Non-Interventional Study
C4671054

A Retrospective Observational Non-Interventional Study (NIS) to assess Patient Characteristics and Healthcare Resource Use (HCRU) among COVID-19 Patients Receiving Treatment with Nirmatrelvir; Ritonavir (PAXLOVID TM) in the Kingdom of Saudi Arabia (KSA)

Statistical Analysis Plan
(SAP)

Version: 2

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Date: 16th September 2024

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
BMI	Body Mass Index
CDC	Center for disease Control and prevention
COVID-19	Corona Virus Disease 2019 caused by SARS-CoV-2
eCRF	electronic Case Report Form
ECMO	extracorporeal mechanical oxygenation
EDC	Electronic Data Capture
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients
ER	Emergency Room
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
HCRU	Healthcare Resource Use
HFNC	High-flow nasal cannula
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IMV	Invasive Mechanical Ventilation
IRB	Institutional Review Board

Abbreviation	Definition
ISMF	Investigator Site Master File
KSA	Kingdom of Saudi Arabia
LOS	Length of Stay
MENA	Middle East and North Africa
NIH	National Institutes of Health
NIMV	Non-invasive Mechanical Ventilation
NIS	Non-interventional Study
NIV	Non Invasive Ventilation
PCR	Polymerase Chain Reaction
RWE	Real World Evidence
SAP	Statistical Analysis Plan
SAS	Statistical Analyses System
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
USA	United States of America
PHEIC	Public Health Emergency of International Concern
PhD	Doctor of Philosopy
WHO	World Health Organization

2 AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Effective Date	Change Type	Section	Summary of Revisions
1.0	22-May-2023	Not Applicable	-	First version of SAP
1.1	26-June-2023	Amended	7.2 Statistical Analysis	Entire analysis content for "Overall" only and not stratified by Cohorts
		Removed	4.2 Subgroups	Section "Nirmatrelvir, ritonavir treatment completion (if available)" as data is not captured
		New	4.2 Subgroups	Days from COVID 19 symptoms onset to dispensing (if available)
		New	4.2 Subgroups	Days from COVID 19 symptoms onset to nirmatrelvir, ritonavir prescription (if available)
		Amended	9 List of Tables and Table shells	Title of tables
1.2	26-July-2023	Amended	3.1 Study Design	Updated patients section method
1.3	16-August-2023	Added	4.2 Subgroups	Added analysis for number of previous COVID-19 infection
1.4	31-August-2023	Amended	4.2 Subgroups	Removed Pre-omicron period subgroup analysis.
1.5	05-December-2023	Added	4.2 Subgroups	Stratifications added for COVID-19 variant and Duration to COVID-19 negative result(s)
		Added	7.2 Statistical Analysis	Added analysis section for COVID-19 variant and Duration to COVID-19 negative result(s)

2.0	16-September-2024	Amended	3.1 Study Design	Sample size updated
		Amended	7.3 Additional exploratory analysis	Additional analyses: • Stratified analysis of Paxlovid prescription at index by demographic and clinical characteristics • Stratified analysis of HCRU (Healthcare Resource use) at index date by demographic and clinical characteristics. • Examine the association between patients' hospitalization due to COVID-19 related reasons and Covariates*, using logistic regression model at the index date.
		Amended	9. List of tables and Table shells	As per additional exploratory analyses, list of tables updated, and corresponding table shells added in the excel. **The analysis already performed influenced amendment mentioned in the section 7.3**

3 INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***. The protocol version 1.0 dated on 17 March 2023 was used to develop the SAP.

Background

Coronaviruses are a group of viruses of zoonotic origin, of which seven species have been identified thus far as infectious to humans.[1] In December, 2019, clusters of patients with idiopathic pneumonia were identified in Wuhan, China, with clinical presentation including fever, cough, dyspnea, and chest discomfort.[2] A novel coronavirus sequence was isolated from the cluster of patients, termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the associated respiratory disease termed COVID-19.[1] By January 30th, 2020, the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern (PHEIC) due to rapid community transmission via respiratory droplets, leading to an exponential surge in the number of cases and severity, especially in a context where knowledge on this novel virus' epidemiology and potentiality was scarce.[3] COVID-19 was declared as a pandemic on 11 March 2020,[4] and as of February 2023, more than 679 million cases and 6.8 million deaths have been confirmed globally in 228 countries and territories.[5]

COVID-19 clinical presentation and severity is vastly heterogenous, whereby patients may experience asymptomatic infection, mild illness, moderate illness, severe illness, or critical illness requiring hospitalization. Common symptoms include cough, fever, dyspnea, fatigue, sore throat, anosmia, and nausea.[6] Critical illness is characterized by severe respiratory failure, systemic inflammatory response, septic shock, and multi-system dysfunction and failure, including the cardiovascular system, central nervous system, gastrointestinal system, renal system, and skin.[7,8] Recent data related to COVID-19 symptom severity have revealed that approximately 80% of cases are mild-to-moderate, 15% are severe, and 5% are critical.[9] Whilst the majority of cases are indeed asymptomatic or mild,[10] COVID-19 patients who are hospitalized due to infection are at great risk of prolonged disease, complications, increased hospital length of stay (LOS), high morbidity and mortality.[11-15]

Based on the most recent treatment guidelines put forth by the National Institutes of Health (NIH), management of non-hospitalized adults with acute COVID-19 infection includes supportive care (e.g., adequate hydration, rest, monitoring body temperature, and taking antipyretics and analgesics to reduce symptom severity), advice on reducing viral transmission, and advice on when to seek healthcare provision or in-person evaluation.[16] Adults that do not require hospitalization or supplemental oxygen yet are at high-risk of disease progression to severe/critical illness (eg, patients with malignancies, neurological diseases, hypertension, diabetes mellitus, obesity, and immunocompromised conditions), may additionally receive antiviral therapy to reduce risk of progression, hospitalization, or death.[16] Current COVID-19 antiviral therapeutic options, in order of preference, include ritonavir-boosted nirmatrelvir (Paxlovid™) or remdesivir.[17]

Molnupiravir may additionally be considered as an alternative therapeutic option only when the aforementioned are unavailable, infeasible, or clinically inappropriate to use.[17]

The Saudi MoH Protocol for Patients Suspected of/Confirmed with COVID-19 Supportive care and antiviral treatment of suspected or confirmed COVID-19 infection (Version 3.7) September 29th, 2022 follows the same guidance described above.[18]

Nirmatrelvir, ritonavir is an antiviral therapy consisting of two active substances that reduce the ability of SARS-CoV-2 to multiply in the body, and thus prevent disease progression.[19] *The first active substance, nirmatrelvir (PF-07321332), works by blocking viral enzyme activity and subsequent multiplication.*[19] *The second active substance, ritonavir, delays breakdown of nirmatrelvir; thus, maintains sufficient levels of nirmatrelvir in the body to allow it to continue its effect on reducing viral multiplication.*[19] *Nirmatrelvir, ritonavir should be initiated after confirmed COVID-19 diagnosis and within 5 days of symptom onset; administered as 300 mg of nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) together, every 12 hours, for 5 days.*[20] *Based on the guidelines put forth by the Center for Disease Control and Prevention (CDC), COVID-19 patients who are at high-risk of disease progression to severe COVID-19 include patients aged >50 years, those who are unvaccinated or incompletely vaccinated, in addition to specific underlying medical conditions including asthma, cancer, chronic lung diseases, chronic liver diseases, Diabetes mellitus, and Down's syndrome.*[21]

