NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	A standing cohort to understand the characteristics of patients with COVID-19 and contextualize the COVID-19 complication and safety events of interests using US OPTUM EHR data
Protocol number	C4671040
Protocol version identifier	3.0
Date	23 August 2022
EU Post Authorization Study (PAS) register number	EUPAS48654
Active substance	Nirmatrelvir/Ritonavir (ATC code J05AE30)
Medicinal product	Paxlovid
Research question and objectives	Research Questions: What are the demographic and clinical characteristics and healthcare utilization of all Coronavirus Disease 2019 (COVID-19) patients (ie, all patients with a diagnosis of COVID-19 in the Optum database (Overall Source Cohort); and multiple subcohorts including, COVID-19 patients with characteristics similar to the Paxlovid clinical trial programs (Trial Similar Cohorts) and COVID-19 patients treated with Paxlovid (Paxlovid Subcohort)? What is background incidence of clinical manifestations of COVID-19 among COVID-19 patients including subpopulation of interests (eg, hospitalized patients, trial similar patients)?

	What are the background rates of events that may be potential Paxlovid safety concerns among COVID-19 patients? What are the incidences of long COVID-19 or post-acute sequalae SARS CoV-2 (PASC) the characteristics of patients with long COVID? What is the feasibility to assess the Real-world effectiveness of Paxlovid? The following are the research objectives that will be addressed in this study: ***Primary Objectives:*** Objective 1: Describe the distribution of demographics, co-morbid conditions, medical history, selected biomarkers, and healthcare utilization at baseline for COVID-19 patients (including subpopulation with long COVID). Objective 2: Describe the time to clinical events (eg, hospitalization, intensive care unit (ICU) admission, death). Objective 3: Estimate background incidence of COVID-19 manifestations/complications and safety outcome of interests following COVID-19 infection or Paxlovid exposure. Objective 4: Estimate incidence of long COVID-19 or PASC and assess health effects of Long COVID. Objective 5: Describe the health equity and demographic and clinical characteristics (eg, co-morbid conditions, outcomes, treatment patterns, healthcare utilization) among patients treated with Paxlovid. ***Secondary Objectives:*** Objective 1: Estimate the incidence of oxygen supplementation among COVID-19

	patients hospitalized with mechanical ventilation/ECMO.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ARDS	Acute (or adult) respiratory distress syndrome
BMI	Body mass index
CABG	Coronary artery bypass graft
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CVD	Cardiovascular disease
ER	Emergency room
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl co-enzyme A
ICD	International class disease
IEC	Independent Ethics Committee

Abbreviation	Definition
ILD	Interstitial lung disease
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
NA	Not Applicable
NIH	National Institute of Health
NI	Non-interventional
PAH	Pulmonary arterial hypertension
PAS	Post-Authorization study
PASS	Post-Authorization Safety Study
PCR	Polymerase chain reaction
RWD	Real world data
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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

In Annex 1 stand alone document.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1 administrative	24 May 2022	Title Page and section 8	Added research question: What is the feasibility to assess the Real-world effectiveness of Paxlovid? Added Exploratory objective 3: Assess the feasibility of Real-world effectiveness of Paxlovid in reducing the COVID 19 related outcomes (eg, hospitalization).	Understanding Real-world effectiveness of Paxlovid can provide useful data to help expand the leaning from the previous clinical trials and accelerate on-going or future clinical trials
		Title page	Added PASS information to title page.	Study was evaluated as voluntary PASS study and wording had to be aligned with internal requirements.
		Section 7	Added mandatory PASS wording	Study was evaluated as voluntary PASS.
		Section 9.2.2.3	Added: Method to refine index date per research question will be defined in Statistical analysis plan (SAP)	*To clarify the language of index date and follow up.*
		Section 9.3	Added: Potential effectiveness of interests* • Hospitalization • All-cause mortality • ICU/Mechanical Ventilation • In Hospital death *The outcomes may be removed or added depending on the data availability for proper analyses.	These 4 outcomes were added, because they are severe COVID 19 outcomes aligned with Paxlovid indication
		Section 9.8	Added: To assess the feasibility of real-world effectiveness of Paxlovid, we will apply propensity score matching (PSM) method to control confounding and prescription time distribution method (PTDM) to handle immortal bias.	One of the challenges using real world data is to deal with confounding and bias. PSM and PTDM were selected to allow us better control confounding and cope with immortal bias

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
2 substantial	23 Aug 2022	Title page	Corrected format and information on title page. Deleted Exploratory objectives.	To align with correct title page for PASS study conducted in USA. Title page should only show primary and secondary objectives.
		Section 3	Added "NIS Lead" to table. Deleted table of Co-Investigators.	To align with requirements, the role of "NIS Lead" was added to the table. This table is for studies with study sites, which is not the case for this study.
		Section 4	Added section for abstract.	Since this is a PASS the protocol abstract is required.
		Section 5	Added new table for amendments and updates.	The correct table has been added to list all the amendments and updates.
		Section 6	Milestones were updated.	Update of milestones was done to align with current status.
		Section 9.1	Added that this is a secondary structured data collection.	For clarification the study type was added to this section.
		Section 9.2.1	Added a sentence describing what a validation substudy is.	This sentence was added for clarification.
		Section 9.3.1 and section 9.3.2	Rearranged inclusion and exclusion criteria:	Change was done to be aligned with template and facilitate understanding
		Section 9.4	Added clarification of COVID-19 Re-infection and Rebound	This sentence was added for clarification.
		Section 9.6	Added 2 sentences at the end of the section.	Text was added to describe new data source starting at the end of 2022.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Section 10.1	Deletion of second sentence in this section.	The deleted sentence was in the wrong section, it is part of section 11.
		Section 11	Changed text to align with correct safety wording.	This study does not have any unstructured data, safety wording was aligned.
		Section 12	Clarified that there will be one final study report and multiple publications.	There will be no interim report. Interim data analysis will be published as scientific manuscript.
		Section 14	Added section 14.	Section 14 was added to list the figures.
		Annex 1	Added table in annex 1.	Table in annex 1 was added because the stand alone abstract is required.
		Throughout the protocol	Minor editorial edits and correction of spelling mistakes.	NA

