NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	*Coronavirus Disease 2019 (COVID-19) Vaccination and Breakthrough Infections Among Persons with Immunocompromising Conditions in the United States*
Protocol number	*C4591035*
Protocol version identifier	*1.0*
Date	*25 August 2021*
EU Post Authorization Study (PAS) register number	*Study is not a post-approval safety study (PASS) and is not registered* *Date assessed: 09 August 2021*
Active substance	Tozinameran
Medicinal product	Research name: BNT162b2 Brand name: Comirnaty
Research question and objectives	**Primary Objectives** **Aim 1:** Describe profiles, vaccine utilization and resource use among subjects with immunocompromising (IC) conditions vaccinated with BNT162b2 **Aim 2:** Evaluate incidence rates of breakthrough infections among subjects with IC conditions fully vaccinated with BNT162b2 **Aim 3**: Evaluate the clinical presentation of vaccine breakthrough cases among subjects with IC conditions, including time to infection and severity of disease (hospitalization, mortality)

	Secondary Objectives Evaluate Aims 1, 2, 3 and healthcare resource utilization (HCRU) / costs over time and stratified by relevant patient characteristics (eg, age), in specific IC conditions and by vaccination type (eg, any Messenger ribonucleic acid (mRNA)). **Exploratory Objective** Generate early estimates of the effectiveness of BNT162b2 in preventing COVID-19 infection, stratified by relevant patient characteristics (eg, age) and in specific IC conditions. While the analyses will be focused on the IC population, analyses will also be conducted (in part or entirely) on the non-IC population, the total (IC + non-IC) population or relevant subgroups (eg, other high-risk conditions, vaccination status) to support the interpretation of findings.
Author	PPD *(see section below for full list of study investigators)*

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin Converting Enzyme Inhibitors
AIDS	Acquired Immunodeficiency Syndrome
ARB	Angiotensin-Receptor Blockers
CDC	Centers for Disease Control and Prevention
CDM	Charge Description Master
CI	Confidence Interval
CKD	Chronic Kidney Disease
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CPT-4	Current Procedural Terminology, 4th Edition
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESRDEUA	Emergency Use Authorization
FDA	US Food and Drug Administration
GPP	Guidelines for Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HCRU	Healthcare Resource Utilization
HIPAA	Health Insurance Portability and Accountability Act

HIV	Human Immunodeficiency Virus
IC	Immunocompromising
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision, Procedure Coding System
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Immuno-Modulators
IMV	Invasive Mechanical Ventilation
IRB	Institutional Review Board
IS	Immunosuppressive
ISPE	International Society for Pharmacoepidemiology
J&J	Johnson & Johnson
LOS	Length of Stay
mRNA	Messenger Ribonucleic Acid
N	Number
N/A	Not Applicable
NDC	National Drug Code
NEC	Not Elsewhere Classified
NOS	Not Otherwise Specified

PASS	Post-Approval Safety Study
PCS	Procedure Coding System
PCV	Proportion of Subjects with Breakthrough SARS-CoV-2 Infections that are Vaccinated
PV	Proportion of the Population that is Vaccinated
Q1	First Quartile
Q3	Third Quartile
QC	Quality Check
RCT	Randomized Controlled Trial
RTIE	Real-Time Insights and Evidence
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States
VE	Vaccine Effectiveness
Vx	Vaccine
WBCs	White Blood Cells
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name	Job Title	Affiliation / Email	Address
PPD	PPD	Pfizer / PPD	Pfizer, Collegeville
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PPD	PPD	Pfizer / PPD	Pfizer, Madrid
PPD	PPD	PPD	Pfizer, Collegeville
PPD	PPD	Pfizer / PPD	Pfizer, NYC
PPD	PPD	Pfizer / PPD	Pfizer, Collegeville
PPD	PPD	Pfizer / PPD	Pfizer, NYC
PP D	PPD	Pfizer / PPD	Pfizer, Collegeville
PPD	PPD	Pfizer / PPD	Pfizer, NYC
PPD	PPD	Pfizer / PPD	Pfizer, Collegeville
PPD	PPD	Pfizer / PPD	Pfizer, NYC

