NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	A Retrospective Observational Non-Interventional Study (NIS) to assess Patient Characteristics and Healthcare Resource Use (HRU) among COVID-19 Patients with or without Nirmatrelvir/Ritonavir (PAXLOVID™) treatment in the Kingdom of Bahrain.
Protocol number	C4671050
Protocol version identifier	1.0
Date	16 November 2023
Active substance	PF-07321332; ATC code J05AE30
Medicinal product	nirmatrelvir; ritonavir (PAXLOVID™)
Research objectives	Primary objective: 1. To describe the baseline demographic and clinical characteristics, including pre-existing comorbidities, of adult COVID-19 patients treated with and those not treated with nirmatrelvir, ritonavir. Secondary objectives: 1. To evaluate the number and proportion of COVID-19 patients who meet the most up-to-date WHO recommendations for the use of therapeutics in the treatment of COVID-19 (ie, version 14, published 10Nov2023) in comparison to Kingdom of Bahrain national recommendations. 2. To assess adult COVID-19 patients' HRU and outcomes within the 28-day period

	Exploratory objective: 1. Assess HRU and outcomes at day 5, 7 and 21 as exploratory analyses
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
CDC	Centers for Disease Control
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CT	Computed Tomography
DDI	Drug-drug interaction
DPIA	Data Protection Impact Assessment
eGFR	Estimated Glomerular Filtration Rate
EC	Ethics Committee
EHR	Electronic Health Record
ER	Emergency Room
EUA	Emergency Use Authorization
FDA	Food and Drug Administration

Abbreviation	Definition
GDPR	Global Data Privacy Rule
GPP	Good Pharmacoepidemiology Practices
HRU	Healthcare Resource Utilization
ICD-10	International Classification of Diseases-10th Edition
ICU	Intensive Care Unit
IPTW	Inverse Probability of Treatment Weighting
IMV	Invasive Mechanical Ventilation
IQR	Interquartile Range
I-SEHA	Kingdom of Bahrain National Health Information System
ISPE	International Society of Pharmacoepidemiology
LOA	List of Abbreviations
LOS	Length of Stay
NIH	National Institutes of Health
NIS	Non-Interventional Study
PCR	Polymerase Chain Reaction (COVID-19 test)
POS	Place of Service

Abbreviation	Definition
PSM	Propensity Score Matching
RCSI	Royal College of Surgeons in Ireland
RQ	Research Question
SD	Standard Deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States
VOC	Variant of Concern
WHO	World Health Organization
YRR	Your Reporting Responsibilities

[redacted]

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

Not applicable.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone and/or Deliverable Description (Provider must use Pfizer CT24 designated templates for Study Deliverables)	Planned Timeline/Dates
Draft study protocol	19 February 2023
Final study protocol	30 November 2023
Start of data collection	15 January 2024
End of data collection	15 February 2024
Start of data analysis	15 March 2024
End of data analysis	31 April 2024
Final Study Report	15 June 2024

7. RATIONALE AND BACKGROUND

In December 2019, COVID-19 was identified as a new, potentially fatal, respiratory infection caused by the novel coronavirus, SARS-CoV-2. The WHO declared COVID-19 a Public Health Emergency of International Concern[1] on 30 January 2020 and further characterized the disease outbreak as a pandemic on 11 March 2020.[2] As of 01 January 2022, more than 289,000,000 cases have been confirmed worldwide, and at least 5,440,154 deaths have occurred.[3] Despite widespread use of COVID-19 vaccine since 2020 in Bahrain, COVID-19 caused 702830 cases, 26194 hospitalizations and 1546 deaths during the period 2020-2023 in Kingdom of Bahrain.

The clinical presentation of COVID-19 varies widely, ranging from an asymptomatic infection to critical illness characterized by respiratory failure, septic shock and other multiple organ dysfunction or failure.[4] Although the majority of cases are asymptomatic or mild,[5] patients who are hospitalized with COVID-19 may have significant morbidity and mortality.[6,7] Between February 2020 and September 2021, the United States CDC estimated that of a total of 146.6 million infections, 85% of patients were symptomatic and only 5% required hospitalization for treatment.[8]

According to the NIH guidelines, management of non-hospitalized patients with acute COVID-19 should include supportive care, advise on when to contact a health care provider and seek an in-person evaluation, and COVID-19 specific therapy for patients who have a high risk of disease progression. [9] More specifically, non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk of clinical progression may receive (listed in order of preference) nirmatrelvir (PF-07321332)/ritonavir (Paxlovid™), sotrovimab, remdesivir, or molnupiravir.[10]

Kingdom of Bahrain:

Kingdom of Bahrain is one of the leading countries in COVID-19 outpatient treatment care. A unique outpatient clinic has been established in May 2021 to provide outpatient care for patients with positive Coronavirus. Treatment including monoclonal antibodies such as Bamlamivimab, Regen-Cov, Sotorovimab and Paxlovid™ are offered for all high-risk and close contact patients, such treatments are in line with the guidelines of the FDA.