6. MILESTONES

Milestone	Planned date
Start of data collection	1 May 2022
Registration in the European Union (EU) PAS register	19 August 2022
End of data collection	28 February 2025
Final study report	30 January 2026

7. RATIONALE AND BACKGROUND

Background: A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2), was first identified in December 2019 as the cause of a respiratory illness designated COVID-19.[1] The infection may be asymptomatic but symptomatic cases may present with cough, fever, dyspnea, headache, diarrhea, altered mental status, myalgia etc. Serious disease may manifest as acute respiratory distress syndrome, septic shock, and multi-organ dysfunction. As of January 2022, at least 324,196,758 cases have been confirmed worldwide, and at least 5,531,843 deaths have occurred.[2]

A number of different classes of drugs are being evaluated or newly developed for treatment or post-exposure prophylaxis of COVID-19. As of the date of issuance of clinical trial of Paxlovid (PF-07321332/ritonavir), only 1 anti-viral drug with activity against SARS-CoV-2, remdesivir, an Ribonucleic acid (RNA) polymerase inhibitor, has received approval in hospitalized patients with COVID-19[3] Monoclonal antibodies (containing casirivimab and imdevimab or bamlanivimab and estesevimab) received emergency use authorization for mild to moderate COVID19 in recently diagnosed high risk nonhospitalized patients. Both of these options are administered intravenously and require administration by healthcare professionals. As of October 2021, there were no approved oral alternatives to PF-07321332/ritonavir for the treatment of mild-to-moderate COVID-19 in adult patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[4-6]

There is an urgent and unmet need for antiviral agents that could be used for the treatment of non-hospitalized persons with COVID-19. Paxlovid, a potent and selective inhibitor of the SARS-CoV-2 3CL protease, was developed by Pfizer Inc. as an oral treatment in patients with COVID-19 in outpatient setting. The coronavirus 3CL protease is a virally encoded enzyme that is critical to the SARS-CoV-2 replication cycle, analogous to other obligatory virally encoded proteases (eg, human immunodeficiency virus (HIV) Protease, Hepatitis C virus (HCV) Protease) [7] In December 2021, Food and Drug Administration (FDA) has authorized the emergency use of Paxlovid in adult and pediatric patients 12 years of age and older (weighing at least 88 pounds (40 kg)]) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[8].

There is limited information about the safety and effectiveness of using Paxlovid, to treat people with mild-to-moderate COVID-19 in real-world setting.[8] Understanding the epidemiology and clinical manifestations of COVID-19, as well as the background rates of potential Paxlovid related adverse events (AEs) among COVID-19 patients who are at high and standard risk of progression to severe illness in real world setting can provide critical context for interpreting potential safety events and clinical manifestations in on-going clinical trials post-marketing, with broaden patient population. This population based cohort study using United States (US) OPTUM COVID-19 EHR data will provide background rates of safety events of interest to support Paxlovid program. The Phase 3 clinical trial inclusion and exclusion criteria will be applied to a subgroup of the population to create a trial similar cohort. This study is being conducted in anticipation of the need to address possible questions about safety emanating from reports of AEs associated with the Paxlovid. The timeframes for this study will consider the health impacts as well as changes in healthcare utilization that COVID-19 may have in interpreting our understanding of potential safety events. Additional outcome events and subgroups may be incorporated in this study over time. Given the global scale of COVID 19 pandemic, there is an increasing need to better understand and characterize the PASC or long COVID.[9-10] This study will also aim at describing the characteristics of COVID-19 outcome/long COVID including those exposed to Paxlovid in real-world setting. Such information may inform clinical trial design and disease management for the long-term health effects of the COVID patients. Moreover, this study provides insights into understanding of potential racial disparities among patients using Paxlovid. The exploratory analyses may help identify predictors of severe COVID-19 outcomes/ manifestations and long Covid and predict the risk developing the severe outcomes/ manifestations and long Covid at individual level in real world setting.

This non-interventional study (NIS) is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

Research Question:

What are the demographic and clinical characteristics and healthcare utilization of all COVID-19 patients (Overall Source Cohort); and multiple subcohorts including COVID-19 patients with characteristics similar to the Paxlovid clinical trial programs (Trial Similar Cohorts) and COVID-19 patients treated with Paxlovid (Paxlovid Subcohort)?

What is background incidence of clinical manifestations of COVID-19 among COVID-19 patients including subpopulation of interests (eg, hospitalized patients, trial similar patients)?

What are the background rates of events that may be potential Paxlovid safety concerns among COVID-19 patients?

What are the incidences of long COVID-19 or post-acute sequalae SARS CoV-2 (PASC) the characteristics of patients with long COVID?

What is the feasibility to assess the Real-world effectiveness of Paxlovid?