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Draft study protocol	09 August 2021
Final study protocol	20 August 2021
Internal compliance and registration (Quality check (QC), ct.gov)	09 August 2021 – 24 August 2021
Start of data analysis	25 August 2021 (anticipated)
End of data analysis	30 December 2021
Final study report	Interim: 23 September 2021 Final: 28 January 2022

6. RATIONALE AND BACKGROUND

In December of 2019, the first cluster of cases of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, were reported to the World Health Organization.[1] By the end of 2020, the number of COVID-19 cases in the United States had reached 20,402,814 with 369,742 deaths attributed to the illness.[2] In December 2020 two vaccines were issued Emergency Use Authorization (EUA) by the United States (US) Food and Drug Administration (FDA) for active immunization to prevent COVID-19: BNT162b2 (Pfizer/BioNTech) and mRNA1273 (Moderna).[3,4] A third vaccine (Ad26.COV2.S, Janssen) was issued EUA on 27 February 2021.[5] These three vaccines demonstrated efficacy in randomized controlled trials (RCTs) against COVID-19 illness, including severe disease; the mRNA vaccines demonstrated efficacies of 94% to 95% in preventing symptomatic COVID-19 illness.[6] At the time of this study, the mRNA vaccines were the most widely administered in the US and evidence is accumulating under real-world conditions that they are highly effective for protecting against SARS-CoV-2 infection, symptomatic COVID-19 illness, and COVID-19-related hospitalization and death, with findings generally consistent with the RCTs.[6]

As vaccination coverage continues to increase across the US and in other countries, it is important to understand vaccine effectiveness (VE) in subpopulations, especially those who were under-represented in RCTs, may have suboptimal immune responses to vaccines, and may be at higher risk for COVID-19-related complications, such as those persons with an immunocompromising (IC) condition.[7, 8] There is emerging real-world evidence that people with an IC condition may not develop as a robust of an immune response as the general population to COVID-19 vaccines and are at increased risk of poor outcomes.[8-12] Currently, there is sparse information in the published literature on whether suboptimal generation of an

immune response to the COVID-19 mRNA vaccines in people with an IC condition leads to reduced VE. In the RCTs of the mRNA vaccines, those with an IC condition were largely excluded from the study populations.[13, 14] A few recently conducted real-world studies that contained subpopulations with IC conditions have found that while the COVID-19 vaccines were effective in this patient group, VE against SARS-CoV-2 infection, symptomatic illness, and COVID-19-related hospitalization was lower than observed in the general populations of these studies.[15-23]

On 12 August 2021, the FDA amended the EUA for the mRNA COVID-19 vaccines to allow for the use of an additional dose for certain immunocompromised subjects with moderate to severe IC conditions. According to the Centers for Disease Control and Prevention (CDC) guidelines (COVID-19 Vaccines for Moderately to Severely Immunocompromised People | CDC), the additional dose should be administered at least 28 days following the two-dose regimen of the same vaccine to individuals 18 years of age or older (ages 12 or older for Pfizer-BioNTech) who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. A third dose of the same Mrna vaccine should be used; however, if the Mrna vaccine product given for the first two doses is not available or is unknown, either Mrna COVID-19 vaccine product may be administered.

Further study of patients with various IC conditions is warranted to gain a better understanding of which IC conditions may predispose people to reduced COVID-19 VE to guide further prevention efforts.

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this study is to evaluate characteristics, vaccine utilization and outcomes among vaccinated subjects with IC conditions. The primary analysis will be conducted on subjects vaccinated with BNT162b2. A variety of subgroup analyses are planned, along with multiple sensitivity analyses that will test how variations in study design affect results.

Primary Objectives:

Aim 1: Describe profiles, vaccine utilization and resource use among subjects with IC conditions vaccinated with BNT162b2

Aim 2: Evaluate incidence rates of breakthrough infections among subjects with IC conditions fully vaccinated with BNT162b2

Aim 3: Evaluate the clinical presentation of vaccine breakthrough cases among subjects with IC conditions, including time to infection and severity of disease (hospitalization, mortality)

Secondary Objectives

Evaluate Aims 1, 2, 3 and HCRU/costs over time and stratified by relevant patient characteristics (eg, age), in specific IC conditions and by vaccination type (eg, any Mrna).

