NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

Study Information

Title	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™) in the Kingdom of Saudi Arabia (KSA).
Protocol number	C4671054
Protocol version identifier	1.0
Date	17 March 2023
Active substance	PF-07321332; no anatomical therapeutic chemical (ATC) code yet
Medicinal product	Nirmatrelvir; ritonavir (PAXLOVID™)
Research objectives	Primary objective: 1. To describe the baseline demographic and clinical characteristics, including pre-existing comorbidities, of adult Corona Virus Disease 2019 caused by SARS-CoV-2 (COVID-19) patients who have been prescribed nirmatrelvir, ritonavir treatment. Secondary objective: 1. To assess adult COVID-19 patients' HCRU within the 30-day period following nirmatrelvir, ritonavir prescription, including: • Overall HCRU in inpatient and outpatient settings.
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2. 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

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Not Applicable.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	01 July 2023
Interim report 1*	01 October 2023
End of data collection	01 February 2024
Final Study Report	01 November 2024

*If the target sample size is achieved from Cohort 1 (and Cohort 2 is not initiated), then the interim analysis will not be required.

DISCLAIMER AND USE

This protocol template is to be used as a guide for countries to develop a real-world evidence (RWE) study evaluating the real-world usage of nirmatrelvir, ritonavir. The research objectives in this protocol are contingent on the availability of data elements and data capture methods per country. It should be noted that this document should only be used as a guide and may be adapted as necessary to accommodate for missing data. Protocols should undergo necessary local, global reviews and approvals.

7. RATIONALE AND BACKGROUND

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 (eg, 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. 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.

8. RESEARCH QUESTION AND 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.

Primary objective:

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

Secondary objective:

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

    - Overall HCRU in inpatient and outpatient settings.

9. RESEARCH METHODS

9.1. 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 500 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, data retrospectively from medical records (electronic and/or paper if necessary) of patients who meet the study eligibility criteria (see Section 9.2.1) 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.

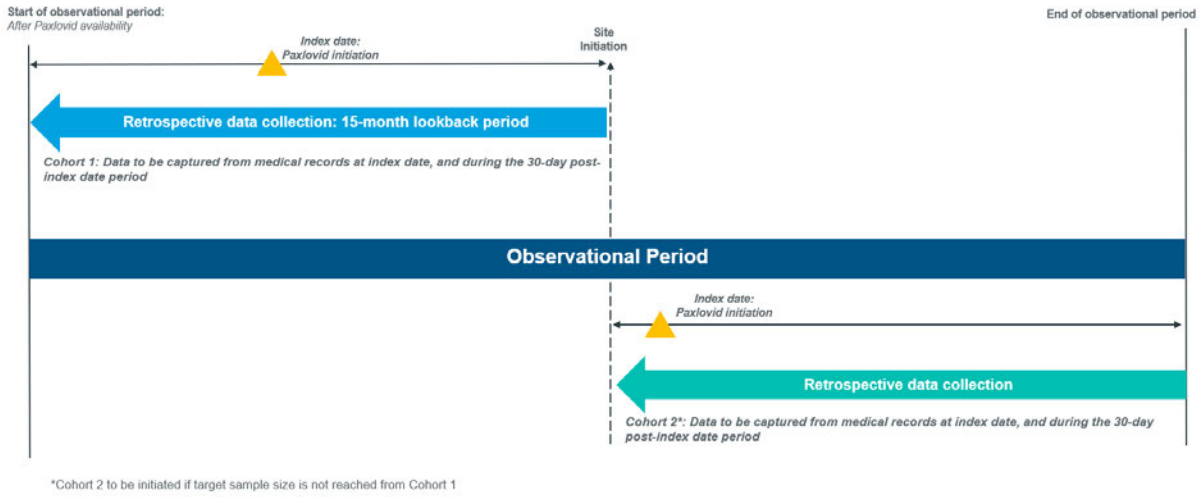
Cohort 2:

If the minimum target sample size of 500 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 9.2.1), 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 30-day period post-index date.

Patients in Cohort 1 will be enrolled in the study either in a sequential manner or selected via computer-generated random allocation in case the number of eligible patients is significantly larger than the sample size. For Cohort 2, patients will be enrolled in the study in a sequential manner. 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



9.2. Setting

Data will be collected for all eligible adult COVID-19 patients who have been prescribed nirmatrelvir, ritonavir across 3 selected sites in KSA. 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 500 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. For both Cohorts, patient data will be collected at index date and during the 30-day post-index period. Available data from patient medical records that meet the study aims will be abstracted and entered into the eCRFs.