The following are the research objectives that will be addressed in this study:

Primary Objectives:

Objective 1: Describe the distribution of demographics, co-morbid conditions, medical history, selected biomarkers, and healthcare utilization at baseline for COVID-19 patients(including subpopulation with long COVID)

Objective 2: Describe the time to clinical events (eg, hospitalization, ICU admission, death)

Objective 3: Estimate background incidence of COVID-19 manifestations/complications and safety outcome of interests following COVID-19 infection or Paxlovid exposure

Objective 4: Estimate incidence of long COVID-19 or post-acute sequalae SARS CoV-2 (PASC) and assess health effects of Long COVID.

Objective 5: Describe the health equity and demographic and clinical characteristics (eg, co-morbid conditions, outcomes, treatment patterns, healthcare utilization) among patients treated with Paxlovid

Secondary Objectives:

Objective 1: Estimate the incidence of oxygen supplementation among COVID-19 patients hospitalized with mechanical ventilation/ECMO

Exploratory Objectives:

Objective 1: Identify predictors of COVID-19 severe outcomes/manifestations and Long COVID with machine learning (ML) methods

Objective 2: Predict risk of developing severe outcomes/manifestation and Long COVID with machine learning (ML) methods at the patient level

Objective 3: Assess the feasibility of Real-world effectiveness of Paxlovid in reducing the COVID 19 related outcomes (eg, hospitalization).

9. RESEARCH METHODS

9.1. Study Design

This is a secondary structured population-based database cohort study with ongoing retrospective and prospective data collection utilizing electronic healthcare data in the US. This study will include adults (≥18 years of age) and pediatric patients (<18 years of age) with COVID-19 diagnosis (ie, positive polymerase chain reaction (PCR) or antigen results of direct SARS-CoV-2 viral testing or have confirmed COVID 19 diagnosis codes). All Paxlovid users will be included in the study. Within the population-based general cohort (COVID-19 Cohort), a subcohort will be created based on similar eligibility criteria as those used in select Paxlovid clinical trials (eg, C4671005, C4671002) to attempt to emulate the characteristics of select clinical trial program populations (Paxlovid Trial Similar COVID-19 Subcohorts).

9.2. Setting

This study will be conducted using Optum's COVID-19 Electronic Health Record Data during the period of January 01, 2020, to June 30, 2024. Details about the database are found in Section 9.6. The COVID-era cohorts will be refreshed annually to include additional individuals, follow-up time, and events. These refreshes and cohorts will accordingly be described in a Statistical Analysis Plan (SAP) or protocol amendment as appropriate.

9.2.1. Study Population and Cohorts

The study population will consist of patients who tested positive or were diagnosed for COVID-19 (ie, positive PCR or antigen results of direct SARS-CoV-2 viral testing or have confirmed COVID-19 diagnosis codes). All Paxlovid users will be included in the study.

Within the study population, three source cohorts of general population with COVID-19 will be formed (Figure 1):

- 1a: Overall COVID-19 patients.
- 1b: Hospitalized patients (ie, hospitalized within 30 days of index date) for COVID-19
- 1c: Non-hospitalized patients (ie, not hospitalized within 30 days of index date) with COVID-19

Within source cohort of 1a, 1b, and 1c, the following trial similar subcohorts, will be formed:

*Patients at high risk of progression to severe illness (*Figure 1*)*

- 2a: Subgroup of the general population cohort 1a who meet relevant inclusion/exclusion criteria of the Paxlovid clinical trial (C4671005).
- 2b: Subgroup of the hospitalized patient cohort 1b who meet relevant inclusion/exclusion criteria of the Paxlovid clinical trial (C4671005).
- 2c: Subgroup of the non-hospitalized patient cohort 1c who meet relevant inclusion/exclusion criteria of the Paxlovid clinical trial (C4671005).

Patients at standard risk of progression to severe illness Figure 1*)*

- 3a: Subgroup of the general population cohort 1a who meet relevant inclusion/exclusion criteria of the Paxlovid clinical trial (C4671002).
- 3b: Subgroup of the hospitalized patient cohort 1b who meet relevant inclusion/exclusion criteria of the Paxlovid clinical trial (C4671002).

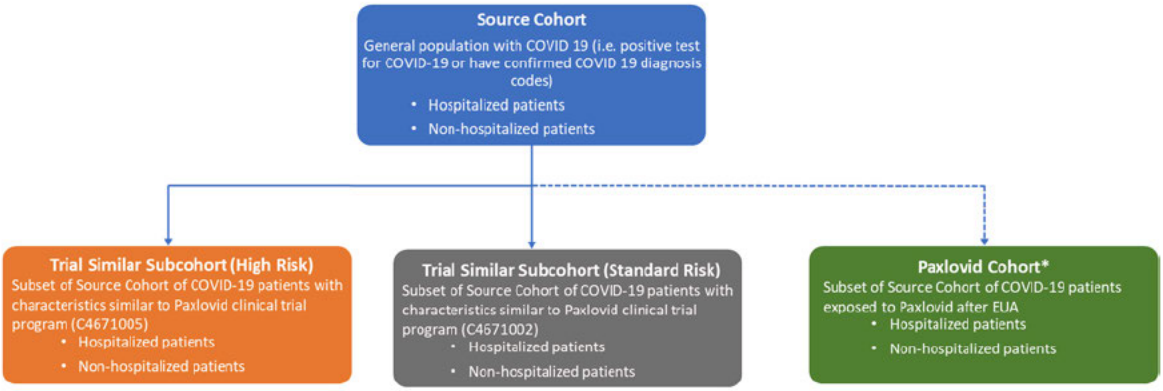
- 3c: Subgroup of the non-hospitalized patient cohort 1c who meet relevant inclusion/exclusion criteria of the Paxlovid clinical trial (C4671002).