Exploratory Objective

Generate early estimates of the effectiveness of BNT162b2 in preventing COVID-19 infection, stratified by relevant patient characteristics (eg, age), in specific IC conditions.

8. RESEARCH METHODS

8.1. Study design

This study will be a retrospective database analysis utilizing data sets within the HealthVerity database (Philadelphia, Pennsylvania) covering the time period 01 December 2018 through 08 July 2021 (or latest data available) to describe the characteristics of subjects with IC conditions vaccinated with BNT162b2 and to evaluate the incidence of SARS-CoV-2 breakthrough infections.

Study period: 01 December 2018 – 08 July 2021 (or latest data available)

Index identification period: 11 December 2020 – 08 July 2021 (or latest data available; inclusive)

Index date: The first record for a SARS-CoV-2 vaccine (primary analysis: BNT162b2; sensitivity analyses: any Mrna, any authorized vaccine) from a medical claim, pharmacy claim, or chargemaster record.

Baseline period: 12-month period prior to the index vaccination date

Follow-up period: Variable period beginning after the index date and continuing until the earliest of the following: end of the study or end of continuous insurance enrollment.

8.2. Setting

The primary analysis of this study will include all people at least 12 years of age with at least one vaccine claim (primary analysis: BNT162b2; sensitivity analyses: any Mrna, any authorized vaccine) between 11 December 2020 and 08 July 2021 (or latest date available) from the HealthVerity HealthCare Database. Patients included in the study will be required to have 12 months of continuous medical enrollment prior to the receipt of their first vaccine and have no evidence of a SARS-CoV-2 infection in the year prior to being vaccinated.

The study population will be stratified into two cohorts: non-immunocompromised and immunocompromised. Patients with IC conditions will be identified using a modified implementation of an algorithm developed by Greenberg et al – and later modified and

expanded by Patel et al – for administrative claims based on claims and healthcare records identified in the 12 month baseline period.[24, 25]

8.2.1. Inclusion criteria

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

1. Unique enrollees in the HealthVerity Vaccine dataset any time **after** 10 December 2020

2. At least 12 years on the index date (ie, first vaccination date)

3. No evidence of prior COVID-19 infection (a medical claim, pharmacy claim, or chargemaster record with an International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis code of U07.1) in the 12 months prior to the index date

4. Have 12 months of continuous enrollment with medical benefits (with or without pharmacy benefits) prior to the index date

Subjects with an IC condition were identified via an algorithm originally developed and validated by Greenberg et al[24] for use in administrative claims database studies. For this study, this algorithm will be modified and expanded based on expert medical opinion. The algorithm is depicted in Figure 1.

Subjects will be identified as immunocompromised 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 IC case definition will incorporate 8 groups based on clinical diagnoses only, 1 group based on both clinical diagnoses and usage of immunosuppressive medication, and 2 other groups based on usage of immunosuppressive medication only, for a total of 11 groups with an IC condition (Figure 1). Subjects with >1 IC condition will also be assessed, for a total of 12 mutually exclusive groups for inclusion in this study. The list of ICD-10-CM codes used to identify IC cases by diagnosis and list of immunosuppressive medications are shown in the Annex.

Eight of the disease groups will include subjects with 1) symptomatic human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS); 2) solid malignancy; 3) bone marrow transplant; 4) organ transplant (excluding bone marrow); 5) rheumatologic or other inflammatory condition; 6) a primary immunodeficiency; 7) other immune conditions; and 8) chronic kidney disease (CKD) or end stage renal disease (ESRD). Subjects in these IC groups (shown as "Group 1" in Figure 1) will be further stratified by treatment status: those with usage of immunosuppressive medications for >14 days anytime during the baseline period and those without any evidence of >14 days of usage of an immunosuppressive medication during the baseline period. Subjects with a bone marrow or

organ transplant will be further stratified by those who received their 1st vaccine dose >100 days prior to their transplant and those who received it <100 days prior to their transplant. Subjects with a solid malignancy will be further stratified by their treatment type: chemotherapy or radiation therapy or immunomodulator, or a mix of these treatments.