The clinic has a dedicated call center providing different services to ease the patient treatment process and provides follow-up care. The overall aim of the clinic is to target mild to moderate high risk COVID-19 patients and provide outpatient treatment as early as possible to reduce disease progression, including hospitalization and death.

On 01 January 2022, the National Health Regulatory Authority (NHRA) approved the emergency use of Paxlovid™ for mild-moderate cases who are at high risk – identified as per WHO definition of high-risk group – of developing severe COVID-19. Since approval, Paxlovid™ has been established as the first line therapy along with Sotrovimab in the Kingdom of Bahrain.

In the EPIC-HR trial, Paxlovid™ reduced the risk of hospitalization or death by 88% compared to placebo in non-hospitalized adults with laboratory-confirmed SARS-CoV-2 infection and a risk factor for progression to severe disease, when treatment was initiated within 5 days of symptom onset.[10,11] Other efficacies reported for COVID-19 therapies, include sotrovimab (ie, 85% relative reduction reported),[10,12] and remdesivir (ie, 87% relative reduction reported)[10,13] and molnupiravir (ie, 30% relative reduction reported).[10,14] Furthermore, *in vitro* analyses, suggested that Paxlovid™ is active against the B.1.1.529 (Omicron) variant of concern (VOC).[15]

COVID-19 has put significant pressure on the healthcare system worldwide and caused an enormous economic burden to society. While patient characteristics, healthcare resource utilization (HRU) and healthcare costs of patients hospitalized with COVID-19 have previously been described in US studies, [16-26] such data are limited among non-US countries.[27,28] Furthermore, while the majority of current research focuses on hospitalized COVID-19 patients, little is known about COVID-19 patients identified in an outpatient setting.

The availability of antiviral treatments in the outpatient setting, such as Paxlovid™, have potential to complement vaccination strategies during the COVID-19 pandemic and further reduce the burden on healthcare system capacity in the short- and long-term. There is a need to identify patients in the real-world setting globally, who are diagnosed with COVID-19 and may be at an increased risk of healthcare resource utilization, as prior literature suggests these patients are most likely to benefit from outpatient therapies. With the authorization (ie, EUA) of Paxlovid™, there is also a growing need to complement clinical trial findings and address data gaps by generating real-world evidence that may help inform healthcare decision-making globally during this early EUA utilization phase.

This study aims to describe the characteristics, outcomes and treatment patterns of COVID-19 patients, who are receiving Paxlovid™ in Bahrain according to the local drug label.

8. RESEARCH QUESTION AND OBJECTIVES

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

Primary objective:

1. To describe the baseline demographic and clinical characteristics, including pre-existing comorbidities, of adult COVID-19 patients treated with and those not treated with nirmatrelvir, ritonavir.

Secondary objectives:

1. To evaluate the number and proportion of COVID-19 patients who meet the most up-to-date WHO recommendations for the use of therapeutics in the treatment of COVID-19 (ie, version 14, published 10Nov2023) in comparison to Kingdom of Bahrain national recommendations.

2. To assess adult COVID-19 patients' HRU and outcomes within the 28-day period

Exploratory objective:

1. To assess HRU and outcomes at day 5, 7 and 21 as exploratory analyses

9. RESEARCH METHODS

9.1. Study Design

This will be a retrospective observational cohort study of patients diagnosed with COVID-19 in the Kingdom of Bahrain. Treated patients are defined as those have been prescribed nirmatrelvir, ritonavir and managed in the outpatient setting (eg, receiving medical treatment without being admitted to a hospital for COVID-19) while control group is those not treated with nirmatrelvir, ritonavir. Data will be from the *I-Seha electronic medical records* and descriptive analyses will be conducted for these two cohorts and will compare healthcare resource use in patients treated with nirmatrelvir, ritonavir and those not treated with nirmatrelvir, ritonavir.

Table 1. Cohort Definitions

Name	Criteria	Identification Period	Index Date	Follow Up Period
Treated patients	Patients diagnosed with COVID-19 and treated with Paxlovid™	After Paxlovid™ availability during the same dominant variant (ie, Omicron or Delta etc.) era timeframe as Cohort	Paxlovid™ prescription written date or dispense date* If neither of the above are available, the COVID-19 diagnosis date may be used as the index date	28 -days follow up
Control group	Patients diagnosed with COVID-19 and not treated with Paxlovid™	After Paxlovid™ availability during the same dominant variant (ie, Omicron or Delta etc.) era timeframe as Cohort	Date of COVID-19 diagnosis	28 -days follow up

*If both dates are available in the data source, the most recent date should be used as the index date for Cohort.

9.2. Setting

9.2.1. Inclusion Criteria

- Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study: Age 18 years and older
- Patients with a diagnosis of COVID-19 whose information can be extracted from the I-Seha database

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3 Variables

The following variables are used to obtain comprehensive descriptive results.