A sub-cohort of patients who were exposed to Paxlovid in real world settings will be created.

If a patient had an exposure to paxlovid without COVID PCR/antigen testing/diagnosis data, this patient can be captured in the Paxlovid cohort.

Additional special populations (eg, immunocompromised patients, pediatric population, severe renal impairment, etc.) may be added as a subset.

A validation substudy will be a subpopulation randomly drawn from within the OPTUM EHR database.Figure 1. Flowchart Outlining the Study Cohort and Subcohorts



Note: Any addition of a special population (eg, immunocompremised patients, pediatric population, severe renal cohort etc.) as well as patients with multiple infections of COVID 19 or patients received COVID 19 vaccines can be a subset of either source cohort or high/standard risk cohort

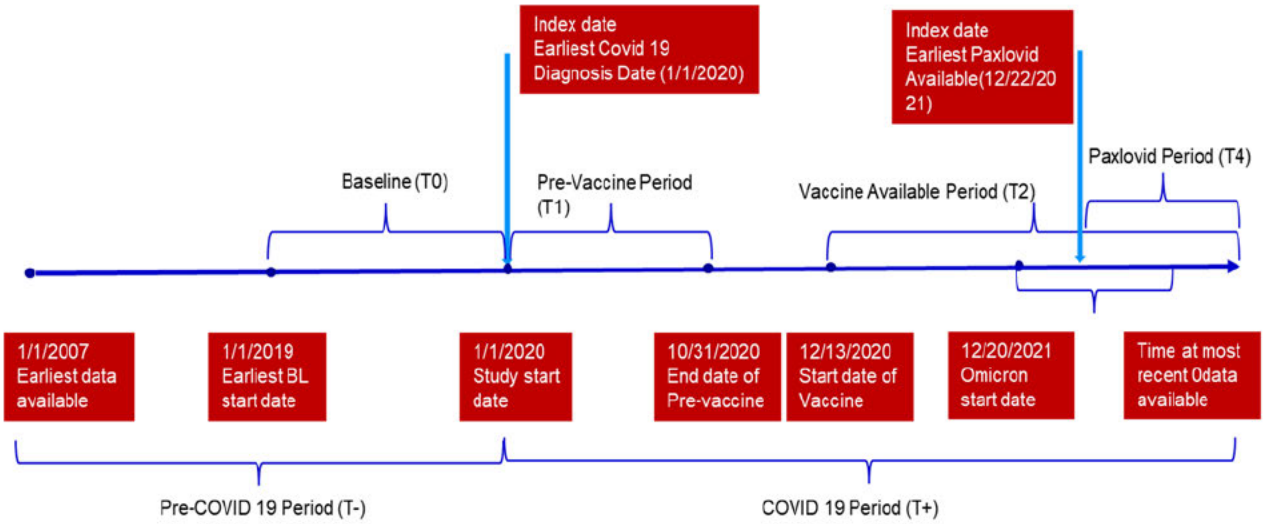
*For Paxlovid cohort, if a patient had an exposure to paxlovid without COVID PCR testing/diagnosis data, this patient can be captured in the Paxlovid cohort.

9.2.2. Time Periods

9.2.2.1. Study Period

The study will include an overall study period and four sub-periods for each source cohort and subcohort (Figure 2):

Figure 2. Flowchart Outlining the Study Periods



- Study period: COVID-19-era (T+) will include Jan 1, 2020 – most recent data available at the time of analytic dataset creation. The study period will be further stratified as follows:
  - Study period i (T1): Active COVID-19-era (Pre-Vaccine Period) will include Jan 1, 2020 – Oct 31, 2020
  - Study period ii (T2): Active COVID-19-era (Vaccine Available Period) will include Dec 13, 2020 – most recent data available at the time of analytic dataset creation.
  - Study period iii (T3): Omicron Period (Approximate time period when Omicron is dominated) will include Dec 20, 2021 – (TBD).
  - Study period iv (T4): Paxlovid Period (Paxlovid Available after EUA) will include Dec 22, 2021 (ie, EUA approval) to most recent data available at the time of analytic dataset creation.
  - Note: The period(s) for future variant(s) may be added.

9.2.2.2. Baseline Period

The 365 days before index date (see Section 9.2.2.3) will be the baseline period (Figure 2).

9.2.2.3. Index Date

The index date for the COVID-19 Source and the Trial Similar Subcohort will be defined as the date of first date tested positive or diagnosed for COVID-19 (ie, positive PCR or antigen results of direct SARS-CoV-2 viral testing or have confirmed COVID-19 diagnosis codes) during the study period.

Method to refine index date per research question will be defined in SAP.

The index date for the Paxlovid cohort will be defined as the date of first prescription of Paxlovid during the study period.