Nirmatrelvir, ritonavir EUA was based on data from an interim analysis of a Phase II-III randomized, double-blind, placebo-controlled clinical trial in non-hospitalized adult patients with a confirmed COVID-19 diagnosis, who were symptomatic, and had at least 1 risk factor for progression to severe disease.[22,23] *Interim analysis results from this trial, titled "Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR)" (NCT04960202), revealed 89% reduced risk of COVID-19-related hospitalization and 28-day mortality among the Paxlovid group compared to the placebo group.*[23,24] *A meta-analysis on the efficacy and safety of nirmatrelvir, ritonavir for COVID-19 treatment has additionally shown an Overall 78% reduction in COVID-19-related mortality and hospitalization.*[24] *Whilst the trial was conducted prior to the emergence of the SARS-CoV-2 omicron variants, recent studies in real-world settings have shown that nirmatrelvir, ritonavir is also effective against these variants.*[25-27] *Other COVID-19 antiviral therapies with reported risk reduction of hospitalization or death include remdesivir (87% reduced risk),*[28] *sotrovimab (85% reduced risk),*[29] *and molnupiravir (50% reduced risk).*[30] *Sotrovimab is no longer authorized to treat COVID-19 in any United States of America (USA) region due to increases in the proportion of COVID-19 cases caused by the Omicron BA.2 sub-variant.*[31] *Bebtelovimab has also been authorized for emergency use, and available data from the BLAZE-4 clinical trial have revealed reduced viral load and improvement in symptoms, however, no clinical efficacy data of patients at risk of progressing to severe COVID-19 is available yet.*[32] *Since November 2022 bebtelovimab is not currently authorized for emergency use in the USA because it is not expected to neutralize Omicron subvariants BQ.1 and BQ.1.1.*[33]

Real-world studies assessing nirmatrelvir, ritonavir effectiveness and health impact are limited, and there are no studies yet that assess patients' treatment patterns. A real-world study conducted in Israel among high-risk patients showed nirmatrelvir, ritonavir to be highly effective, and was significantly associated with reducing the rate of progression to severe COVID-19 and COVID-19-specific mortality.[26] Another study conducted in Hong Kong to assess the effectiveness of molnupiravir and nirmatrelvir, ritonavir during the Omicron BA.2 variant of COVID-19 among patients initially not requiring oxygen therapy revealed shorter time to achieve lower viral load, lower risk of disease progression, reduced hospital LOS, and lower risk of all-cause mortality.[34] In Shanghai, China, results from a study assessing nirmatrelvir, ritonavir among immunocompromised inpatients further revealed treatment effectiveness in terms of faster viral load clearance, and shorter time to viral elimination, with patients having better prognosis when treatment was initiated ≤5 days following COVID-19 diagnosis.[35]

Several countries have incorporated nirmatrelvir, ritonavir within their national COVID-19 treatment protocols after regulatory body approval for emergency use, including the USA,[8] several countries in Europe including the United Kingdom,[36] and European Union (EU) countries including Italy, Germany, and Belgium,[19,37] and the Middle East and North Africa (MENA) region, including the KSA and Bahrain.[18,38] Moreover, it is expected that additional countries will adopt the use of nirmatrelvir, ritonavir within their protocol as it becomes more readily available, particularly considering near-future decentralization and generic production of nirmatrelvir, ritonavir across a larger number of countries, including low- and middle-income countries.[39]

Rationale

The COVID-19 pandemic has exacerbated healthcare systems globally, with dire repercussions on patients, healthcare infrastructure, resources, and finances.[40] Although COVID-19 patient characteristics and disease course in healthcare settings have been described in the literature since the beginning of the pandemic in various regions including the USA,[41,42] EU,[43-45] and the MENA region;[46-48] there is limited data related to COVID-19 patient characteristics, treatment patterns, and HCRU identified in an outpatient setting, particularly in the MENA region. One study reported that among other factors such as age, male gender, and underlying medical conditions; being of Arab ethnicity was associated with increased risk of severe COVID-19 and related mortality.[26]

In KSA, nirmatrelvir, ritonavir has been approved and conditionally registered by the Saudi Food and Drug Authority (SFDA) for patients aged ≥12 years, weighing ≥40 kg with mild-to-moderate COVID-19 symptoms and at high-risk for progression to severe COVID-19 infection.[18] The availability of antiviral therapies such as nirmatrelvir, ritonavir in an outpatient setting has the ability to reduce disease progression, hospitalization, and COVID-19-related mortality, when eligible patients are treated.[39] With the current EU authorization and subsequent use of nirmatrelvir, ritonavir, there is a need to generate -RWE during this early EUA utilization phase to inform decision-making on national levels.

As such, this study aims to describe the baseline demographic, clinical characteristics, and HCRU of adult COVID-19 patients who have been prescribed nirmatrelvir, ritonavir treatment in KSA.

3.1 STUDY DESIGN

This is a multi-center, retrospective observational study that will be conducted in KSA. The aim of this study is to capture data on the baseline demographic, clinical characteristics, and HCRU of adult COVID-19 patients who have been prescribed nirmatrelvir, ritonavir treatment.

An overview of the study design is depicted in Figure 1. The sample size for this study depends on the number of COVID-19 patients visiting the selected sites, in addition to nirmatrelvir, ritonavir prescription practices by the treating physician in line with local prescription guidelines in KSA. However, based on feasibility assessments, the minimum target sample size for the study is approximately 250 evaluable patients across 3 sites in KSA. The study will aim to meet this target sample size with a single Cohort of patients identified retrospectively prior to the date of site initiation (Cohort 1); however, if the target sample size is not met, then a second Cohort of patients will be initiated after the site initiation date (Cohort 2).

Cohort 1:

The study will involve collection of pre-defined, structured data retrospectively from medical records (electronic and/or paper if necessary) of patients who meet the study eligibility criteria (see Section 3.1.2) and who have been prescribed nirmatrelvir, ritonavir treatment within a 15-month lookback period from the date of site initiation (Cohort 1). The lookback period will span from 01 April 2022 to 30 June 2023. Data abstracted from patients' medical records will include patient demographics and clinical characteristics at index date (defined as the date of nirmatrelvir, ritonavir treatment prescribing), in addition to patients' HCRU during the 30-day period post-index date.

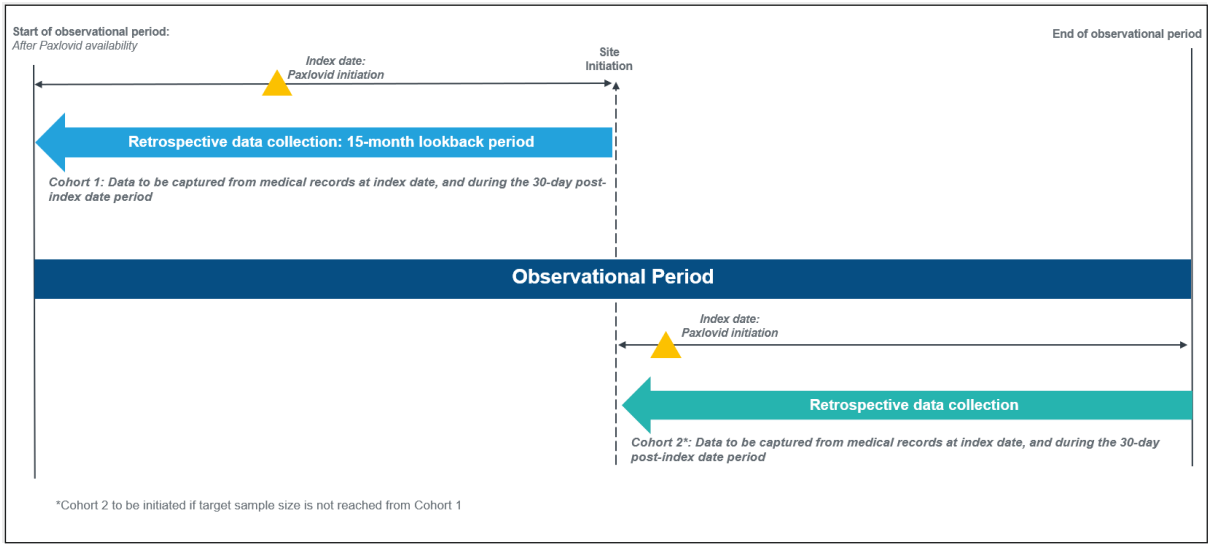
Cohort 2:

If the minimum target sample size of 250 patients is not achieved from Cohort 1, then a second Cohort of patients (Cohort 2) will be initiated and will be included in the study until the target sample size is met. Cohort 2 patients are those who meet the eligibility criteria (see Section 3.1.2), and who have been prescribed nirmatrelvir, ritonavir treatment after the date of site initiation. As for patients in Cohort 1, the following data will be collected for patients in Cohort 2: demographics and clinical characteristics at index date, and HCRU during the 30day period post-index date.