1. Demographics
2. Date of symptoms
3. Viral variant analysis where available (type of viral variant ie, omicron, delta etc.)
4. PCR date along with CT Value

5. Co-morbidities and
6. BMI if ≥30
7. Symptoms at presentation
8. COVID 19 vaccine status (NB 92% of population has been vaccinated -with at least one dose of COVID 19 vaccine- in Bahrain)
9. Hospital admission
10. Follow up looking at compliance and reason of non-compliance
11. Day 5,7, 21 and 28 symptoms for COVID-19 patients who receive and HRU limited to admission (ICU, ward, need for oxygen therapy) or death
12. Date of symptoms resolution if applicable

Table 2Table 2 below depicts the patient demographics that will be accessed during the baseline and follow-up periods. The baseline period is defined as one year before the index date. Comorbidities (full list in Table 6) and maintenance medication usage for chronic conditions (eg, statins, antihypertensives, etc.) will be described during the baseline period and follow-up periods and are listed in Table 3.

Risk factors for severe COVID-19, intensive care unit (ICU) usage, invasive mechanical ventilation (IMV) usage, supplemental oxygen use, non-invasive ventilation, and high-flow nasal cannula usage are depicted in Table 5 and will be extracted from the *I-Seha* national electronic health record database.

Where applicable, emerging treatment patterns may be assessed as the time from symptom onset to COVID-19 diagnosis, time from symptom onset to treatment initiation, and the time from COVID-19 diagnosis to treatment initiation as illustrated in Table 5.

10Nov23 WHO recommendations[30] for Paxlovid treatments to define: 1. COVID-19 patients who meet the WHO criteria for “strongly recommended” 2. COVID-19 patients who meet the WHO criteria for “conditionally recommended”, and 3. COVID patients who are not falling into categories 1 or 2 will be used.

9.4. Data Sources

There is a database of all patients who were eligible for Paxlovid™ therapy and details of those that accepted Paxlovid™ therapy and those that did not. Between 16 February 2022 and 30 November 2022, there were 8263 patients that met all study inclusion and exclusion criteria eligible for Paxlovid™ therapy of whom at least 3000 patients were treated with Paxlovid™ therapy and 1000 were not. All records from the participant cohort of 8263 will be reviewed.

Data on these patients that were treated with Paxlovid™ therapy and those that did not will be extracted from the I-Seha Electronic Health Record (EHR). I-Seha EHR will be used to collect the variables listed below including: medical, biochemical and pharmacy data, HER data, and patient registry data. The I-Seha EHR data contains unstructured data that will be anonymized. I-Seha uses a large, geographically diverse administrative claims dataset which comprises patients served by a number of different health systems, providers and benefit structures. Complete information regarding all healthcare utilization submitted for payment is included in database.

9.4.1. EHR Database

There is a database of all patients who were eligible for Paxlovid™ therapy and details of those that accepted Paxlovid™ therapy and those that did not. Data on these patients that were treated with Paxlovid™ therapy and those that did not will be extracted from the I-Seha EHR. A retrospective review will be undertaken of patients symptom database to discern patient-reported symptoms (eg, time from onset, duration, severity, frequency) will be described in this study. Following Paxlovid™ treatment initiation, patients were followed up by a telephone call, regarding their symptom onset and severity; review of this standard of care data will be used to complement emerging treatment patterns and clinical characteristics throughout this study. For those that did not take Paxlovid™ treatment, data will be extracted by the CRAs from the EHR on patient reevaluation in a healthcare facility, admission to hospital or death.

Table 2. Patient Demographic and Clinical Characteristic Variables at Index

Variable	Operational definition
Age	Age will be defined as of the index date and will be used to assign patients to age groups: 18-29, 30-49, 50-64, 65-74, ≥75 years and unknown/missing age.
Gender	Defined as of the index date as the distribution of female, male and unknown/missing sex patients.
Region	Kingdom of Bahrain
Nationality	Nationality of the patient will be mentioned
Enrollment Date Place of Service (POS)	Distribution of patients by the type of outpatient encounter during the enrollment date (eg, office visit, emergency room (ER), outpatient hospital, other, etc.).
Enrollment Date	Date (defined as MM/YYYY) of the enrollment date specified for each Cohort.