The 9th subject group (shown as "Group 2" in Figure 1) will include those with a hematologic malignancy, required to have usage of an immunosuppressive medication (chemotherapeutic agent, immunomodulator, or systemic corticosteroid) for >14 days anytime during the baseline period; this subject group will be further stratified by their use of an immunosuppressive medication >6 months or ≤ 6 months prior to their index date.

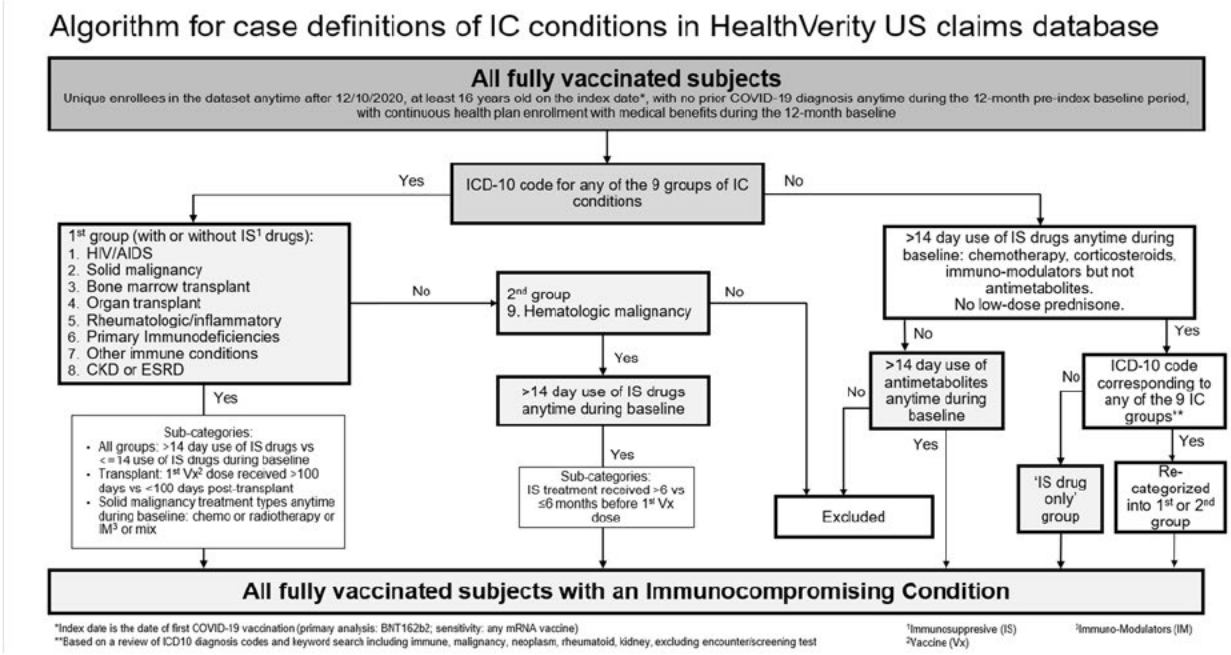
The 10th subject group will include subjects with usage of an immunosuppressive medication (chemotherapeutic agent, immunomodulator, or systemic corticosteroid excluding low-dose [<60mg/day] prednisone) for >14 days anytime during the baseline period, but without any ICD-10-CM diagnosis codes indicating the above listed IC conditions on a healthcare claim anytime during the baseline period. Subjects with >14 days usage of antimetabolites anytime during the baseline period will be excluded from this subject group and placed in the 11th subject group.

