1 and Table 4-2.

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

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

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Asthma	J45 J46	Asthma Status asthmaticus	None	
Cancer	C00-C97	Malignant neoplasms	L01A L01B L01C L01X L01FB L01FC L01FD L01FE L01FF	Alkylating agents Antimetabolites Plant alkaloids and other natural products Other antineoplastic agents CD22 (Clusters of Differentiation 22) inhibitors CD38 (Clusters of Differentiation 38) inhibitors HER2 (Human Epidermal Growth Factor Receptor 2) inhibitors EGFR (Epidermal Growth Factor Receptor) inhibitors PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors

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

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)
Cerebrovascular disease	G45	Transient cerebral ischaemic attacks and related syndrome	None
	I61	Intracerebral haemorrhage	
	I63	Cerebral infarction	
	I64	Stroke, not specified as haemorrhage or infarction	
	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	
	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	
	I67.8	Other specified cerebrovascular diseases	
	I67.9	Cerebrovascular disease, unspecified	
Chronic kidney disease	N18.2	Chronic kidney disease, stage 2	None
	Other codes will not be identified as a separate entity. Other codes already included to identify the target population of patients with moderate or severe renal impairment		
Chronic lung disease			
Bronchiectasis	J47	Bronchiectasis	None
	Q33.4	Congenital bronchiectasis	
COPD (chronic obstructive pulmonary disease)	J40	Bronchitis, not specified as acute or chronic	None
	J41	Simple and mucopurulent chronic bronchitis	
	J42	Unspecified chronic bronchitis	
	J43	Emphysema	
	J44	Other chronic obstructive pulmonary disease	
Interstitial lung disease	J84	Other interstitial pulmonary diseases	None
	J99.0	Rheumatoid lung disease	
	M05.1	Rheumatoid lung disease	
Pulmonary embolism	I26	Pulmonary embolism	None
Pulmonary hypertension	I27.0	Primary pulmonary hypertension	B01AC09 epoprostenol B01AC21 treprostinil C02KX01 bosentan C02KX02 ambrisentan C02KX03 sitaxentan C02KX04 macitentan C02KX05 riociguat C02KX52 ambrisentan and tadalafil C02KX54 macitentan and tadalafil
	I27.2	Other secondary pulmonary hypertension	
Chronic liver diseases			
Cirrhosis	Will not be identified as a separate entity. Codes already included to identify the target population of patients with moderate or severe hepatic impairment		

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

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Non-alcoholic fatty liver disease	K76.0	Non-alcoholic fatty liver disease		
Alcoholic liver disease	Will not be identified as a separate entity. Codes already included to identify the target population of patients with moderate or severe hepatic impairment			
Autoimmune hepatitis	Will not be identified as a separate entity. Codes already included to identify the target population of patients with moderate or severe hepatic impairment			
Cystic fibrosis	E84	Cystic fibrosis	R07AX02 R07AX30 R07AX31 R07AX32	ivacaftor ivacaftor and lumacaftor ivacaftor and tezacaftor ivacaftor, tezacaftor and elexacaftor
Type 1 or 2 diabetes	E10 E11 E12 E13 E14 O24.0 O24.1 O24.2 O24.3 G63.2 H36.0 N08.3	Type 1 diabetes mellitus Type 2 diabetes mellitus Malnutrition-related diabetes mellitus Other specified diabetes mellitus Unspecified diabetes mellitus Pre-existing type 1 diabetes mellitus Pre-existing type 2 diabetes mellitus Pre-existing malnutrition-related diabetes mellitus Pre-existing diabetes mellitus, unspecified Diabetic polyneuropathy Diabetic retinopathy Glomerular disorders in diabetes mellitus	A10	Drugs used in diabetes
Disabilities	Individual disabilities are listed separately in the table below			
Heart conditions				
Heart failure	I11.0 I13.0 I13.2 I50	Hypertensive heart disease with (congestive) heart failure Hypertensive heart and renal disease with (congestive) heart failure Hypertensive heart and renal disease with both (congestive) heart failure and renal failure Heart failure	C01A C01D B01A	Cardiac glycosides Vasodilators used in cardiac diseases Antithrombotic agents