9.2.2.4. Follow-up

The follow-up period starts at index date and participants will be followed until the date of the first occurring of the following events:

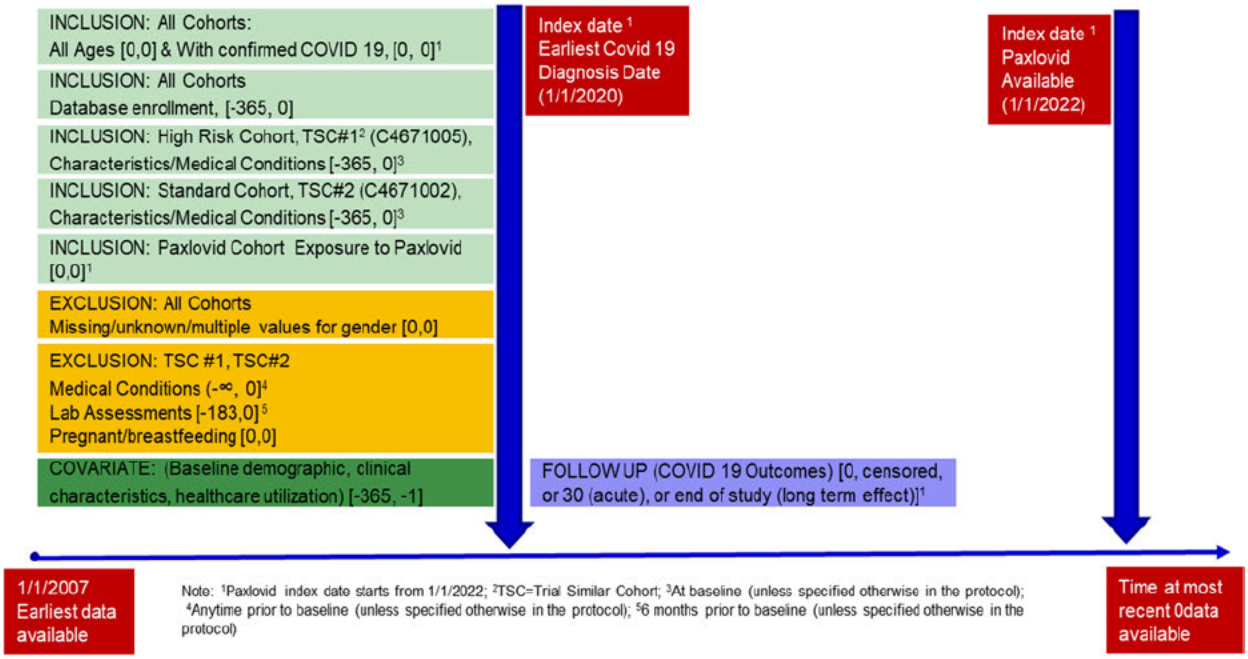
- Death;
- At the end of their database disenrollment from the database;
- At the end of study period (Section 9.2.2.1);
- Occurrence of the outcome of interest.

Follow-up time for hospitalized patients will meet the criterion in Section 9.2.1 (ie, hospitalized within 30 days of COVID 19 diagnosis or index date). Details as well as follow-up windows for long COVID will be defined in SAP.

9.3. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the source cohort, trial similar cohorts (TSC), and Paxlovid cohort are described respectively in this section. Figure 3 shows the inclusion and exclusion assessment windows.

Figure 3. Inclusion & Exclusion Assessment Windows (Days)



9.3.1. Inclusion Criteria

9.3.1.1. COVID- 19 Source Cohort, TSC Standard Risk Cohort and TSC High Risk Cohort

Patients in the COVID-19 Source cohort, TSC – standard risk (C4671002) or high risk cohort (C4671005), must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Tested positive or diagnosed for COVID-19 (i.e. positive PCR or antigen results of direct SARS-CoV-2 viral testing or have confirmed COVID-19 diagnosis codes: SARS-CoV-2L severe acute respiratory syndrome coronavirus 2; PCR: polymerase chain reaction) during the study period.

2. At least 12 months of ≥1 healthcare activity prior to index date (Section 9.2.2.3)

3. Integrated delivery network information to allow linkage of outpatient and inpatient records

In addition to inclusion criteria above, patients in the high risk cohort (C4671005) must meet the following inclusion criteria:

1. Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 at baseline (unless specified otherwise) including:

    a. ≥60 years of age at the index date;

b. Body mass index (BMI) >25 kg/m^2;

c. Current smoker (cigarettes smoking at baseline).

d. Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:

- Has received treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to index date.
- HIV infection.

e. Chronic lung disease (ie, Asthma, chronic obstructive pulmonary disease [COPD], interstitial lung disease [ILD]);

f. Known diagnosis of hypertension;

g. Cardiovascular disease (CVD), defined as history of any of the following: myocardial infarction, stroke, transient ischemic attack (TIA), heart failure (HF), angina with prescribed nitroglycerin, coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), carotid endarterectomy, and aortic bypass;

h. Type 1 or Type 2 diabetes mellitus;

i. Chronic kidney disease (CKD) (excluding dialysis or end stage of renal disease);

j. Sickle cell disease;

k. Neurodevelopmental disorders or other conditions that confer medical complexity;

l. Any cancer diagnoses, other than localized skin cancer (i.e. NMSC) at baseline, within one year prior to index date.

9.3.1.2. Paxlovid Cohort

Paxlovid patients are those who met the inclusion criteria in source cohort and exposed to Paxlovid after EUA approval on December 22, 2021. If a patient had an exposure to paxlovid without COVID PCR or Antigen testing/diagnosis data, this patient can be captured in the Paxlovid cohort.

9.3.2. Exclusion Criteria

Participants in all cohorts are excluded from the study if the following criterion applies:

1. Missing, unknown, or multiple values for gender.

9.3.2.1. TSC Standard Risk Cohort and TSC High Risk Cohort

Patients meeting any of the following criteria in the TSC high risk cohort (C4671005) or TSC standard risk cohort (C4671002) will not be included in the study:

1. Females who are pregnant or breastfeeding within 9 months prior to index date.

Any time prior to index date, unless specified otherwise:

2. History of hospitalization within 30 days prior to Index date.

3. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, or acute liver failure.