9.2.1. 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.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

Table 1 below depicts patient demographics, clinical characteristics, COVID-19 vaccination history, and nirmatrelvir, ritonavir prescription data. Table 2 presents COVID-19 infection data, and Table 3 presents HCRU variables. Detailed operational definitions of variables are listed below.

Table 1. Patient Baseline Demographics and Clinical Characteristics Variables

Variable	Operational definition
Patient demographics	• Age (years) • Gender (male; female) • Ethnicity (Arab; Afro-Asian; Asian/Pacific Islander; Black/African American, Hispanic/Latino; Native American/Alaskan Native; White/Caucasian, Multiracial/Biracial; Unknown; Other [specify]) • Education (no formal education/primary school/secondary school/undergraduate university degree/master's degree/PhD or doctorate) • Employment status (full-time employment, part-time employment, homemaker, student, retired, disabled/too ill to work, unemployed)
Patient clinical characteristics	• Height (m) • Weight (kg) • Body Mass Index (BMI) (kg/m^2) • Smoking status (never smoker; former smoker; current smoker) • Pre-existing comorbidities (specify) • Concomitant medications for comorbidities at index date (no/yes

Variable	Operational definition
	[specify]) • Medications used to treat COVID-19 (antiviral (specify), antibiotic (specify), steroid (specify), anti-thrombotic (specify), monoclonal antibody, hydroxychloroquine); other medications [specify]) • Previous COVID-19 infection during the last 6 months (yes/no)
COVID-19 vaccination history	• Patient has received COVID-19 vaccination (yes/no) • Type of vaccine, number of doses and dates (if available)
Nirmatrelvir, ritonavir prescription data	• Index date (prescription date) (DD/MM/YYYY) • Specialty of provider at index date • Prescription data (dose, frequency and dispensed amount) • Dispensed date if available

BMI: body mass index; COVID-19: Corona Virus Disease 2019 caused by SARS-CoV-2; PhD: Doctor of Philosophy.

Table 2. COVID-19 Infection Data

Variables	Operational definition
COVID-19 infection data	• Positive COVID-19 PCR/antigen test date (DD/MM/YYYY) before initiating treatment with nirmatrelvir, ritonavir • COVID-19 symptoms onset date (DD/MM/YYYY) • COVID-19 variant (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], XBB.1.5., other [specify])
	• COVID-19 PCR and / or antigen test result(s) following index date (positive; indeterminate; negative) (if available)

COVID-19: Corona Virus Disease 2019 caused by SARS-CoV-2; PCR: polymerase chain reaction.

Table 3. HCRU Data

Variables	Operational definition
HCRU data	At index date and during the 30-day post-index period: • Patient hospitalization (specify cause if available), LOS [days]) • Intensive care unit (ICU) admission, and LOS (days) • Supplemental oxygen use (yes [type: oxygen mask, nasal prongs, NIMV, HFNC, IMV, ECMO]/no), vasopressor use (yes [specify]/no), patient intubation (yes/no)) • Outpatient visits (yes/no) (reason if available) • ER visits (yes/no) (reason if available)

COVID-19: Corona Virus Disease 2019 caused by SARS-CoV-2; 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.

9.4. Data Sources

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 4 below depicts the data collection schedule for the study.

Table 4. 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.

9.5. Patient Medical Records

The investigator or authorized physician will record all data related to patient demographics, clinical characteristics, COVID-19 vaccination history, nirmatrelvir, ritonavir prescription data, and HCRU data into an eCRF per patient.

9.6. Study Size

This is an observational study without any pre-defined hypothesis to be tested; rather, it addresses descriptive objectives. As such, power calculations are not applicable. However, based on feasibility assessments, a planned minimum total sample size of 500 patients for this study will ensure adequate exploration of the study objectives, and sufficient generalizability of findings.

9.7. Data Management

This study will use anonymized secondary data, collected through medical records. A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed-up for resolution.

High data quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

9.7.1. Electronic Case Report Forms (eCRFs)

As used in this protocol, the term CRF[/DCT] should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

An eCRF is required and should be completed for each patient included. The completed original eCRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the eCRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the eCRFs are true. Any corrections to entries made in the eCRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital/physician's chart or medical records. In these cases, data collected on the eCRFs must match those charts.

In some cases, the eCRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the eCRF, and for which the eCRF will stand as the source document.

9.8. Statistical Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (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.

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. The corresponding analysis plan will be defined.[21]

9.8.1. 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.