Variable	Operational definition
Specialty of Provider at enrollment Date	Distribution of the provider specialties present during the enrollment date. Patients with no provider specialty recorded will be included in an "Unknown/missing specialty" category.
Patient-reported COVID-19 symptoms	List of COVID-19 symptoms to be added by study team (US, CDC definition). 1- Stuffy or runny nose 2- Sore throat 3- Shortness of breath 4- Cough 5- Low energy/tiredness/fatigue 6- Muscle ache/body aches 7- Headache 8- Chills or shivering 9- Feeling hot/feverish 10- Nausea or vomiting 11- Diarrhea 12- Loss of sense of smell 13- Loss of sense of taste
COVID-19 Symptom Onset Date	Date of symptom onset during the post-Paxlovid™ availability timeframe.
Time to COVID-19 Symptom Resolution	The number of continuous days with the same COVID-19 symptom. When available, the number of consecutive days will be reported as counts and percentages. The date of symptom resolution (last date recorded) will be reported when available.
Date of COVID-19 Vaccination	Date of each COVID-19 vaccination received. Note: patient-specific vaccination history may require more than 6-months pre-index time period.
Date of Paxlovid™ prescription written and/or fill history (eg, prescription claim)	Date of Paxlovid™ prescription written or fill history. Note: if both dates are available within the database, use the most recent date provided.

Table 3. Clinical Characteristic Variables

Variable	Operational definition
Comorbidities	**A full list of comorbidities is detailed below and according to eCRF:** Distribution of patients diagnosed with each comorbid condition during the baseline and follow-up periods. Comorbid conditions will include, but are not limited to, asthma, emphysema, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, obesity, cerebrovascular disease, neurological disease, chronic kidney disease, chronic liver disease, malignancy, etc.

Risk Factors for Severe COVID-19	Distribution of patients with each of the following risk factors during the baseline and follow-up periods:
	• Age ≥50 years
	• Obesity (BMI ≥30
	• Chronic kidney disease (eGFR ≥30 ml/min)
	  • Diabetes Mellitus
	  • Primary and Secondary Immunosuppressive disease or immunosuppressive treatment
	  • Cardiovascular disease (including congenital heart disease) or hypertension
	  • Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
	  • Sickle cell disease
	  • Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
	  • Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])

Death	Distribution of patients who died on or after the enrollment date in the follow up period.

Variable	Operational definition
Inpatient Death	Distribution of patients who died during a hospitalization in the follow-up period.

Table 4. HRU Data

Variable	Operational definition
Hospital Length of Stay	The total length of stay (LOS) recorded for all hospitalizations during the baseline period and follow-up period in days (excluding within 24 hours of Paxlovid™ initiation).
ICU/Non-ICU LOS	The total number of days in the intensive care unit (ICU) and the number of days that were not spent in the ICU (non-ICU) recorded for all hospitalizations during the baseline period and follow-up period in days (excluding within 24 hours of Paxlovid™initiation).
IMV/No IMV LOS	The total number of days with and without invasive mechanical ventilation (IMV) recorded for all hospitalizations during the baseline period and follow-up period in days (excluding within 24 hours of Paxlovid™ initiation).
Hospitalizations (Count and Percentage)	The count and percentage of patients with all-cause and COVID-related hospitalizations (excluding within 24 hours of Paxlovid™ initiation) during the baseline and follow-up period.
Number of Hospitalizations per Patient	The number of hospitalizations per patient in the baseline and follow-up periods for all-cause and COVID-related hospitalizations (excluding within 24 hours of Paxlovid™ initiation) will be described.
Number of Hospitalizations per Patient among Patients with Readmissions	The number of all-cause and COVID-related hospitalizations (excluding within 24 hours of Paxlovid™ initiation) per patient in the baseline and follow-up periods will be described among patients with readmissions during the same period. The cause for readmission will be reported when available.
Time to First Outpatient Encounter	Time from COVID-19 diagnosis to the earliest outpatient encounter to occur after diagnosis during the baseline period.

Table 5. COVID-19 Disease Outcome Variables

Variable	Operational definition
ICU Admission	Patients with ICU admission during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid™ initiation).
IMV Usage	Distribution of patients with IMV (ie, intubation and mechanical ventilation) usage, including extracorporeal membrane oxygenation (ECMO), during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid™ initiation).
Supplemental Oxygen Usage	Distribution of patients with supplemental oxygen usage during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid™ initiation).
Non-invasive Ventilation Usage	Distribution of patients with non-invasive ventilation usage during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid™ initiation).
High-flow Nasal Cannula Usage	Distribution of patients with high-flow nasal cannula usage during COVID-related hospitalizations in the baseline and follow-up periods (excluding within 24 hours of Paxlovid™ initiation).
Hospital Discharge Status	Distribution of patient discharge status for COVID-related hospitalizations during the baseline and follow-up periods (excluding within 24 hours of Paxlovid™ initiation). Discharge status should include transfer to skilled nursing facility, transfer to another healthcare facility, home, expired (dead), transfer to other long-term care facility, transfer to hospice based on the values recorded in the database.
Time from COVID-19 Test to Paxlovid™ Treatment	Time from the earliest COVID-19 test in the baseline period to the earliest date of Paxlovid™ prescription written date AND dispense date.
COVID-19 Lab Tests with Positive Result	The count and percentage of patients with a COVID-19 lab test with a positive result during the baseline and follow-up periods will be reported.
COVID-19 Lab Test with Variant Type	When available, the count and percentage of patients with each COVID-19 variant of concern (VOC) during the baseline period will be reported.
Monoclonal Antibody Usage	Patients with monoclonal antibody usage during the baseline and follow-up periods. Monoclonal antibody usage will include tocilizumab and bamlanivimab/etesevimab.
Antiviral Usage	Patients with antiviral therapy usage during the baseline and follow-up periods. Antiviral therapy usage will include remdesivir, nirmatrelvir/ritonavir (Paxlovid™) and molnupravir.
Steroid therapy	Patients with steroid therapy during admission