Patients in Cohort 1 will be enrolled in the study in a consecutive manner from start of site initiation till lookback period until we reach desired sample size, in case the number of eligible patients is significantly larger than the sample size[52-54]. For Cohort 2, patients will be enrolled in the study in a consecutive manner from start of site initiation until we reach desired sample size. *An electronic Case Report Form (eCRF) will be available for*

the selected sites to fill in for each patient included in Cohort 1 or Cohort 2. Patient data will be extracted from the medical records and entered into the eCRFs by trained site study personnel. Participation in this study is not intended to change the routine treatment patients receive, as determined by their prescribing physicians; all treatment decisions, type and timing of the disease monitoring are per routine clinical care, and at the discretion of the treating physician and patient.

Figure 1. Study Design



3.1.1 Study population

Data will be collected for all eligible adult COVID-19 patients who have been prescribed nirmatrelvir, ritonavir across 3 selected sites in KSA which are National Guard Hospital-Riyadh, King Faisal Specialist Hospital- Riyadh and King Faisal Specialist Hospital-Jeddah. These 3 healthcare centers are the largest COVID-19 care providers in KSA representing the majority of COVID-19 patients who have been prescribed nirmatrelvir, ritonavir at the national level. In addition, these three healthcare centers have the same guidelines for treatment and management of patients with COVID-19.

The selected sites with well-established clinical research infrastructures, are situated in the major cities of KSA, where COVID-19 patients are most prevalent. They provide medical attention to any COVID-19 patient and provide healthcare to complicated patients, including immunocompromised patients.

These facilities also maintain patient records and have access to electronic medical records for patient data retrieval.

The minimum target sample size is 250 patients. Patient eligibility will be assessed at patient index date. Patients in Cohort 1 will be identified during a 15-month lookback period prior to the date of site initiation, and patients in Cohort 2 will be identified

following the date of site initiation if the minimum target sample size for the study is not achieved from Cohort 1.

3.1.2 Inclusion Criteria

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

1. *Confirmed COVID-19 infection during the study observation period.*
2. *Age ≥18 years old.*
3. *Nirmatrelvir, ritonavir written prescription.*

3.1.3 Exclusion Criteria

There are no exclusion criteria for this study.

3.1.4 Data source

This is an observational, non-interventional study (NIS) involving retrospective collection of data throughout the observation period, obtained from the source outlined below.

- *Medical records of patients prescribed nirmatrelvir; ritonavir: The authorized physician or study investigator will record patient demographics, clinical characteristics, COVID-19 vaccination history, nirmatrelvir, ritonavir prescription data, and HCRU data from patients' medical records into an eCRF.*

All data collected in this study are intended to capture COVID-19 patient demographics, clinical characteristics, and patients' HCRU in a real-world setting. An eCRF will primarily be used for data collection, located on a secure web-based electronic data capture (EDC) system. The use of a standardised eCRF will ensure data is captured consistently across all sites. The eCRF must be signed by the investigator, and the signature serves to attest that the information contained in the eCRF is true. At all times, the investigator has the final responsibility for the accuracy and authenticity of all clinical and laboratory data entered into the eCRFs.

Table 1 below depicts the data collection schedule for the study.

Table 1. Data Collection Schedule

Variables	***Cohort 1***		***Cohort 2***	
	Index date[a]	***During the 30-day post-index period[b]***	***Index date[a]***	***During the 30-day post-index period[c]***
Patient demographics	*X*		*X*	
Patient clinical characteristics	*X*		*X*	
COVID-19 vaccination history	*X*		*X*	
COVID-19 infection data	*X*	*X*	*X*	*X*
Nirmatrelvir, ritonavir prescription data	*X*		*X*	
HCRU data	*X*	*X*	*X*	*X*

COVID-19: Corona Virus Disease 2019 caused by SARS-CoV-2; HCRU: Healthcare Resource Use.
[a] Cohort 1/Cohort 2: Index date is defined as the date of nirmatrelvir, ritonavir prescription.
[b] Cohort 1: Post-index period is defined as the 30-day period after the index date and prior to the site initiation date.
[c] Cohort 2: Post-index period is defined as the 30-day period after the index date and after the site initiation date.

3.1.5 Patient Medical Records

The authorized physician or study investigator will record patient demographics, clinical characteristics, COVID-19 vaccination history, nirmatrelvir, ritonavir prescription data, and HCRU data from patients' medical records into an eCRF.

3.2 STUDY OBJECTIVES

The aim of this study is to describe the baseline demographic, clinical characteristics, and HCRU of adult (≥18 years) COVID-19 patients who have been prescribed nirmatrelvir, ritonavir treatment.

3.2.1 Primary objective:

To describe the baseline demographic and clinical characteristics, including pre-existing comorbidities, of adult COVID-19 patients who have been prescribed nirmatrelvir, ritonavir treatment.

3.2.2 Secondary objective:

To assess adult COVID-19 patients' HCRU within the 30-day period following nirmatrelvir, ritonavir prescription, including:

- *Overall HCRU in inpatient and outpatient settings.*

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

The Full Analysis Set will contain all patient's data who fulfil the eligibility criteria (*see Section 2.1.2*).

4.2 SUBGROUPS

Exploratory stratifications will be conducted, as appropriate and where the sample size permits, to explore differences by:

- *Age groups: 18–49, 50–64, 65–74, ≥75 years of age;*
- *Gender;*
- *BMI categories: (<18.5 = underweight, 18.5–24.9 = normal, 25–29.9 = overweight, ≥30 = obese);*
- *Smoking status;*
- *Medications used to treat COVID-19 in addition to nirmatrelvir, ritonavir;*
- *Previous COVID-19 infection;*
- *COVID-19 vaccination history;*
- *Nirmatrelvir, ritonavir treatment completion (if available)*
- *Days from COVID-19 diagnosis to nirmatrelvir, ritonavir index date;*
- *Days from prescription to dispensing (if available).*
- *Days from COVID 19 symptoms onset to dispensing (if available).*
- *Days from COVID 19 symptoms onset to nirmatrelvir, ritonavir prescription (if available).*

For each stratification variable, the full analysis set will be segmented into non-overlapping subgroups based on the stratification variable values. The stratifications may not be meaningful, if there are no patient's data in some of the groups or there are many variables with a lot of missing data.

The exploratory stratifications will be conducted for the following study objectives if enough data are available:

Secondary objective: To assess adult COVID-19 patients' HCRU within the 30-day period following nirmatrelvir, ritonavir prescription, including: Overall HCRU in inpatient and outpatient settings.

The specific stratifications, and their corresponding reporting labels will be the following:

- *Age groups:* Age at time of PAXLOVID™ prescription will be further categorized into 18–49, 50–64, 65–74, ≥75 years. Descriptive summary tables for subgroup analysis by defined age groups for the specified study objectives will be created as shown in ***Table Shells 10.***

Gender (Male, Female); Descriptive summary tables for subgroup analysis by gender for the specified study objectives will be created as shown in ***Table Shells 11***

- *BMI categories:* Body Mass Index (BMI) at time of PAXLOVID™ prescription will be further categorized as <18.5 = underweight, 18.5–24.9 = normal, 25–29.9 = overweight, ≥30 = obese. Descriptive summary tables for subgroup analysis by defined BMI categorization for the specified study objectives will be reported as shown in ***Table Shells 12.***

- *Smoking status (*Never smoker; Former smoker; Current smoker)*;* Descriptive summary tables for subgroup analysis by smoking status in terms of never smoker, former smoker and current smoker for the specified study objectives will be reported as shown in ***Table Shells 13.***

- *Medications used to treat COVID-19 in addition to nirmatrelvir, ritonavir;* Descriptive summary tables for subgroup analysis by Medications used to treat COVID-19 in addition to nirmatrelvir, ritonavir at time of PAXLOVID™ prescription for the specified study objectives will be reported as shown in ***Table Shells 14.***

- *Previous COVID-19 infection (Yes, No);* Descriptive summary tables for subgroup analysis by Previous COVID-19 infection for the specified study objectives will be created as shown in ***Table Shells 15.*** Additionally, Number of previous COVID-19 infections before the index date will be reported and further stratified by 0, 1, 2 and more. Descriptive summary tables for these groups will be reported as shown in ***Table Shell 15.1*** (If sufficient data available).

