NON-INTERVENTIONAL STUDY PROTOCOL ABSTRACT

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

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Rationale and background:

During the pandemic of COVID-19 a number of different classes of drugs are being evaluated or newly developed for treatment or post-exposure prophylaxis of COVID-19. Remdesivir has received approval in hospitalized patients with COVID-19. Monoclonal antibodies (containing casirivimab and imdevimab or bamlanivimab and estesevimab) received emergency use authorization for mild to moderate COVID-19 in recently diagnosed high risk non-hospitalized patients. Both of these options are administered intravenously and require administration by healthcare professionals. 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. 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.

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

Research question and objectives

What are the demographic and clinical characteristics and healthcare utilization of all COVID-19 patients (Overall Source Cohort), 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) and the characteristics of patients with long COVID?

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

Main objectives are:

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.

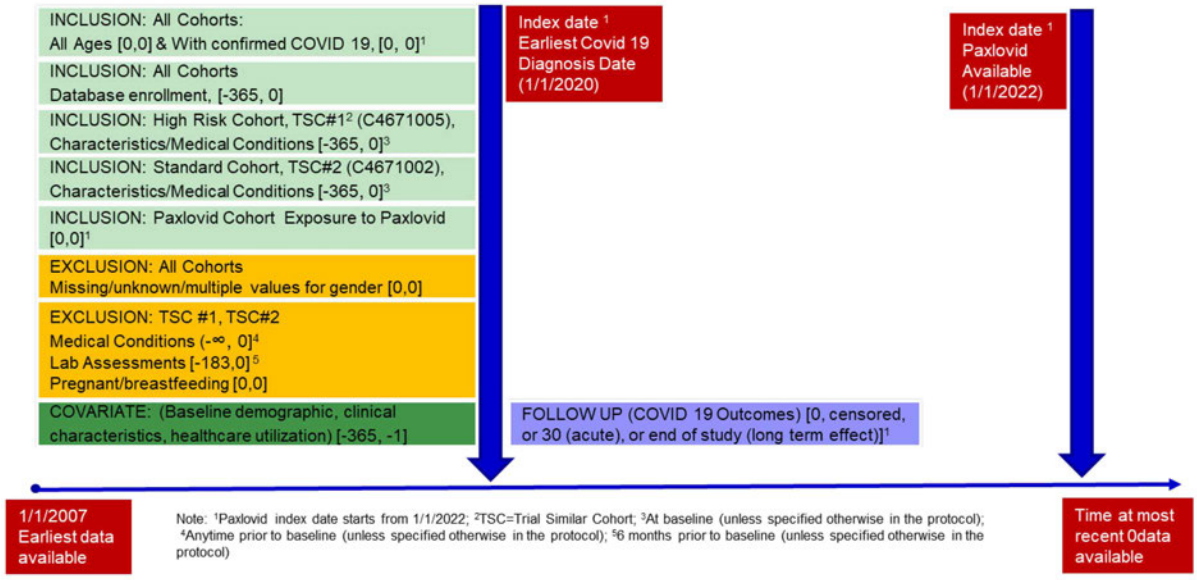
Study design

This is a population-based database cohort study with 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 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).

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) between January 01, 2020 and June 30, 2024. Two Trial-similar Subcohorts will be formed. COVID-19 patients who met the inclusion and exclusion criteria of the Paxlovid clinical trial (C4671005) will be considered at high risk of progression to severe illness and those who met the inclusion and exclusion criteria of Paxlovid clinical trial (C4671002) will be considered at standard risk of progression to severe illness.. All Paxlovid users will be included in the study.

Figure 1. Inclusion & Exclusion Criteria Assessment Windows (Days)



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

The index date for the COVID-19 Source Cohort and the Trial Similar Subcohorts will be 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. The index date for the Paxlovid cohort will be the date of first prescription of Paxlovid during the study period.

Variables

The list of outcome events including potential safety outcomes of interests, COVID-19 complications/interventions, COVID-19 long term health effects, 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. Patients will be followed from the index date 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; occurrence of the outcome of interest.

Covariates will include baseline demographic, clinical characteristics, medications, and health utilization, as well as those needed for the study cohort inclusion and exclusion criteria.

Data Sources

The data will be extracted from Optum COVID-19 EHR dataset, which is 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 including elements of demographics, mortality, as well as clinical interventions, laboratory results, and vital signs and other biometric measures. 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. 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.

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.

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. Cumulative incidence and its 95% 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.

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

Milestones

Milestone	Planned date
Start of data collection	1 May 2022
Registration in the EU PAS register	24 May 2022
Interim report	30 August 2022
End of data collection	30 June 2024
Final study report	31 September 2024