Variable	Operational definition
Treatment drugs being receiving at the Index date	Use Positive test as the INDEX Date and record use of any medicine listed in the potential DDI/Contraindications section of the EUA/Label

9.5. Study Size

This is a retrospective observational study using a sample afforded by the I-Seha Electronic health record. While this study will be descriptive in nature, feasibility queries show that, between 16 February 2022 and 30 November 2022, there were 8263 patients that met all study inclusion and exclusion criteria eligible for Paxlovid™ therapy of whom at least 3000 patients were treated with Paxlovid™ therapy and 1000 were not. All records from the participant cohort of 8263 will be reviewed.

9.6. Data Management

EHR data will be obtained via a retrospective review of participant charts and used to discern participant-reported symptom onset, symptom duration, and relevant laboratory findings for diagnostic criteria or other related information described in Table 2 and Table 3.

The unstructured data that is extracted will be put into the eCRF, will then be anonymized by the clinical research assistants and presented in the format requested by the statistician at the time of analysis.

The study will abide to European GDPR legislation for maintaining confidentiality of data.

A Data Protection Impact Assessment (DPIA) will be performed to help identify and minimize the data protection risks of the study.

The EHR database is unstructured data. Individual medical records will be extracted and anonymized and populated into an eCRF. All data will be kept securely. Details of outcome measures and adverse events will be documented in hospital healthcare records. Individual research participant data is stored in an encrypted electronic database. The study investigators will adhere to hospital protocols pertaining to healthcare record use and storage to protect the research participant's identity, a unique identification code will be assigned by the Investigator, or authorized designee, to each study participant. These will be used in lieu of the participant's name, and the unique individual study code for each participant will be used for adverse events reporting and/or other study related data to be reported. This coded form of identification, instead of the participant's name, will appear on all documents/databases and will be cross-referenced by the participants date of birth (month/year). This server has managed access and password protection. The information that this server contains is backed up every 24 hours.

Personal information will be treated as confidential, but may need to be reviewed by authorized representatives of the Sponsor (such as monitors and auditors), the Contract Research Organization, the ethics committee and the regulatory authorities. The investigators and authorized designees will ensure that the confidentiality of the participants data is preserved.

9.6.1. Case Report Forms

As used in this protocol, the term CRF 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.

A CRF is required and will be completed for each included participant. The completed original CRFs 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 party performing medical record review, Royal College of Surgeons in Ireland, Medical University of Bahrain, RCSI Bahrain, shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

RCSI Bahrain has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs 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 CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the third party responsible for performing medical record review, RCSI Bahrain agrees to keep all study-related records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), copies of all eCRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by RCSI Bahrain according to local regulations or as specified in the *Statement of work*, whichever is longer. RCSI Bahrain must ensure that the records continue to be stored securely for so long as they are retained.

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

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

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

9.7. Data 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.

A separate statistical analysis plan will provide analysis and programming details along with detailed table shells. A sample of the table of results expected from the primary aim of this descriptive study is listed in Table 8.

All descriptive statistics will be presented as n, % for the categorical variables, or mean ±SD, median (interquartile range) for the numerical (continuous variables), as appropriate.

Study sample will be stratified by age group: 18-29, 30-49, 50-64, 65-74, ≥75. Numerical outcomes included the number of COVID-19 vaccines received, date of last vaccination, days from last COVID-19 vaccination to date of Paxlovid™ treatment (eg, Prescription and dispensing date), days from COVID-19 diagnosis to date of Paxlovid™ treatment (eg, dispensing date), days from COVID-19 symptom onset to date of Paxlovid™ treatment (eg, dispensing date).

Categorical outcomes included comorbid conditions and COVID-19 therapy. Possible comorbid conditions include obesity (BMI ≥ 30), chronic kidney disease, diabetes mellitus, primary and Secondary Immunosuppressive disease or immunosuppressive treatment, cardiovascular disease (including congenital heart disease) or hypertension, active immunosuppressive disease (such as lymphoma, leukemia, etc.), active Immunosuppressive treatment (Chemo, Steroids, etc.) (Immunocompromised, defined in ANNEX 2. IMMUNOCOMPROMISED ICD-10 CODE LIST).