- *COVID-19 vaccination history;* Descriptive summary tables for subgroup analysis by COVID-19 vaccination history for the specified study objectives will be reported as shown in ***Table Shells 16.***

- *Days from COVID-19 diagnosis to nirmatrelvir, ritonavir index date;* Duration in days from COVID-19 diagnosis to nirmatrelvir, ritonavir index date will be further categorized as 0-2 days, 3-5 days, more than/equal to 6 days. Descriptive summary tables for subgroup analysis by defined duration categorization for the specified study objectives will be reported as shown in ***Table Shells 17.***

- *Days from prescription to dispensing (if available):* Duration in days from prescription to dispensing will be further categorized as 0-2 days, 3-5 days, more than/equal to 6 days. Descriptive summary tables for subgroup analysis by defined duration categorization for the specified study objectives will be reported as shown in Table Shells ***Table Shells 18.***

- *Days from COVID 19 symptoms onset to dispensing (if available):* Duration in days from COVID 19 symptoms onset to dispensing as 0-2 days, 3-5 days, more than/equal to 6 days. Descriptive summary tables for subgroup analysis by defined duration categorization for the specified study objectives will be reported as shown in Table Shells ***Table Shells 19***.

- *Days from COVID 19 symptoms onset to nirmatrelvir, ritonavir prescription (if available):* Duration in days from COVID 19 symptoms onset to prescription as 0-2 days, 3-5 days, more than/equal to 6 days. Descriptive summary tables for subgroup analysis by defined duration categorization for the specified study objectives will be reported as shown in Table Shells ***Table Shells 20.***

Additionally, the exploratory stratifications will be conducted for COVID-19 variant and Duration to COVID-19 negative result(s) if enough data are available and will be reported as shown in Table Shells ***Table Shells 22.1 to 22.7*** and ***Table Shells 23.1 to 23.10*** respectively**.**

5 ENDPOINTS AND COVARIATES

Descriptive summary tabulations will describe the demographic, clinical characteristics as well as pre-existing comorbidities of the patients in the study population at the time of PAXLOVID™ prescription, and Healthcare Resource Use during the 30 days post index date.

5.1 PRIMARY ENDPOINT

This study focuses on the patients who have received PAXLOVID™ for COVID-19 infection. The primary endpoints that describe the primary objectives in the study population will be:

- The baseline demographics (age, gender, ethnicity, education, employment status), clinical characteristics (height, weight, BMI, smoking status, pre-existing comorbidities), concomitant medications at index date and previous COVID-19 infection during the last 6 months, duration between last infection and index date, of the study population at the time of PAXLOVID™ prescription.

- COVID-19 vaccination history (Receipt of vaccination (yes/no), type of vaccine, duration between vaccination and Index date), number of doses, at the time of PAXLOVID™ prescription.

- Nirmatrelvir, Ritonavir prescription (total dose of Nirmatrelvir/Ritonavir, dose of Nirmatrelvir, dose of Ritonavir, Frequency of dose, dispensed amount) at the time of PAXLOVID™ prescription.

- Medications used to treat COVID-19 infection (Antiviral, Antiviral, Steroid, Anti-thrombotic, Monoclonal antibody, Hydroxychloroquine and Other medications) at the time of PAXLOVID™ prescription.

- HCRU characteristics in terms of patient hospitalization status, COVID-19 related hospitalization, length of days in the hospitalization due to COVID-19, Intensive care unit (ICU) admission and length of stay in the ICU due to COVID-19, supplemental oxygen use, vasopressor use, patient intubation, outpatient visits and ER Visits due to COVID-19 at the time of PAXLOVID™ prescription.

5.2 SECONDARY ENDPOINT

- HCRU characteristics in terms of patient hospitalization status, COVID-19 related hospitalization, length of days in the hospitalization due to COVID-19, Intensive care unit (ICU) admission and length of stay in the ICU due to COVID-19, supplemental oxygen use, vasopressor use, patient intubation, outpatient visits and ER Visits due to COVID-19 during the 30-day post-index period.

- COVID-19 PCR and/or antigen test result(s), PCR test result(s), Antigen test result (s), Duration to negative COVID-19 test during the 30 days post-index period.

5.3 COVARIATES AND VARIABLE DEFINITIONS

Table 2 depicts patient demographics, clinical characteristics, COVID-19 vaccination history, nirmatrelvir, ritonavir prescription data, COVID-19 infection, HCRU variables and Detailed operational definitions of variables.

Variables and detailed definitions of the variables are provided in Table 2.

6 HANDLING OF MISSING VALUES

Should missing data occur, the data will be analyzed as they are recorded in the eCRFs, and no imputation of missing data will be performed. The number of missing values for data elements will be reported.

All data analysis in this study will be performed on the Full Analysis Set containing all patients who fulfil the eligibility criteria, and thus missing data is not used as criteria for excluding the patients from the data analysis.

For both categorical and continuous variables, the amount of missing data will be reported. For categorical variables, the missing values will be analysed in the descriptive summary tables as a category. The missing values in the continuous variables will be ignored when calculating the summary statistics of mean, median, standard deviation, and quantiles.

If some of the variables of interest show to have a large amount or proportion of missing data, the summary statistics of the variable to be interpreted accordingly.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

This is a descriptive study, and as such, no statistical testing will be conducted. Analyses will be conducted using Statistical Analysis System (SAS) (version 9.3 or higher). Summary statistics for patient demographics, clinical characteristics, treatment patterns, and patient HCRU will be performed. Continuous variables will be summarized using standard summary statistics such as number of observations (n), mean, median, standard deviation (SD), first and third quartile, minimum and maximum value. Categorical variables will be summarized in frequency tables as counts and proportions of the total study population, and by subgroups where appropriate. The proportion of missing data will be reported for each variable.

Ad hoc population analyses would include stratification by demographic characteristics and presence of Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19.

All patients who fulfill the study eligibility criteria will be included in the data set for analyses.

One interim analysis will be conducted after 3 months of recruitment only if the target sample size is not achieved from Cohort 1 i.e. Cohort 2 is initiated.

7.2 STATISTICAL ANALYSES

Note: Cohort 2 will be included in the study only if the target sample size is not achieved from Cohort 1.

Patients' enrollment will be summarized as shown in ***Table Shell 1***.

Primary analysis: ***To describe the baseline demographic and clinical characteristics, including pre-existing comorbidities, of adult COVID-19 patients who have been prescribed nirmatrelvir, ritonavir treatment.***

Patient and disease characteristics will be summarized using descriptive statistics. In terms of sociodemographic characteristics age, gender, ethnicity, education, and employment status will be reported as shown in ***Table Shell 2.*** Clinical characteristics in terms of weight, height, Body Mass Index (BMI), smoking status, pre-existing comorbidities, duration between pre-existing comorbidities and Index date in months, concomitant medications used to treat comorbidities at index date, most common concomitant medications (Trade name or generic name) for comorbidities, and most common Indication for comorbidities at index date will be reported as shown in ***Table shell 3***.

Patient's COVID-19 vaccination history in terms of patient vaccinated/not vaccinated, total numbers of dose, type of vaccine, duration between vaccination and index date will be reported as shown in the ***Table shell 4***.