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

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Coronary artery disease	I20	Angina pectoris		
	I21	Acute myocardial infarction		
	I22	Subsequent myocardial infarction		
	I23	Certain current complications following acute myocardial infarction		
	I24	Other acute ischaemic heart diseases		
	I25	Chronic ischaemic heart disease		
	T82.2	Mechanical complication of coronary artery bypass and valve grafts		
	Z95.1	Presence of aortocoronary bypass graft		
	Z95.5	Presence of coronary angioplasty implant and graft		
Cardiomyopathies	I25.5	Ischaemic cardiomyopathy		
	I42	Cardiomyopathy		
	I43	Cardiomyopathy in diseases classified elsewhere		
	O90.3	Cardiomyopathy in the puerperium		
HIV infection	B20	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases	J05AE01	saquinavir
			J05AE02	indinavir
			J05AE04	nelfinavir
			J05AE03	ritonavir
	B21	Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms	J05AE05	amprenavir
			J05AE07	fosamprenavir
			J05AE08	atazanavir
	B22	Human immunodeficiency virus [HIV] disease resulting in other specified diseases	J05AE09	tipranavir
			J05AE10	darunavir
			J05AF01	zidovudine
	B23	Human immunodeficiency virus [HIV] disease resulting in other conditions	J05AF02	didanosine
			J05AF03	zalcitabine
			J05AF04	stavudine
	B24	Unspecified human immunodeficiency virus [HIV] disease	J05AF06	abacavir
			J05AG01	nevirapine
			J05AG02	delavirdine
	O98.7	Human immunodeficiency virus [HIV] disease complicating pregnancy, childbirth and the puerperium	J05AG03	efavirenz
			J05AG04	etravirine
			J05AG05	rilpivirine
			J05AG06	doravirine
			J05AR	all in chapter
Mental health conditions				
Mood disorders (including depression)	F30-F39	Mood [affective] disorders	None	
	F92.0	Depressive conduct disorder		
	F41.2	Mixed anxiety and depressive disorder		

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

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Schizophrenia spectrum disorders	F20 F21 F22 F23.1 F23.2 F25	Schizophrenia Schizotypal disorder Persistent delusional disorders Acute polymorphic psychotic disorder with symptoms of schizophrenia Acute schizophrenia-like psychotic disorder Schizoaffective disorders	None	
Neurological conditions: dementia	F00 F01 F02 F03 G31.0 G31.8	Dementia in Alzheimer disease Vascular dementia Dementia in other diseases classified elsewhere Unspecified dementia Circumscribed brain atrophy, which includes frontotemporal dementia Other specified degenerative diseases of nervous system, which includes Lewy body(ies) (dementia) (disease)	None	
Obesity (BMI > 30)	E66	Obesity	A08AB A08AA	Peripherally acting anti-obesity products Centrally acting anti-obesity products
Physical inactivity	Will not be identified as a separate entity			
Pregnancy (current or recent)	The algorithms used in the PASS pregnancy protocol (C4671037) will be used			
Primary immunodeficiencies	D80 D81 D82 D83 D84	Immunodeficiency with predominantly antibody defects Combined immunodeficiencies Immunodeficiency associated with other major defects Common variable immunodeficiency Other immunodeficiencies	None	
Smoking (current or former)	F17 Z72.0	Mental and behavioral disorders due to use of tobacco Tobacco use	N07BA01 N07BA03 N07BA04	Nicotine Varenicline Cytisinicline