Descriptive summary statistics will be conducted for Cohort 1 and Cohort 2 patients, as well as the overall population:

Cohorts 1 and 2:

- Patient demographics: age, gender, ethnicity, education, employment status;
- Patient clinical characteristics: BMI, smoking status, pre-existing comorbidities, concomitant medications at index date, medications used to treat COVID-19, and previous COVID-19 infection during the last 6 months;
- COVID-19 vaccination history: vaccinated/unvaccinated patient, number of doses and dates (if available);
- Nirmatrelvir, ritonavir prescription data: specialty of provider at index date, prescription data, time from symptom onset (if available);
- COVID-19 infection data: COVID-19 variant, PCR/antigen test result following index date (if available).

9.8.2. 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.

Descriptive Summary statistics will be conducted for the following:

Cohorts 1 and 2:

- Patient HCRU (hospitalization and LOS, ICU admission and LOS, supplemental oxygen use and type, outpatient visits, and ER visits

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

- Age groups: 18–29, 30–49, 50–64, 65–74, ≥75 years of age;

- Gender;
- BMI categories: (<18.5 = underweight, 18–24.9 = 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).

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.

9.9. Quality Control

Investigators will be trained with an initial on-site visit to the clinic on the protocol, EDC system (ie, eCRF), investigator site master file (ISMF), documentation, and any applicable study processes. Any new information relevant to the performance of this NIS will be forwarded to the medical staff during the study. Remote data monitoring will be conducted during the life of the study to ensure timely reporting of safety data, data integrity and consistency. The eCRFs for all included patients will be made available to the remote data monitor for review. A list of critical variables will be created as required elements for review during the remote data monitoring process. The study sites will be queried and managed to request resolution to any issues that may arise during the study.

Monitoring visits may be made, if necessary, to monitor study process by Pfizer, Inc. or its delegate. In the event of a visit, direct access to original source data will be required for monitoring visits and/or inspections/audits, which will be carried out with due consideration for data protection and patient confidentiality. Items routinely checked during on-site visits include:

- Documentation of the informed consent process.
- Compliance with patient eligibility criteria.
- Proper maintenance of records, such as study protocol.

- Completed eCRFs.
- Documentation of adverse events (AEs), and transmission of serious adverse events (SAEs).
- Identification of patients lost to follow-up.
- Study correspondence.
- Compliance with Institutional review board (IRB)/Independent ethics committee (IEC) approval requirements.
- Review of the ISMF.
- Archiving of the study documents will be performed according to Pfizer standard operating procedures (SOPs).

9.10. Strengths and Limitations of the Research Methods

Strengths

A strength of this study includes the 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.

To ensure the completion of the eCRF is conducted in a systematic manner, eCRF completion guidelines will be supplied to sites to provide consistent instructions on the completion of the eCRF. Metrics for data quality and completeness will be reviewed, which will help to proactively identify sites with potential issues in data abstraction. Training will also be provided to ensure that all investigators understand the minimum dataset requirements in this study and help prevent major differences between sites with regards to the data abstracted.

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

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 (ie, individual may have symptoms for long but if there is not an interaction with the health system, it will be unknown.

9.11. Other Aspects

Not Applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. The personal data will be stored at the study site in eCRF (encrypted electronic and/or paper form) and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by a single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the CSA and applicable privacy laws.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPPs) issued by the Public Policy Committee, International Society for Pharmacoepidemiology (ISPE), Declaration of Helsinki and its amendments, and any applicable national guidelines. This study will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[49]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the eCRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- For exposure during pregnancy in studies of pregnant women, data on the exposure to Nirmatrelvir, ritonavir during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness," "Study Drug," and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format."

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics."*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training statements must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities (YRR) with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report detailing the final study protocol and the analysis results will be provided when the study is complete. 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 investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

Any publication of the results from this study must be consistent with Pfizer's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated December 2019.[50] All reporting will be consistent with the STROBE Initiative checklist for cohort studies.[49]

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. ADDITIONAL INFORMATION

Annex Table 1 WHO Clinical Progression Scale.[51]

Patient State	Definition	Score
Hospitalized: moderate disease	Hospitalization without oxygen therapy	4
	Hospitalization with oxygen therapy by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized with oxygen therapy by NIV or HFNC	6
	Intubation and mechanical ventilation or vasopressors	7
	Mechanical ventilation or vasopressors	8
	Mechanical ventilation and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

ECMO: extracorporeal membranous oxygenation; HFNC: high-flow nasal cannula; NIV: non-invasive ventilation.

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