WHO guidelines on COVID-19 therapeutics include the following groups

- **High risk**: people who are immunosuppressed; estimated hospitalization rate of 6%.
- **Moderate risk**: >65 years of age, conditions like obesity, diabetes and/or chronic conditions including chronic obstructive pulmonary disease, kidney or liver disease, cancer, with disabilities, and with comorbidities of chronic disease; estimated hospitalization rate of 3%.

- **Low risk**: those who are not in the high or moderate risk categories; low risk of hospitalization (0.5%) – most people are low risk.

Data will be evaluated looking at frequency and percentage of COVID-19 patients who will fall in those criteria to understand strongly recommended or conditionally recommended use of Paxlovid™ in comparison to the country of issue recommendations.

9.8. Quality Control

Quality control for each project is performed by a specific audit team member assigned to the study. Quality control practices include, but are not limited, to:

- Having qualified individuals who did not have a role in the study review data analyses and any final study report documentation for accuracy
- Ensuring proper documentation of data sources and key analytical steps
- Auditing all software programs and results both with respect to computer output and final tables
- Performing internal consistency checks of data presentations
- Aligning dissemination materials with external requirements.

Regarding statistical programming, each program undergoes interim tests to ensure the program is working as expected. A study member will apply one or more testing methods as appropriate.

9.9. Limitations of the Research Methods

This is a retrospective observational study and therefore can only demonstrate association and not causality. The results of this study may not be generalizable to the entire population.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

The EHR database is unstructured data. Individual medical records will be extracted, anonymized and entered into the eCRF.

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. Such measures will include omitting participant names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Participant personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. RCSI Bahrain 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, RCSI Bahrain 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, any participant 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 this single, participant-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each participant'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 clinical study agreement and applicable privacy laws.

10.2. Participant 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)/Ethics Committee (EC)

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/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the 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.[29]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of participant-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 participant 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 data collection tool (eg, chart abstraction form) 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 Paxlovid™ 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.

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 RCSI Bahrain 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.

[redacted]

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14. LIST OF TABLES

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Table 6. Additional Variables

Category	Variables of Interest
Comorbidities	• Cancer (active or history of cancer) • Chronic kidney disease (CKD) at any stage • Chronic liver disease (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis) • Chronic lung diseases • Chronic lung diseases: Interstitial lung disease, pulmonary fibrosis • Chronic lung diseases: COPD, emphysema and chronic bronchitis • Chronic lung diseases: Asthma (moderate to severe) • Chronic lung diseases: Cystic fibrosis • Chronic lung diseases: Pulmonary embolism • Chronic lung diseases: Pulmonary hypertension • Chronic lung diseases: Bronchopulmonary dysplasia • Chronic lung diseases: Bronchiectasis • Dementia or other neurological conditions • Diabetes (type 1 or type 2) • Down syndrome • Heart conditions (heart failure, coronary artery disease, or cardiomyopathies) • HIV infection • Hypertension • "Immunocompromised state (primary caused by genetic defects; secondary/acquired from prolonged use of corticosteroids or other • immune weakening medicines)" • Immunocompromised state: HIV/AIDS

Category	Variables of Interest
	• Immunocompromised state: Solid malignancy • Immunocompromised state: Bone marrow transplant • Immunocompromised state: Organ transplant • Immunocompromised state: Rheumatologic/inflammatory • Immunocompromised state: Primary immunodeficiency • Immunocompromised state: Other immune conditions • Immunocompromised state: CKD or ESRD • Immunocompromised state: Hematologic malignancy • Immunocompromised state: IS drug only • Immunocompromised state: Anti-metabolites • Immunocompromised state: >1 IC condition • Mental health conditions (mood disorders, including depression, and schizophrenia spectrum disorders) • Overweight and obesity • Pregnancy and recent pregnancy (for at least 42 days following end of pregnancy) • Sickle cell disease (SCD) or thalassemia • Smoking, current or former • Solid organ or blood stem cell transplant (includes bone marrow transplants) • Stroke or cerebrovascular disease • Peripheral vascular disease • Transient Ischemic Attack • Substance use disorders (alcohol, opioid, or cocaine use disorder) • Tuberculosis

Table 7. Potentially Significant Drug Interactions

Drug Class	Product name
Antianginal	RANOLAZINE
Antiarrhythmics	BEPRIDIL
	LIDOCAINE (SYSTEMIC)
Anticancer agents	ABEMACICLIB
	CERITINIB
	DASATINIB
	ENCORAFENIB
	IBRUTINIB
	IVOSIDENIB
	NERATINIB
	NILOTINIB
	VENETOCLAX
	VINBLASTINE
	VINCRISTINE
Anticoagulants	WARFARIN
	RIVAROXABAN
Antidepressants	BUPROPION
	TRAZODONE
Antifungals	KETOCONAZOLE
	VORICONAZOLE
	ISAVUCONAZONIUM SULFATE
	ITRACONAZOLE
Anti-HIV protease inhibitors	AMPRENAVIR
	ATAZANAVIR
	DARUNAVIR
	FOSAMPRENAVIR
	INDINAVIR
	NELFINAVIR