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

At-risk medical conditions identified by diagnosis codes	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)	
Solid organ or blood stem cell transplantation	Z94.0	Kidney transplant status	None	
	Z94.1	Heart transplant status		
	Z94.2	Lung transplant status		
	Z94.3	Heart and lungs transplant status		
	Z94.4	Liver transplant status		
	T86.0	Bone-marrow transplant rejection		
	T86.1	Kidney transplant failure and rejection		
	T86.2	Heart transplant failure and rejection		
	T86.3	Heart-lung transplant failure and rejection		
	T86.4	Liver transplant failure and rejection		
	Y83.0	Surgical operation with transplant of whole organ		
Tuberculosis	A15	Respiratory tuberculosis, bacteriologically and histologically confirmed	J04AC01	isoniazid
			J04AC51	isoniazid, combinations
			J04AD02	tiocarlide
	A16	Respiratory tuberculosis, not confirmed bacteriologically or histologically	J04AD03	ethionamide
			J04AK01	pyrazinamide
			J04AK02	ethambutol
	A17	Tuberculosis of nervous system	J04AK03	terizidone
			J04AK04	morinamide
	A18	Tuberculosis of other organs	J04AK05	bedaquiline
	A19	Miliary tuberculosis	J04AK06	delamanid
	B20.0	HIV disease resulting in mycobacterial infection	J04AK07	thioacetazone
			J04AK08	pretomanid
	B90	Sequelae of tuberculosis	J04AM01	streptomycin and isoniazid
	J65	Pneumoconiosis associated with tuberculosis	J04AM02	rifampicin and isoniazid
			J04AM03	ethambutol and isoniazid
	K23.0	Tuberculous oesophagitis	J04AM04	thioacetazone and isoniazid
	K67.3	Tuberculous peritonitis		
	K93.0	Tuberculous disorders of intestines, peritoneum and mesenteric glands	J04AM05	rifampicin, pyrazinamide and isoniazid
			J04AM06	rifampicin, pyrazinamide, ethambutol and isoniazid
	M01.1	Tuberculous arthritis		
	M49.0	Tuberculosis of spine	J04AM07	rifampicin, ethambutol and isoniazid
	M90.0	Tuberculosis of bone		
	N33.0	Tuberculous cystitis	J04AM08	isoniazid, sulfamethoxazole, trimethoprim and pyridoxine
	N74.0	Tuberculous infection of cervix uteri		
	N74.1	Female tuberculous pelvic inflammatory disease		
	P37.0	Congenital tuberculosis		
Use of immunosuppressive medications including corticosteroids	None		H02	Corticosteroids
			L04A	Immunosuppressants
Overweight (BMI > 25 but < 30)	Will not be identified as a separate entity		None	
Sickle cell disease	D57	Sickle-cell disorders	B06AX01	crizanlizumab
			B06AX03	voxelotor

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

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

BMI = body mass index; HIV = human immunodeficiency virus; ICD-10 = *International Classification of Diseases, 10th Revision*.

Source of risk factors: CDC[44]

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

At-risk medical conditions identified by diagnosis codes: disabilities	Diagnosis code (ICD-10)	Medicinal product proxy(ies) (ATC code)
Attention-deficit/hyperactivity disorder (ADHD)	Included in neurodevelopmental disorders	None
Autism	Included in neurodevelopmental disorders	None
Cerebral palsy	G80 Cerebral palsy	None
Charcot foot	M14.6 Neuropathic arthropathy	None
Chromosomal disorders	Q90-Q99	None
Chromosome 17 and 19 deletion	Included among chromosomal disorders	None
Chromosome 18q deletion	Included among chromosomal disorders	None
Cognitive impairment	None	None
Congenital hydrocephalus	Q03 Congenital hydrocephalus	None
Congenital malformations	Major congenital malformations, will be defined as the study outcome major congenital malformations	None
Deafness/hearing loss	Z45.3 Adjustment and management of implanted hearing device H90 Conductive and sensorineural hearing loss Z46.1 Fitting and adjustment of hearing aid H91 Other hearing loss Z97.4 Presence of external hearing-aid	None
Disability indicated by Barthel Index	None	None
Down syndrome	Included among chromosomal disorders	None
Fahr's syndrome	G23.8 Other specified degenerative diseases of basal ganglia	None
Fragile X syndrome	Included among chromosomal disorders	None
Gaucher disease	E75.2 Other sphingolipidosis	A16AX10 eliglustat A16AX06 miglustat A16AB01 alglucerase A16AB02 imiglucerase A16AB11 taliglucerase alfa A16AB10 velaglucerase alfa
Hand and foot disorders	Will not be identified as a separate entity	None
Learning disabilities	Will not be identified as a separate entity	None
Leber's hereditary optic neuropathy (LHON) or autosomal dominant optic atrophy (ADOA)	H35.5 Hereditary retinal dystrophy H47.2 Optic atrophy	None
Leigh syndrome	G31.8 Other specified degenerative diseases of nervous system	None
Limitations with self-care or activities of daily living	Z73.6 Limitation of activities due to disability	None