4. Receiving dialysis or end stage of renal disease.

Additionally, patients meeting any of the following criteria in the TSC standard risk cohort (C4671002) will not be included in the study:

Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19, including:

- ≥65 years of age at the index date.
- BMI≥30 kg/m^2.
- "High Risk Cohort – Inclusion Criteria 1.c – 1.l " (Section 9.3.1.1).

9.4. Variables

Outcome events will be the pre-specified potential safety concerns, including those that were part of Paxlovid or identified after the EUA post marketing.[8] The list of events of interest is provided below. This list of outcome events was chosen based on clinician's expert opinion, biologic plausibility, and feasibility of identification in EHR or claims data. Other potential safety concerns that arise during the post marketing, clinical trials, or based on emerging literature related to Paxlovid safety will be included in subsequent refreshes of the cohorts, or as rapid queries in response to regulatory authority requests.

Potential Safety Outcomes of Interests*

1. Renal impairment.

2. Hepatic impairment.

3. Other potential safety events of interest (eg, Diarrhea, Dysgeusia, Hypersensitivity reaction/allergic reactions, and other additional potential safety events of interest may be added over time).

* The potential safety outcomes of interests listed above can be further evaluated by the covariates including (demongraphics, drug-drug interactions etc.).

Potential effectiveness of interests*

- Hospitalization;
- All-cause mortality;
- ICU/Mechanical Vitalization;
- In Hospital death.

*The outcomes may be removed to added depending on the data availability for proper analyses.

COVID-19 complications/interventions (within 30 days of COVID 19 diagnosis):

- Pneumonia;
- Kidney failure;
- Thrombotic event;
- Acute respiratory distress syndrome (ARDS);
- HF;
- Sepsis/septic shock;
- Hospitalization;
- All-cause mortality;
- In hospital death;
- Multi-organ dysfunction/failure;
- Mechanical ventilation/ECMO (Extracorporeal membrane oxygenation).
- Vasopressor use

Time to clinical events:

- Time from index date (Section 9.2.2.3) to admission;
- Time from index date (Section 9.2.2.3) to the events above.

COVID-19 long term health effects:

The following conditions may be considered for COVID-19 long term effects. This is not an exclusive list. Specific definition and follow up windows of long COVID (eg, greater than 4 weeks, 12 weeks, or 6 months after a COVID diagnosis)[9-10] will be further defined in SAP.

- Abdominal pain;
- Acute kidney injury;
- Alopecia;
- Body aches;
- Chest pain;
- Cognitive impairment;
- Confusion/delirium;
- Nasal congestion;
- Cough;
- Anxiety disorders;
- Depressive disorder (includes major depressive disorder, dysthymic disorder);
- Post-traumatic stress disorder;
- Substance use disorders;
- Suicidal behavior and suicide ideation;
- Diarrhea;
- Nausea;
- Palpitations or fast-beating or pounding heart;
- Fatigue;
- Hair loss;
- Headache;

- Intermittent fever;
- Arthralgia or joint pain;
- Anosmia or loss of smell;
- Ageusia or loss of taste;
- Lung function abnormalities;
- Myalgia or muscle pain;
- Myocarditis;
- Pericarditis;
- Post-COVID syndrome (ie, PASC defined by international classification of disease -10-CM (ICD-10-CM) code U09.9);
- Rash;
- Dyspnea or shortness of breath;
- Insomnia;
- Others to be added.

COVID-19 Re-infection:

Re-infection of COVID-19 within certain time windows after previous COVID 19 infection or rebound with COVID-19 infection within certain time window post Paxlovid prescription date (as needed). This will be further defined in SAP.

9.5. Covariates

Covariates will include baseline demographic, clinical characteristics, medications, and health utilization, as well as those needed for the study cohort inclusion and exclusion criteria. These are not intended to be the exclusive lists. Adjustments of the covariates may be made and additional variables may be added in SAP as needed over time. The code lists of conditions and medications (if applicable) will be provided in SAP.

Demographics:

- Age;
- Gender;

- Race;
- Ethnicity;
- Region;
- Insurance.

Clinical Characteristics:

- Asthma;
- Autoimmune diseases.
    - Multiple Sclerosis; Sjogren's syndrome; Guillain-Barre; idiopathic thrombocytopenia purpura; autoimmune thyroiditis; giant cell arteritis; psoriasis; systemic or cutaneous lupus erythematosus; autoimmune arthritis/rheumatoid arthritis, glomerulonephritis.
- BMI.
- Cancer.
- Cerebrovascular disease or stroke (including transient ischemic attack).
- CKD.
- COPD.
- ILD.
- Coronary heart disease.
- Cardiomyopathies.
- Deyo-Charlson Comorbidity Index Score.
- Hepatitis B virus (HBV), HCV, HIV infection.
- Hyperlipidemia.
- Hypertension.
- Liver disease.
- Sickle cell disease.

- Smoking.
- Diabetes mellitus.
- Pregnancy status.
- C-Reactive Protein (CRP; within 10 days prior to the index date).
- Lactate dehydrogenase (LDH; within 10 days prior to the index date).
- Ferritin (within 10 days prior to the index date).
- D-dimer (within 10 days prior to the index date).
- Note: A focus of these lab tests would be for inpatients.