Drug Class	Product name
	SAQUINAVIR
	TIPRANAVIR
Anti-HIV	DIDANOSINE
	DELAVIRDINE
	EFAVIRENZ
	MARAVIROC
	NEVIRAPINE
	RALTEGRAVIR
	ZIDOVUDINE
Anti-infective	CLARITHROMYCIN
	ERYTHROMYCIN
Antimycobacterial	BEDAQUILINE
	RIFABUTIN
Antipsychotics	QUETIAPINE
Calcium channel blockers	AMLODIPINE
	DILTIAZEM
	FELODIPINE
	NICARDIPINE
	NIFEDIPINE
Cardiac glycosides	DIGOXIN
Endothelin receptor antagonists	BOSENTAN
Hepatitis C direct acting antivirals	ELBASVIR/GRAZOPREVIR
	GLECAPREVIR/PIBRENTASVIR
	SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR
	OMBITASVIR/PARITAPREVIR/RITONAVIR AND DASABUVIR
HMG-CoA reductase inhibitors	ATORVASTATIN
	ROSUVASTATIN
Hormonal contraceptive	ETHINYL ESTRADIOL

Drug Class	Product name
Immunosuppressants	CYCLOSPORINE
	TACROLIMUS
	SIROLIMUS
Long-acting betaadrenoceptor agonist	SALMETEROL
Narcotic analgesics	FENTANYL
	METHADONE
Sedative/hypnotics	MIDAZOLAM (ADMINISTERED PARENTERALLY)
Systemic corticosteroids	BETAMETHASONE
	BUDESONIDE
	CICLESONIDE
	DEXAMETHASONE
	FLUTICASONE
	METHYLPREDNISOLONE
	MOMETASONE
	PREDNISONE
	TRIAMCINOLONE

Table 8. [SAMPLE] Results Table

	Treated COVID-19 patients (N = n) Control Group Untreated COVID-19 patients (N = n)	
Baseline Variables		
1.0 Demographics		
1.1 Age	-	
1.2 Gender	-	
2.0 Clinical Characteristics	-	
2.1 Comorbidities (ICD-10)	-	
2.2 Vaccination Status (incl. date)	-	
2.3 Baseline Medication Usage	-	
2.4 COVID-19 Symptom (incl. date)	-	
2.5 COVID Diagnosis Date (index)	-	
Outcome Variables	-	
3.0 HRU	-	
3.1 Hospitalizations	-	
3.2 Outpatient Visits	-	
3.3 Emergency Room Visits	-	
3.4 Procedures	-	
3.5 Laboratory Tests (incl. COVID-Related)	-	
4.0 Medical Costs (incl. COVID-Related)	-	
4.1 Outpatient Costs	-	
4.2 Inpatient Costs	-	
4.3 Emergency Room Costs	-	
4.4 Ancillary Costs	-	
5.0 Pharmacy Costs (incl. COVID-Related)	-	

	Treated COVID-19 patients (N = n) Control Group Untreated COVID-19 patients (N = n)	
6.0 Medication Usage (incl. written date of prescription and fill history)	-	
6.1 Antibiotic	-	
6.2 Antiviral (incl. Paxlovid™, COVID-19 monoclonal antibodies)	-	
6.3 Antithrombotic	-	
6.5 Anti-inflammatory (incl. steroids)	-	

ANNEX 3. IMMUNOCOMPROMISED ICD-10 CODE LIST

Participants will be identified as immunocompromised (IC) if they had ≥1 hospitalization or ≥2 outpatient visits on separate dates with an ICD-10-CM code on a healthcare claim indicating an IC condition or if they had usage of specific immunosuppressive medications during the 12-month baseline period.

The list of ICD-10-CM codes used to identify IC cases by diagnosis and list of immunosuppressive medications are shown below in Table 9

Table 9. ICD-10 Code List for Immunocompromised Patients

IC Condition	ICD-10 Code
HIV/AIDS*	B20-B24
Solid malignancy	
Organ/system malignant tumors	C00-C07; C11-C19; C22-C80; Z85
Neuroendocrine tumors	C7A; C7B; D3A
Neoplasms of uncertain behavior	D00-D49
Bone marrow transplant	Z94.81
Organ transplant	
Complications of transplanted organ	T86
Organ transplant status	Z94 except Z94.81; Z98.85
Rheumatologic or other inflammatory condition	
Sarcoidosis	D86
Amyloidosis Not Otherwise Specified (NOS)	E85
Familial Mediterranean fever	E85.0; M04
Amyloidosis Not Elsewhere Classified (NEC)	E85.1; E85.3; E85.8
Multiple sclerosis	G35
Other Central Nervous System (CNS) demyelination	G36; G37.1; G37.3; G37.8; G37.9
Acute infective polyneuritis	G61.0; G61.9
Acute myocarditis	I40
Polyarteritis nodosa and other	M30
Allergic alveolitis/pneumonitis NOS	T78.40; J67.9
Other alveolar pneumonopathy	J84.01; J84.02; J84.09
Enteritis and colitis	K50-K52