Similarly, data on previous COVID-19 infection will be reported in terms of Number of previous COVID-19 infection, duration between previous infection to the index date, Medication used to treat previous COVID-19 infection as shown in the ***Table shell 5.*** COVID-19 Positive infection data at index date will be reported in terms of Type of COVID-19 Test (PCR or Antigen test), Result of COVID-19 Test (PCR or Antigen test), result of PCR test only, result of Antigen test only, duration between COVID-19 symptoms onset to index date, variant of COVID-19, medication used to treat the infection as shown in the ***Table shell 6.***

Data related to Nirmatrelvir/Ritonavir prescription in terms of specialty of provider total dose of Nirmatrelvir/Ritonavir, in case of "other" dose specified of Nirmatrelvir and Ritonavir (if available), frequency, dispensed amount, type dispensed, days from COVID-19 diagnosis to nirmatrelvir, ritonavir at index date, days from prescription to dispensing (if available), days from COVID 19 symptoms onset to dispensing (if available) and days from COVID 19 symptoms onset to nirmatrelvir, ritonavir prescription (if available) will be summarized in descriptive statistics and reported as shown in the ***Table shell 7.***

Data of Patient hospitalization, primary cause of patient hospitalization, length of hospitalization stay, Intensive Care Unit (ICU) admission, length of stay in Intensive Care Unit (ICU),supplemental oxygen use, type of oxygen, vasopressor use, patient intubation, outpatient visits, reason of outpatient visits, Emergency Room visits, and reason of Emergency Room visits at index date will reported as shown in the ***Table shell 8.***

Secondary analysis: ***To assess adult COVID-19 patients' HCRU within the 30-day period following nirmatrelvir, ritonavir prescription, including*****: *Overall HCRU in inpatient and outpatient settings.***

Healthcare Resource Use (HCRU) data will be summarized using descriptive statistics in terms of patient hospitalization, number of time patient hospitalization, cause of patient hospitalization, length of stay in the hospitalization, Intensive Care Unit (ICU) admission,

number of Intensive Care Unit (ICU) admission, length of stay in Intensive Care Unit (ICU), supplemental oxygen use, type of oxygen, vasopressor use, patient intubation, outpatient visits, number of outpatient visits and reason of outpatient visits during the 30 days post index date and reported as shown in the ***Table Shell 9.*** Further stratification will be performed as described in section 3.2.

COVID-19 PCR and /antigen test result(s), Result(s) by PCR only, Result(s) by antigen test only, duration to COVID-19 negative result(s) by PCR and/antigen tests from the index date will be reported will be reported as shown in the ***Table shell 21.***

COVID-19 variant by following stratifications will be reported as shown in the ***Table shell 22.1 to 22.7:*** *(if sample size permits)*

- Age groups: ***Table shell 22.1***
- Gender: ***Table shell 22.2***
- BMI categories: ***Table shell 22.3***
- Smoking status: ***Table shell 22.4***
- Previous COVID-19 infection: ***Table shell 22.5***
- COVID-19 vaccination history: ***Table shell 22.6***
- Underlying medical conditions: ***Table shell 22.7***

Duration to COVID-19 negative result(s) by following stratifications will be reported as shown in the ***Table shell 23.1 to 23.10:*** *(if sample size permits)*

- Age groups: ***Table shell 23.1***
- Gender: ***Table shell 23.2***
- BMI categories: ***Table shell 23.3***
- Smoking status: ***Table shell 23.4***
- Previous COVID-19 infection: ***Table shell 23.5***
- COVID-19 vaccination history: ***Table shell 23.6***
- Underlying medical conditions: ***Table shell 23.7***
- Medications used to treat COVID-19 in addition to nirmatrelvir, ritonavir: ***Table shell 23.8***
- Days from COVID-19 diagnosis to nirmatrelvir, ritonavir index date: ***Table shell 23.9***
- Days from prescription to dispensing *(if available):* ***Table shell 23.10***

7.3 ADDITIONAL EXPLORATORY ANALYSIS

Summary

The following exploratory analysis will be conducted:

1. Stratified analysis of Paxlovid prescription at index by demographic and clinical characteristics.

2. Stratified analysis of HCRU (Healthcare Resource use) at index date by demographic and clinical characteristics.

3. Examine the association between patients' hospitalization due to COVID-19 related reasons at the index date and Covariates*, using logistic regression model. **Covariates: Age groups, Gender, BMI categories, smoking status, Pre-existing comorbidities, previous*

Statistical analysis description

1. "Stratified analysis of Paxlovid prescription at index by demographic and clinical characteristics"

Data related to Nirmatrelvir/Ritonavir prescription in terms of specialty of provider total dose of Nirmatrelvir/Ritonavir, in case of "other" dose specified of Nirmatrelvir and Ritonavir, frequency, dispensed amount, type dispensed, days from COVID-19 diagnosis to nirmatrelvir, ritonavir at index date, days from prescription to dispensing days from COVID-19 symptoms onset to dispensing and days from COVID-19 symptoms onset to nirmatrelvir, ritonavir prescription will be summarized in descriptive statistics by:

- Age groups: 18–49, 50–64, 65–74, ≥75 years
- Gender
- BMI categories: (<18.5 = underweight, 18.5–24.9 = normal, 25–29.9 = overweight, ≥30 = obese).
- Smoking status.
- Previous COVID-19 infection.
- COVID-19 vaccination history.

These tables will be reported as shown in the **table shells 7.1 to 7.6**

2. "Stratified analysis of HCRU (Healthcare Resource use) at index date by demographic and clinical characteristics"

Data of Patient hospitalization, primary cause of patient hospitalization, length of hospitalization stay, Intensive Care Unit (ICU) admission, length of stay in Intensive Care Unit (ICU), supplemental oxygen use, type of oxygen, vasopressor use, patient intubation, outpatient visits, reason of outpatient visits, Emergency Room visits, and

reason of Emergency Room visits at index date will be summarized in descriptive statistics by:

- Age groups: 18–49, 50–64, 65–74, ≥75 years
- Gender
- BMI categories: (<18.5 = underweight, 18.5–24.9 = normal, 25–29.9 = overweight, ≥30 = obese).
- Smoking status.
- Previous COVID-19 infection.
- COVID-19 vaccination history.
  These tables will be reported as shown in the **table shells 8.1 to 8.6**.

3. ***"Examine the relationship between patients' hospitalization due to COVID-19 related reasons and various demographic and clinical factors at the index date."***

We will be utilizing both univariate and multivariate binomial logistic regression to examine the association between patients' hospitalization due to COVID-19 at the index date and demographic and clinical factors mentioned below (covariates). All p-values will be reported as two-sided, and statistical significance will be determined at 0.05 alpha level. Separate univariate binary logistic regression model will be conducted for each covariate listed below and only covariates which will be found significant will be included in the Multivariate model along with clinically significant covariates (e.g BMI, Previous comorbidity status etc.). No interaction terms will be included in the model.

The following binary logistic regression equation will be used to model the relationship:

$\log(\text{odds}) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n * X_n$

Where:

- log(odds) represents the logarithm of the odds of the patients' hospitalization due to COVID-19
- β_0 is the intercept or constant term.
- $\beta_1, \beta_2, \ldots, \beta_n$ are the coefficients associated with the independent variables (covariates) $X_1, X_2, \ldots, X_n$.
- $X_1, X_2, \ldots, X_n$ are the values of the independent variables (Covariates)

Here,

Outcome variable (Dependent variable): patients' hospitalization due to COVID-19 related at index date (Yes=1/No**=0).

***No: No will include both "patients who had no hospitalization" as well as "patients with hospitalization due to non-COVID-19 related reasons".*

Covariates (Independent variables):

- Age groups (Reference group: 18-29 Year)
- Gender (Reference group: Female)
- BMI categories (Reference group: Normal)
- Smoking status (Reference group: Never smoke)
- Pre-existing comorbidities (Yes/No, Reference group: No)
- Previous COVID-19 infection (Yes/No, Reference group: No)
- COVID-19 vaccination history (Yes/No, Reference group: No)

The results will be presented in the terms of odd ratio (by exponentiating the logistic regression coefficient) and corresponding 95% CI. "p-values" and "confidence intervals (CIs)" will be obtained using statistical methods such as maximum likelihood estimation (MLE) or Wald tests.