Medications that are contraindicated with Paxlovid (FDA EUA label):

- Alpha1-adrenoreceptor antagonist: alfuzosin;
- Analgesics: pethidine, propoxyphene;
- Antianginal: ranolazine;
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine;
- Anti-gout: colchicine;
- Antipsychotics: lurasidone, pimozide, clozapine;
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine;
- 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors: lovastatin, simvastatin;
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH);
- Sedative/hypnotics: triazolam, oral midazolam;
- Anticancer drugs: apalutamide;
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin;
- Antimycobacterials: rifampin;

- Herbal products: St. John's Wort (hypericum perforatum).

Medications for treatment of COVID-19/Vaccination for COVID-1:9[11]

Anti-SARS-CoV-2 Antibody Products
Bamlanivimab/Etesevimab
Casirivimab/Imdevimab
Sotrovimab
Tixagevimab/Cilgavimab
Bebtelovimab
Convalescent plasma
Antiviral therapy
Remdesivir
Molnupiravir
Chloroquine /hydroxychloroquine
Azithromycin
Lopinavir/ritonavir
Ivermectin
Nitazoxanide
Ribavirin
Inteferon-beta
Immunomodulators
Systemic Corticosteroids
Dexamethasone
Methylprednisolone
Fluvoxamine
Interleukin inhibitors
Tocilizumab
Sarilumab
Antithrombotic Therapy
Heparin
Covid-19 vaccines

Health Utilization:

- Emergency room (ER) visit;
- Office visits;
- Telemedicine visits;
- Urgent care visits;
- Number of hospitalizations;

- Length of hospital stay.

Paxlovid User Characteristics (in addition to Clinical Characteristics, Medications in "Covariates" in the Section 9.5).

- Demographics.
  - Age.
  - Gender.
  - Race.
  - Ethnicity.
  - Region.
  - Insurance.
- Comorbidities.
  - Renal impairment.
  - Hepatic impairment.
  - Top 50 Comorbidities in the database.
- Medications.
  - Top 50 prescriptions in the database.
- Paxlovid use.
  - Days since index date (Paxlovid prescribed date).
  - Provider.
- Health Utilization:
  - ER visit.
  - Office visits.
  - Telemedicine visits.
  - Urgent care visits

- Number of hospitalizations
- Length of hospital stay

9.6. Data Sources

Given the urgent need to clinically understand the novel virus of COVID-19, Optum developed a low latency data pipeline that enables minimal data lag, while preserving as much clinical data as possible. The data are sourced from Optum's longitudinal electronic health record (EHR) repository, which is derived from dozens of healthcare provider organizations in the US, including more than 700 hospitals and 7,000 clinics. The data are certified as deidentified by an independent statistical expert following the Health Insurance Portability and Accountability Act (HIPAA) of 1996 statistical deidentification rules and managed according to Optum® customer data use agreements. The COVID-19 dataset incorporates a wide swathe of raw clinical data, including new, unmapped COVID19-specific clinical data points from both inpatient and ambulatory electronic medical records, practice management systems, and numerous other internal systems. Information is processed from across the continuum of care, including acute inpatient stays and outpatient visits. The COVID-19 data capture point-of-care diagnostics specific to the COVID-19 patient during initial presentation, acute illness, and convalescence, with over 500 mapped labs and bedside observations, including COVID-19-specific testing.

The Optum COVID-19 EHR dataset elements included patient-level information: demographics, mortality (captured from Social Security Administration Death Master File, electronic medical records and Centers for Medicare and Medicaid Services), as well as clinical interventions, such as medications prescribed and administered, laboratory results, and vital signs and other biometric measures. The data are comprised of multiple tables that can be linked by a common patient identifier (an anonymous, randomized string of characters). The COVID-19 patient data included patients in the EHR database who had documented clinical care from January 2007 through to the most current monthly data release with a documented exposure to, or had been tested for, SARS-CoV-2 (positive or negative result), and/or had a diagnosis of COVID-19, or acute respiratory illness, after February 1, 2020. Thus, not all patients within the Optum® COVID-19 EHR dataset had received a diagnosis of COVID-19. Patients with COVID-19 were identified via a diagnosis code for SARS-CoV-2, a positive test for SARS-CoV-2 active infection (antigen and/or polymerase chain reaction), and/or a positive antibody test. The Optum® COVID-19 EHR dataset included medical records from 2007, allowing for the utilization of patients' medical history in the analysis.

As we are entering new era of COVID 19 toward end of 2022, monthly delivery of OPTUM COVID EHR 19 will be replaced by OPTUM EHR data with longer latency. Additionally, supplemental OPTUM Claims with likely larger size of Paxlovid patients may be used in additional analyses of Paxlovid (if needed) in this study.

9.7. Study Size

This is a descriptive study with no minimum sample size. This study will be updated with new data annually (or as needed) and made readily accessible to address research questions. All eligible patients during the relevant study periods will be included. If there is a need to add on post-hoc comparative studies analyses, which are not part of the scope of this current study, the feasibility of robust comparisons given accrued sample size will be assessed as described in the SAP.

9.8. Data Management

All study data exist as structured data by the time of study. Analyses will be conducted using SAS (version 9.4 or later, SAS Institute, Cary, NC, USA). As the database will be regularly updated, date and version of the database will be specified in the report of the study, and the intermediate datasets will be archived if the report will be submitted to a regulatory agency or will be published.

The study will be conducted by Quantitative Epidemiology and Analytic Team, Global Medical Epidemiology, Pfizer. The analytic datasets and programs will be stored according to Pfizer's procedures.