IC Condition	ICD-10 Code
Lupus erythematosus	L93.0; L93.2; M32
Diffuse connective tissue disease	L94; M35.8; M35.9
Arthropathy with infection	M12.9; M01.X0; M02.10
Crystal arthropathies	M11
Rheumatoid arthritis/inflammatory polyarthropathy	M05-M14
Inflammatory spondylopathies	M46
Polymyalgia rheumatica	M31.5; M35.3
Chronic inflammatory demyelinating polyneuropathy	G61.81
Immune thrombocytopenic purpura	D69.3
Primary Immunodeficiency	
X-linked agammaglobulinemia	D80.8
Common variable immunodeficiency	D83.1; D83.2; D83.8; D83.9
Immunoglobulin A (IgA) deficiency	D80.2
Immunoglobulin G (IgG) sub-class deficiency	D80.3
Severe combined immunodeficiency	D81.1
Di George syndrome	D82.1
Wiskott-Aldrich	D82.0
Ataxia telangiectasia	G11.3
Interferon-gamma/Interleukin 12 axis deficiencies	D84.89
Persistent complement, properdin or Factor B deficiency	D84.1
Received eculizumab for >14 days in the baseline period	
Chronic granulomatous disease	D71
Chediak-Higashi	E70.330
Leukocyte adhesion deficiency	D72: Genetic anomalies of leukocytes
Myeloperoxidase deficiency	D72.89: Other specific disorders of White Blood Cells (WBCs)
Other immune conditions	
Disorders of immune mechanism	D89
Neutropenia	D70
Functional disorders of neutrophils	D71

IC Condition	ICD-10 Code
Genetic anomalies of leukocytes	D72.0
Decreased leukocyte count	D72.81
Leukocyte disease NEC	D72.89
Leukocyte disease NOS	D72.9
Myelofibrosis	D75.81
Blood diseases NEC	D47.4; D75.89; D75.9; D89.2
Blood diseases NOS	D75.9; D75.89
Immunologic findings NEC	R76; R83.4-R87.4; R89.4
Nonspecific immune findings NEC and NOS	R76; R83.4-R87.4; R89.4
Sickle cell disease	D57
Asplenia	Q89.01
Psoriatic arthritis	L40.52
Kidney condition	
Chronic kidney disease	A18.11; A52.75; B52.0; C64.x; C68.9; D30.0x; D41.0x-D41.2x; D59.3; E08.2x; E09.2x; E10.2x; E10.65; E11.2x; E11.65; E13.2x; E74.8; I12.xx; I13.0; I13.1x; I13.2; K76.7; M10.3x; M32.14; M32.15; N01.x-N08.x; N13.1; N13.1x-N13.39; N14.x; N15.0; N15.8; N15.9; N16; N17.x; N18.1-N18.5; N18.8; N18.9; N19; N25.xx; N26.1; N26.9; O10.4xx; O12.xx; O26.83x; O90.89; Q61.02; Q61.1x-Q61.8; Q26.0-Q26.39; R94.4
End stage renal disease	N18.6 AND on dialysis (any type): Z99.2; Z49; Z9115; Z4931; OR Z4901
On hemodialysis	Any participant with the ESRD codes above and ≥1 hemodialysis procedure session during the baseline period identified by at ≥1 of the following codes: Z49.31; Z49.32; I953; A4680; A4690; A4706-A4709; A4730; A4740; A4750; A4755; A4802; A4870; A4890; A4918; E1520; E1530; E1540; E1550; E1560; E1575; E1580; E1590; E1600; E1610; E1615; E1620; E1625; E1636; G0365; G0392; G0393; G8081; G8082; G8085; S9335; 90935; 90937; 90940; 93990; 36800; 36810; 36815
On peritoneal dialysis	Any participant with the ESRD codes above and ≥1 peritoneal dialysis procedure session during the baseline period identified by ≥1 of the following codes: Z49.02; 90945; 90947
Hematologic malignancy**	

IC Condition	ICD-10 Code
Lymphatic and hematopoietic tissue malignancy	C81-C83; C88-C96

CNS: central nervous system; ICD-10: International Classification of Diseases, 10th Revision; IgG: Immunoglobulin G, IgA: Immunoglobulin A, NOS: not otherwise specified; NEC: necrotizing enterocolitis; WBCs: White blood cells.
*Excluded asymptomatic HIV code of ICD-10: Z21.
**Required to have usage of an immunosuppressive medication (chemotherapeutic agent, immunomodulator, or systemic corticosteroids) for >14 days anytime during the baseline period.

Document Approval Record

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