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

At-risk medical conditions identified by diagnosis codes: disabilities	Diagnosis code (ICD-10)	Medicinal product proxy(ies) (ATC code)
Maternal inherited diabetes and deafness (MIDD)	Will not be identified as a separate entity	None
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and risk markers	Included in neuromuscular disorders Risk markers: not included	None
Mobility disability	Included in limitations with self-case	None
Movement disorders	R25 Abnormal involuntary movements R26 Abnormalities of gait and mobility R27 Other lack of coordination G20-26 Extrapyramidal and movement disorders F44.4 Dissociative motor disorders F98.4 Stereotyped movement disorders	None
Multiple disability (referred to in research papers as "bedridden disability")	Included in limitations with self-case	None
Multisystem disease	Will not be identified as a separate entity	
Myoclonic epilepsy with ragged red fibres (MERRF)	Included in neuromuscular disorders	None
Myotonic dystrophy	Included in neuromuscular disorders	None
Neurodevelopmental disorders	F84 Pervasive developmental disorders F90 Hyperkinetic disorders	N06BA11 dexmethylphenidate N06BA15 dexmethylphenidate and serdexmethylphenidate N06BA04 methylphenidate N06BA02 dexamfetamine N06BA12 lisdexamfetamine N06BA09 atomoxetine C02AC02 guanfacine
Neuromuscular disorders	A05.1 Botulism G12 Spinal muscular atrophy and related syndromes G61 Inflammatory polyneuropathy G62 Other polyneuropathies G63 Polyneuropathy in diseases classified elsewhere G70 Myasthenia gravis and other myoneural disorders G71 Primary disorders of muscles G72 Other myopathies G73 Disorders of myoneural junction and muscle in diseases classified elsewhereG12 Spinal muscular atrophy and related syndromes M33.2 Polymyositis	N07XX02 riluzole N07XX14 edaravone N07AA02 pyridostigmine N07AA30 ambenonium M09AX07 nusinersen M09AX10 risdiplam M09AX03 ataluren M09AX08 golodirsen M09AX12 viltolarsen M09AX13 casimersen M09AX04 drisapersen M09AX06 eteplirsen

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

At-risk medical conditions identified by diagnosis codes: disabilities	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)
Neuromyelitis optica spectrum disorder (NMOSD)	G36.0	Neuromyelitis optica [Devic]	None
Neuropathy, ataxia, and retinitis pigmentosa (NARP)	None		None
Perinatal spastic hemiparesis	None		None
Primary mitochondrial myopathy (PMM)	Included in neuromuscular disorders		None
Progressive supranuclear palsy	G23.1	Progressive supranuclear ophthalmoplegia [Steele-Richardson-Olszewski]	None
Senior-Loken syndrome	Q61.5	Medullary cystic kidney	None
Severe and complex disability (referred to in research papers as "polyhandicap disability")	Will not be identified as a separate entity		None
Spina bifida and other nervous system anomalies	Included in major congenital malformations		None
Spinal cord injury	S14 T09.3 S24 S34 P11.5 T91.3	Injury of nerves and spinal cord at neck level Injury of spinal cord, level unspecified Injury of nerves and spinal cord at thorax level Injury of nerves and lumbar spinal cord at abdomen, lower back and pelvis level Birth injury to spine and spinal cord Sequelae of injury of spinal cord	None
Tourette syndrome	F95.2	Combined vocal and multiple motor tic disorder [de la Tourette]	None

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

At-risk medical conditions identified by diagnosis codes: disabilities	Diagnosis code (ICD-10)		Medicinal product proxy(ies) (ATC code)
Traumatic brain injury	S02.0	Fracture of vault of skull	None
	S02.1	Fracture of base of skull	
	S02.7	Multiple fractures involving skull and facial bones	
	S02.8	Fractures of other skull and facial bones	
	S02.9	Fracture of skull and facial bones part unspecified	
	S04	Injury of cranial nerves	
	S06	Intracranial injury	
	S07.1	Crushing injury of skull	
	S07.8	Crushing injury of other parts of head	
	S07.9	Crushing injury of head part unspecified	
	S09.7	Multiple injuries of head	
	S09.8	Other specified injuries of head	
	S09.9	Unspecified injury of head	
	T02.0	Fractures involving head with neck	
	T04.0	Crushing injuries involving head with neck	
	T06.0	Injuries of brain and cranial nerves with injuries of nerves and spinal cord at neck level	
Visual impairment/ blindness	H54	Visual impairment including blindness (binocular or monocular)	None
Wheelchair use	Z99.3	Dependence on wheelchair	None
	Z46.8	Fitting and adjustment of other specified devices	

ICD-10 = *International Classification of Diseases, 10th Revision*.
Source of risk factors: CDC[44]

ANNEX 4. 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,[89] 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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