9.9. Data Analysis

Baseline characteristics will be summarized for Source Cohort, Trial Similar Subcohorts, and Paxlovid cohort. Means with standard deviations, medians with interquartile will be provided for continuous variables. Numbers and percentages will be provided for dichotomous variables or categorical variables.

For dichotomous endpoints such as COVID-19 complications and outcomes, the crude cumulative incidence and incidence rate of each endpoint will be estimated for the Source Cohort and the Trial Similar Subcohorts. For incidence calculation, only the first of each event occurring in the risk window will be included in the numerator. How to handle prevalence cases prior to the index date for incidence calculation will be further described in SAP depending on the nature of outcomes (eg, acute vs. chronic evets). Cumulative incidence and its 95% confidence interval (CI) will be estimated and illustrated using 1-Kaplan-Meier curves. Incidence rate will be calculated as the number of patients who experience the event divided by the total person time at risk, along with the 95% CI. The follow-up will start on the index date and will end on the first occurrence of an endpoint, disenrollment, study end date, or death, whichever comes first. Different endpoints will not censor each other's follow-up. Subpopulation analyses, as needed, will be detailed in SAP that may include those immunocompromised patients, pediatric population, severe renal patients, Paxlovid users with contraindication medications, patients with multiple infections of COVID 19, or patients received COVID 19 vaccines etc.

For exploratory analysis, machine learning models (eg, LASSO Cox regression, Random Survival Forest (RSF), and XGBoosting (XGB) models) will be used to identify important predictors associated with progression to COVID-19 severe outcomes/manifestations as well as long COIVD. An ensemble method will be used to rank predictors across models and find the strongest predictors for each outcome. Patient-level prediction for the risk of developing severe outcomes/manifestation and long COVID will be performed using the top ensemble predictors. C-index and dynamic AUCs will be used to evaluate model performance. To assess the feasibility of real-world effectiveness of Paxlovid, we will apply propensity score matching (PSM) method to control confounding and PTDM to handle immortal bias. To better understand the impact of incidental hospitalization on the same date of COVID 19 diagnosis date or Paxlovid prescription date, medical note review of patients with the same date hospitalization will be conducted by OPTUM. The structured data (Hospitalization on the same date = Yes/No) will be provided by OPTUM to enable the assessment of misclassification of the hospitalization.

All data analysis will be executed using statistical software SAS version 9.4 or later.

Detailed methodology for statistical analyses in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained. 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.

9.10. Quality Control

Analyses are programmed according to the specifications in the protocol, and the SAP, and documented in a programming plan as appropriate. Final deliverables will be reviewed and verified by a second, independent programmer who may also perform double programming. All quality checks will be documented in the programming plan.

9.11. Limitations of the Research Methods

COVID-19 is a new disease with evolving diagnostic mechanisms and care. A COVID-19 diagnosis code was established on 01 April 2020, months after the initial identification of cases and circulation in the US. The validity of the diagnosis codes remains to be determined. The spectrum of clinical manifestations of SARS-CoV-2 is still not fully described. Many infected persons are thought to have mild to unrecognizable symptoms and may therefore not present for care, testing or diagnosis. These infections will likely not be identifiable in the datasets. This may overestimate the incidence of severe disease in relation to overall SARS-CoV-2 infection but should be generalizable in relation to hospitalized patients in relevant analyses.

Similarly, patients with chronic diseases or in inpatient settings, the elderly, or other risk groups may be more likely to be under ongoing care or thought to be at higher risk and therefore may be more likely to seek care or be referred for testing. Differences among at-risk subpopulations may arise from access to care/health care seeking behaviors rather than true differences in risk. Generalizability may be further limited as SARS-CoV-2 testing patterns and treatment are evolving over time.

Other limitations are similar to those from observational studies in general, including the inability to obtain detailed clinical information on disease severity and activity due to the nature of secondary databases. In addition, EHR data only offer the prescribed drug information which does not indicate that the medication was consumed or that it was taken as prescribed. Misclassification in diagnosis data is unavoidable in real world data (RWD). Some conditions to be used to assess long-term health effects (eg, Dysgeusia, Diarrhea, Myalgia etc.) may not be well captured in the database if the patient is not seen by a health care provider to report these types of events. We use the data from the integrated delivery network (IDN) that manages end-to-end healthcare facilities of one or more healthcare centers in a defined geographical location and aims at providing full spectrum service of inpatient and outpatient for a patient to help reduce the concern of the discontinuity in patient service. We also plan to use the linked data to Claims as sensitivity (or additional) analyses when needed to expand the analyses by adding additional patients or patient records beyond EHR via close or open claims. Lastly, we would also like to note that there is a lack of complete similarity between the Trial Similar Subcohort and the clinical trial patients.

9.12. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient Consent

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

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

Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) review is not required.

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 (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report will be generated at the end of the study. Publications might be written throughout the course of the study.

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 party responsible for collecting data from the participant 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.

13. REFERENCES

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14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	NA	23-Aug-2022	Abstract: A standing cohort to understand the characteristics of patients with COVID-19 and contextualize the COVID-19 complication and safety events of interests using US OPTUM EHR data.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

Document Approval Record

Document Name:	C4671040 Non Interventional Study Protocol Amendment 2_Version 3.0_(clean)_23Aug2022
Document Title:	C4671040 Non Interventional Study Protocol Amendment 2_Version 3.0_(clean)_23Aug2022

Signed By:	Date(GMT)	Signing Capacity
Redacted	Redacted	Redacted
Redacted	Redacted	Redacted