These tables will be reported as shown in the **table shells 24 to 24.1**.

8 STRENGTH AND LIMITATION OF THE RESEACRCH METHODS

Strengths

The strength of this study includes use of patients' medical records for data collection, which allows data to be captured on a large, diverse cohort of patients with different characteristics in a quick and efficient manner.

Another strength is the eligibility criteria, which has been selected to be as broad as possible for the target patient population, so as to reflect the real-world clinical setting to the extent possible, and to minimize selection bias.

Limitations and Bias

As this is a retrospective observational study and participant enrolment in the study will be done in a consecutive manner. This approach is associated with low possibility of bias and representativeness of the enrolled sample could be affected, if there is pattern observed among a particular age group or due to any season etc. In case such selection bias is observed, then additional stratification/ subgroup can be reported in the analysis, as required.

Since this study will involve collection of existing data from medical records, misclassification bias due to recording errors is possible. Medical records may not always be complete, the availability and quality/completeness of data may vary

considerably between different sites within KSA, and there may be abstraction errors and differences in reporting standards between the different sites.

Another limitation to be considered is the characteristics of the patient population to be included in the final analysis, which may potentially be biased based on the KSA national recommendations put in place for the management and treatment of COVID-19 during the observational period. This may affect the generalizability of findings from this study across different countries in the real-world setting.

At the patient-level, misclassification of drug exposure has to be considered. Medical records provide detailed information on patient demographics, clinical characteristics, and prescribed nirmatrelvir, ritonavir treatment, but may not contain information on the intended duration of use (days of supply) and may not contain accurate information on the actual treatment pattern of nirmatrelvir, ritonavir medications by the patient ie, patient adherence (if any).

COVID-19 outcomes are dependent on individuals seeking healthcare i.e., individual may have symptoms for long but if there is not an interaction with the health system, it will be unknown.

9 LIST OF TABLES AND TABLE SHELLS

Number	**Description**
Table shells for Primary objectives	
Table shell 1	Summary of patient enrolment at Index date.
Table shell 2	Summary of demographic characteristics of patients at Index date.
Table shell 3	Summary of clinical characteristics of patients at Index date.
Table shell 4	Summary of COVID-19 vaccination history of patients at Index date.
Table shell 5	Summary of previous COVID-19 infection of patients at Index date.
Table shell 6	Summary of COVID-19 Positive infection of patients at Index date.
Table shell 7	Summary of Nirmatrelvir/Ritonavir prescription at Index date.
Table shell 7.1	Summary of Nirmatrelvir/Ritonavir prescription at index date by age groups.
Table shell 7.2	Summary of Nirmatrelvir/Ritonavir prescription at index date by gender.
Table shell 7.3	Summary of Nirmatrelvir/Ritonavir prescription at index date by BMI categories.
Table shell 7.4	Summary of Nirmatrelvir/Ritonavir prescription at index date by smoking status.
Table shell 7.5	Summary of Nirmatrelvir/Ritonavir prescription at index date by previous COVID-19 infection.
Table shell 7.6	Summary of Nirmatrelvir/Ritonavir prescription at index date by COVID-19 vaccination history.
Table shell 8	Summary of Healthcare Resource use at Index date.

Table shell 8.1	Summary of Healthcare Resource use at Index date by age groups.
Table shell 8.2	Summary of Healthcare Resource use at index date by gender.
Table shell 8.3	Summary of Healthcare Resource use at index date by BMI categories.
Table shell 8.4	Summary of Healthcare Resource use at index date by smoking status.
Table shell 8.5	Summary of Healthcare Resource use at index date by previous COVID-19 infection.
Table shell 8.6	Summary of Healthcare Resource use at index date period by COVID-19 vaccination history.

Table shells for Secondary objectives

Table shell 9	Summary of Healthcare Resource use during the 30 days post index date period.

Table shells for stratification analysis – Secondary objectives (HCRU)

Table shell 10	Summary of Healthcare Resource use during the 30 days post index date period by age groups.
Table shell 11	Summary of Healthcare Resource use during the 30 days post index date period by gender.
Table shell 12	Summary of Healthcare Resource use during the 30 days post index date period by BMI categories.
Table shell 13	Summary of Healthcare Resource use during the 30 days post index date period by smoking status.
Table shell 14	Summary of Healthcare Resource use during the 30 days post index date period by most common medication use to treat COVID-19 in addition to nirmatrelvir, ritonavir.
Table shell 15	Summary of Healthcare Resource use during the 30 days post index date period by previous COVID-19 infection.
Table shell 15.1	Summary of Healthcare Resource use during the 30 days post index date period by number of previous COVID-19 infection.
Table shell 16	Summary of Healthcare Resource use during the 30 days post index date period by COVID-19 vaccination history.
Table shell 17	Summary of Healthcare Resource use during the 30 days post index date period by days from COVID-19 diagnosis to nirmatrelvir, ritonavir prescription.
Table shell 18	Summary of Healthcare Resource use during the 30 days post index date period by days from prescription to dispensing (if available).
Table shell 19	Summary of Healthcare Resource use during the 30 days post index date period by days from COVID 19 symptoms onset to dispensing (if available).
Table shell 20	Summary of Healthcare Resource use during the 30 days post index date period by days from COVID 19 symptoms onset to nirmatrelvir, ritonavir prescription (if available).
Table shell 21	Summary of COVID-19 PCR and /antigen test result(s) during the 30 days post index date period. (If available)

Table shell 22.1	Summary of COVID-19 variant by age groups
Table shell 22.2	Summary of COVID-19 variant by gender
Table shell 22.3	Summary of COVID-19 variant by BMI categories
Table shell 22.4	Summary of COVID-19 variant by smoking status
Table shell 22.5	Summary of COVID-19 variant by previous COVID-19 infection
Table shell 22.6	Summary of COVID-19 variant by COVID-19 vaccination history
Table shell 22.7	Summary of COVID-19 variant by underlying medical conditions
Table shell 23.1	Summary of duration to COVID-19 negative result(s) by age groups
Table shell 23.2	Summary of duration to COVID-19 negative result(s) by gender
Table shell 23.3	Summary of duration to COVID-19 negative result(s) by BMI categories
Table shell 23.4	Summary of duration to COVID-19 negative result(s) by smoking status
Table shell 23.5	Summary of duration to COVID-19 negative result(s) by previous COVID-19 infection
Table shell 23.6	Summary of duration to COVID-19 negative result(s) by COVID-19 vaccination history
Table shell 23.7	Summary of duration to COVID-19 negative result(s) by underlying medical conditions at index date
Table shell 23.8	Summary of duration to COVID-19 negative result(s) by medications used to treat COVID-19 in addition to nirmatrelvir, ritonavir
Table shell 23.9	Summary of duration to COVID-19 negative result(s) by days from COVID-19 diagnosis to nirmatrelvir, ritonavir index date
Table shell 23.10	Summary of duration to COVID-19 negative result(s) by days from prescription to dispensing
Table shell 24	Summary of patients' hospitalization due to COVID-19 related reasons at index date by covariates and **univariate binary** logistic models.
Table shell 24.1	Summary of patients' hospitalization due to COVID-19 related reasons at index date by covariates and the **multivariable binary** logistic model

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11 APPENDICES

11.1 ANNEX 1 (TABLE 2): STUDY VARIABLES AND DEFINITIONS

Variables	Role	Time point(s)	Operational definition
Age, Continuous	Patient demographics (Primary endpoint)	At index date	Age will be reported in year
Age, Category	Stratification variable	At index date	The age (Year) will be categorized as: • 18-49 Years • 50-64 Years • 65-74 Years • >75 Years
Gender	Patient demographics (Primary endpoint)	At index date	Gender (Sex) will be reported as: • Male • Female
Ethnicity	Patient demographics (Primary endpoint)	At index date	Ethnicity will be reported as: • Arab • Afro-Asian • Asian/Pacific Islander • Black/African American • Hispanic/Latino • Native American/Alaskan Native • White/Caucasian, • Multiracial/Biracial • Unknown. • Other [specify]
Education	Patient demographics (Primary endpoint)	At index date	Education will be reported as: • No formal education • Primary school • Secondary school • Undergraduate university degree • Master's degree • PhD or doctorate
Employment status	Patient demographics (Primary endpoint)	At index date	Employment status will be reported as: • Full-time employment • Part-time employment • Homemaker • Student • Retired • Disabled/too ill to work • Unemployed

Variables	Role	Time point(s)	Operational definition
Weight (kg)	Patient clinical characteristics (Primary endpoint)	At index date	Weight will be reported in kilograms (kg)
Height (m)	Patient clinical characteristics (Primary endpoint)	At index date	Height will be reported in meters (m)
BMI (kg/m^2)	Patient clinical characteristics (Primary endpoint)	At index date	BMI will be calculated automatically based on the reported weight and height in the unit of kilograms over squared meters (kg/m^2).
BMI category	Stratification variable	At index date	The calculated BMI will be categorized as: • Underweight (< 18.5) • Normal (18.5–24.9) • Overweight (25–29.9) • Obese (≥30)
Smoking Status	Patient clinical characteristics (Primary endpoint)	At index date	Smoking status will be reported as: • Never smoker • Former smoker • Current smoker
Pre-existing comorbidities	Patient clinical characteristics (Primary endpoint)	At index date	Pre-existing comorbidities will be reported as: • No • Yes If yes, will be specified as: • Diagnosis
Date of Pre-existing Comorbidities onset	Patient clinical characteristics (Primary endpoint)	At index date	The date of onset of pre-existing comorbidities will be captured in (DD-MM-YYYY)
Duration between Pre-existing comorbidities onset to index date (Months)	Patient clinical characteristics (Primary endpoint)	At index date	Duration between pre-existing comorbidities onset to index date will be calculated as: (Index date – Date of Pre-existing Comorbidities onset)/30.42
Concomitant medications for comorbidities: Trade name or generic name	Patient clinical characteristics (Primary endpoint)	At index date	Open field, all Concomitant medication will be reported.
Indication	Patient clinical characteristics (Primary endpoint)	At index date	Open field, all indication will be reported.
Date of initiation	Patient clinical characteristics (Primary endpoint)	At index date	The date of indication will be captured in (DD-MM-YYYY)

Variables	Role	Time point(s)	Operational definition
COVID-19 vaccination	COVID-19 vaccination history	At index date	History of COVID-19 vaccination will be reported as: • Yes • No
Number of COVID-19 vaccination dose	COVID-19 vaccination history	At index date	Number of doses will be calculated as: Total count of dose for each patient
Type of vaccination	COVID-19 vaccination history	At index date	Type of COVID-19 vaccination will be reported as: • Protein-Serum Institute of India • Protein-Novavax • RNA-Moderna • RNA-Pfizer/BioNTech • Viral Vector-CanSino • Viral Vector-Janssen • Viral Vector-Oxford/AstraZeneca • Viral Vector-Serum Institute of India • Inactivated-Bharat Biotech • Inactivated-Sinopharm • Inactivated-Sinovac
Date of vaccination (For each dose)	COVID-19 vaccination history	At index date	The date of vaccination will be captured in (DD-MM-YYYY)
Duration between vaccination and index date (Months) (For each dose)	COVID-19 vaccination history	At index date	Duration between vaccination and index date (Months) will be calculated as: (Index date – Date of COVID-19 vaccination) /30.42
Previous COVID-19 infection during the last 6 months	Previous COVID-19 infection	At index date	COVID-19 infection during last 6 month will be reported as: • Yes • No
Number of Previous COVID-19 infection during the last 6 months	Previous COVID-19 infection	At index date	Number of COVID-19 infection during last 6 month will be reported as count
Date of previous COVID-19 infection during the last 6	Previous COVID-19 infection	At index date	Date of previous COVID-19 infection during the last 6 will be captured in (DD-MM-YYYY)
Duration between previous COVID-19 infection during the	Previous COVID-19 infection	At index date	Duration between previous COVID-19 infection during last 6 month from index date will be calculated as:

Variables	Role	Time point(s)	Operational definition
last 6 months and index date			(Index date – Date of previous COVID-19 infection) /30.42
Medication used to treat previous COVID-19 infection during the last 6	Previous COVID-19 infection	At index date	Medications used to treat previous COVID-19 infection during the last 6 will be reported as: • Antiviral (Yes; No) If yes, o Remdesivir o Other, specify • Antibiotic (Yes; No) If yes, o Specify • Steroid (Yes; No) If yes, o Budesonide o Dexamethasone o Prednisolone/Prednisone o Hydrocortisone o Methylprednisolone Sodium succinate o Other, specify • Anti-thrombotic (Yes; No) If yes, o Enoxaparin o Heparin o Other, specify • Monoclonal antibody (Yes; No) If yes, o Infliximab o Tocilizumab o Other, specify • Hydroxychloroquine (Yes; No) If yes, o Specify • Immunosuppressant (Yes, No) If yes, o Baricitinib o Other, specify • Intravenous immune globulin (Yes, No)

Variables	Role	Time point(s)	Operational definition
			If yes, ○ Specify • Other medications (Yes; No) If yes, ○ Specify
Date of Positive COVID-19 PCR/antigen test	COVID-19 infection data	At index date	Date of Positive COVID-19 PCR/antigen test will be captured in (DD-MM-YYYY)
Date of COVID-19 symptoms onset	COVID-19 infection data	At index date	Date of COVID-19 symptoms onset will be captured in (DD-MM-YYYY)
Duration between COVID-19 symptoms onset and index date (Days)	COVID-19 infection data	At index date	Duration of COVID-19 symptoms onset will be calculated as: (Index date – Date of COVID-19 symptoms onset)
COVID-19 variant (If available)	COVID-19 infection data	At index date	Variant of COVID-19 will be reported as (if available): • Alpha [B.1.7 and Q] • Beta [B.1.351] • Gamma [P.1] • Delta [B.1.617.2; AY] • Epsilon [B.1.427; B.1.429] • Eta [B.1.525] • Iota [B.1.526] • Kappa [B.1.617.1];B.1.617.3; • Omicron [B.1.1.529; BA.1; BA.1.1; BA.2; BA.3; BA.4; BA.5] • Zeta [P.2] • Mu [B.1.621;B.1.621.1] • Omicron XBB.1.5. • other [specify]
Medication use to treat COVID-19 infection	COVID-19 Medication data	At index date	Medications used to treat COVID-19 infection will be reported as: • Antiviral (Yes; No) If yes, ○ Ritonavir ○ Other, specify • Antibiotic (Yes; No) If yes, ○ Specify • Steroid (Yes; No)

Variables	Role	Time point(s)	Operational definition
			If yes, o Budesonide o Dexamethasone o Prednisolone/Prednisone o Hydrocortisone o Methylprednisolone Sodium succinate o Other, specify • Anti-thrombotic (Yes; No) If yes, o Enoxaparin o Heparin o Other, specify • Monoclonal antibody (Yes; No) If yes, o Infliximab o Tocilizumab o Other, specify • Hydroxychloroquine (Yes; No) If yes, o Specify • Immunosuppressant (Yes, No) If yes, o Baricitinib o Other, specify • Intravenous immune globulin (Yes, No) If yes, o Specify • Other medications (Yes; No) If yes, o Specify
Prescription date (Index date)	Nirmatrelvir, ritonavir prescription data	At index date	Date of prescription of Nirmatrelvir and Ritonavir will be captured in (DD-MM-YYYY)
Specialty of provider	Nirmatrelvir, ritonavir prescription data	At index date	Specialty of provider will be summarized as: • Infectious Disease • Internist • General Practitioner

Variables	Role	Time point(s)	Operational definition
			• Primary Care Physician • ER • Pulmonologist • Other, specify
Dose	Nirmatrelvir, ritonavir prescription data	At index date	Dose of Nirmatrelvir/Ritonavir will be reported as: • 300 mg (2x150)/100 mg • Other If Other, o Dose of Nirmatrelvir (Open field) o Dose of Ritonavir (Open field)
Frequency	Nirmatrelvir, ritonavir prescription data	At index date	Frequency of Nirmatrelvir/Ritonavir will be reported as: • Twice a day • Other • If Other, Specify (Open field)
Dispensed amount	Nirmatrelvir, ritonavir prescription data	At index date	Open field: Will be captured by Box, Blister and Tablets.
Dispensed date (if available)	Nirmatrelvir, ritonavir prescription data	At index date	Date of dispensed will be captured in (DD-MM-YYYY)
Days from COVID-19 diagnosis to nirmatrelvir, ritonavir prescription date	Nirmatrelvir, ritonavir prescription data	At index date	Days from COVID-19 diagnosis to nirmatrelvir, ritonavir index date will be calculated as: [Prescription date **(**Index date)-Date of COVID-19 diagnosis]
Days from COVID-19 diagnosis to nirmatrelvir, ritonavir prescription date (Categories)	Nirmatrelvir, ritonavir prescription data	At index date	Days from COVID-19 diagnosis to nirmatrelvir, ritonavir index date will be categorized as: • 0-2 days • 3-5 days • ≥ 6 days
Days from prescription to dispensing	Nirmatrelvir, ritonavir prescription data	At index date	Days from prescription to dispensing will be calculated as: [Dispensed date- Prescription date **(**Index date)]
Days from prescription to dispensing (Categories)	Nirmatrelvir, ritonavir prescription data	At index date	Days from prescription to dispensing will be categorized as: • 0-2 days • 3-5 days

Variables	Role	Time point(s)	Operational definition
			• ≥ 6 days
Days from COVID 19 symptoms onset to dispensing (if available)	Nirmatrelvir, ritonavir prescription data	At index date	Days from COVID 19 symptoms onset to dispensing will be calculated as: [Dispensed date- COVID-19 symptoms onset date]
Days from COVID 19 symptoms onset to dispensing (Categories)	Nirmatrelvir, ritonavir prescription data	At index date	Days from COVID 19 symptoms onset to dispensing will be categorized as: • 0-2 days • 3-5 days • ≥ 6 days
Days from COVID 19 symptoms onset to nirmatrelvir, ritonavir prescription (if available)	Nirmatrelvir, ritonavir prescription data	At index date	Days from COVID 19 symptoms onset to nirmatrelvir, ritonavir prescription will be calculated as: [Prescription date **(**Index date)- - COVID-19 symptoms onset date]
Days from COVID 19 symptoms onset to nirmatrelvir, ritonavir prescription (Categories)	Nirmatrelvir, ritonavir prescription data	At index date	Days from COVID 19 symptoms onset to nirmatrelvir, ritonavir prescription will be categorized as: • 0-2 days • 3-5 days • ≥ 6 days
Patient hospitalization	HCRU data	At index date	Patient hospitalization will be reported as: • Yes • No
Cause (Patient hospitalization)	HCRU data	At index date	Cause of patient hospitalization will be reported as (if available); • COVID-19 related • Non COVID-19 related
Outpatient setting	HCRU data	At index date	Outpatient setting will be defined if answer “No” to question “Patients hospitalization”
Length of Stay (Days) (Patient hospitalization)	HCRU data	At index date	Length of patients stay in hospitalization will be captured in days
Intensive Care Unit (ICU) admission	HCRU data	At index date	Intensive Care Unit (ICU) admission will be reported as: • Yes • No

Variables	Role	Time point(s)	Operational definition
Length of Stay (Days) (ICU)	HCRU data	At index date	Length of patients in Intensive Care Unit (ICU) will be captured in days
Supplemental oxygen	HCRU data	At index date	Use of supplemental oxygen will be reported as: • Yes • No
Type of Supplemental oxygen	HCRU data	At index date	Type of supplemental oxygen use will be reported as: • Oxygen mask • Nasal prongs • NIMV • HFNC • IMV • ECMO
Vasopressor use	HCRU data	At index date	Use of Vasopressor will be reported as: • Yes • No
Patient intubation	HCRU data	At index date	Patient intubation data be reported as: • Yes • No
Outpatient visits	HCRU data	At index date	Outpatient visits data be reported as: • Yes • No
Cause (Outpatient visits)	HCRU data	At index date	Cause of Outpatient visits will be reported as (if available). • COVID-19 related • Non COVID-19 related
ER Visits	HCRU data	At index date	ER visits data be reported as: • Yes • No
Reason (ER Visits)	HCRU data	At index date	Reason of ER visits will be reported as (if available); • COVID-19 related • Non COVID-19 related
Patient hospitalization	HCRU data	During the 30 day of post-index period	Patient hospitalization will be reported as: • Yes • No
Primary cause (Patient hospitalization)	HCRU data	During the 30 day of post-index period	Cause of patient hospitalization will be reported as (if available); • COVID-19 related • Non COVID-19 related

Variables	Role	Time point(s)	Operational definition
Outpatient setting	HCRU data	At index date	Outpatient setting will be defined if answer "No" to question "Patients hospitalization"
Length of Stay (Days) (Patient hospitalization)	HCRU data	During the 30 day of post-index period	Length of patients stay in hospitalization will be captured in days
Intensive Care Unit (ICU) admission	HCRU data	During the 30 day of post-index period	Intensive Care Unit (ICU) admission will be reported as: • Yes • No
Length of Stay (Days) (ICU)	HCRU data	During the 30 day of post-index period	Length of patients in Intensive Care Unit (ICU) will be captured in days
Supplemental oxygen	HCRU data	During the 30 day of post-index period	Use of supplemental oxygen will be reported as: • Yes • No
Type of Supplemental oxygen	HCRU data	During the 30 day of post-index period	Type of supplemental oxygen use will be reported as: • Oxygen mask • Nasal prongs • NIMV • HFNC • IMV • ECMO
Vasopressor use	HCRU data	During the 30 day of post-index period	Use of Vasopressor will be reported as: • Yes • No
Patient intubation	HCRU data	During the 30 day of post-index period	Patient intubation data be reported as: • Yes • No
Outpatient visits	HCRU data	During the 30 day of post-index period	Outpatient visits data be reported as: • Yes • No
Cause (Outpatient visits)	HCRU data	During the 30 day of post-index period	Cause of Outpatient visits will be reported as (if available); • COVID-19 related • Non COVID-19 related
ER Visits	HCRU data	During the 30 day of post-index period	ER visits data be reported as: • Yes • No

Variables	Role	Time point(s)	Operational definition
Reason (ER Visits)	HCRU data	During the 30 day of post-index period	Reason of ER visits will be reported as (if available); • COVID-19 related • Non COVID-19 related
COVID-19 PCR and / or antigen test result(s) (If available)	COVID-19 infection data	During the 30 day of post-index period	COVID-19 PCR and / or antigen test result(s) will be reported as: • Positive • Negative • Indeterminate
COVID-19 PCR result (If available)	COVID-19 infection data	During the 30 day of post-index period	COVID-19 PCR test result will be reported as: • Positive • Negative • Indeterminate
COVID-19 Antigen test result (If available)	COVID-19 infection data	During the 30 day of post-index period	COVID-19 Antigen test result will be reported as: • Positive • Negative • Indeterminate
Date of COVID-19 PCR/antigen test	COVID-19 infection data	During the 30 day of post-index period	Date of COVID-19 PCR/antigen test will be captured in (DD-MM-YYYY)
Duration to Negative COVID-19 test (Months)	COVID-19 infection data	During the 30 day of post-index period	Duration to negative COVID-19 test after initiation of Nirmatrelvir, Ritonavir will be calculated as: (Date of Negative COVID-19 result - Index date)/30.42

COVID-19: Corona Virus Disease 2019 caused by SARS-CoV-2; PhD: Doctor of Philosophy; BMI: body mass index; PCR: polymerase chain reaction; ECMO: extracorporeal mechanical oxygenation; ER: emergency room; HCRU: Healthcare Resource Use; HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation; LOS: length of stay; NIMV: non-invasive mechanical ventilation