This algorithm differs from that used in Greenberg et al[26] by the following modifications, considered relevant for COVID-19 based on expert medical opinion: the inclusion of subjects with a solid malignancy who had radiation therapy or any treatment mix; the separation of subjects with a bone marrow transplant and those with an organ transplant; the inclusion of chronic inflammatory demyelinating polyneuropathy and immune thrombocytopenic purpura in the "rheumatologic or other inflammatory condition" group; the inclusion of sickle cell disease, asplenia, and psoriatic arthritis in the "other immune disorders" group; the addition of subjects with primary immunodeficiencies and those with CKD or ESRD; the requirement that subjects with a hematologic malignancy have evidence of usage of an immunosuppressive medication; the reclassification of subjects with only usage of an immunosuppressive medication; the removal of subjects with usage of only low dose prednisone; and the inclusion of an ad-hoc group of subjects who had taken anti-metabolites. Additionally, the following subcategories will be created: the first 9 subject groups were stratified according to treatment status; organ transplant subjects will be stratified according to time of receipt of the first COVID-19 vaccine dose in relation to the date of transplant; and subjects with hematologic malignancy will be stratified by time of receipt of treatment relative to their 1st vaccine dose.

When categorizing subjects with the different types of IC conditions, all the subject groups will be mutually exclusive. Subjects meeting the criteria for classification into only a single IC group will be classified accordingly into subject groups 1-11. Any subjects meeting the criteria for classification into multiple IC groups will be categorized into the >1 IC condition group (12th subject group).

All subjects will be grouped into an overall study population consisting of subjects identified as having an IC condition or not (i.e., non-IC). Subjects with an IC condition will be further categorized into the specific IC condition groups.

Figure 1: Algorithm to define immunocompromising conditions



8.3. Variables

Table 1. Immunocompromising Conditions definition

Variable	Role	Data source(s)	Operational definition
Immunocompromising Conditions	Cohort Definition	HealthVerity Vaccine Data	Subjects will be categorized into the following 12 mutually exclusive IC groups based on the algorithm detailed in Figure 1: Symptomatic HIV/AIDs, solid malignancy, bone marrow transplant recipients, organ transplant recipients, rheumatologic or other inflammatory conditions, primary immunodeficiencies, other intrinsic immune conditions, chronic kidney disease or end stage renal disease, hematologic malignancy, immunosuppressive treatment only, anti-metabolites only, or >1 IC condition.

Table 1. Immunocompromising Conditions definition

Variable	Role	Data source(s)	Operational definition
			Subjects falling into more than one of these categories will be categorized as having >1 IC condition. At a minimum, subjects will be required to have one inpatient claim or two outpatient claims on separate days with the IC condition of interest in the baseline period. In cases when >14 days of treatment are required it will be based on the dispensed day supply or distinct days of treatment in the baseline period. The main diagnosis codes to identify IC conditions are presented in ANNEX 1. LIST OF STAND ALONE DOCUMENTS.

Table 2. Vaccination Status definitions

Variable	Role	Data source(s)	Operational definition
Any vaccination	Cohort Definition	HealthVerity Vaccine Data	Patients with a claim for any vaccine will be considered vaccinated with any vaccine based on the following codes: Pfizer/BioNTech: 91300, 0001A, 0002A, 59267100001, 59267100002, 59267100003 Moderna: 91301, 0011A, 0012A, 80777027310,80777027399,80777027315, 80777027398 Johnson & Johnson: 91303, 0031A, 59676058005,59676058015 Source: https://www.cdc.gov/vaccines/programs/iis/COVID-19-related-codes html
Fully Vaccinated	Cohort Definition	HealthVerity Vaccine Data	Patients will be considered fully vaccinated if they meet any of the following definitions: • Two claims for Pfizer/BioNTech vaccine on separate days with >14 days of follow-up after the 2nd vaccination date. No claims for any other vaccines are allowed.

Table 2. Vaccination Status definitions

Variable	Role	Data source(s)	Operational definition
			• Two claims for Moderna vaccine on separate days with >14 days of follow-up after the 2nd vaccination date. No claims for any other vaccines are allowed. • One claim for the Johnson & Johnson (J&J) vaccine with >14 days of follow-up after the 1st vaccination date. No claims for any other vaccines are allowed
Partially vaccinated	Cohort Definition	HealthVerity Vaccine Data	Patients will be considered partially vaccinated if they meet any of the following criteria: • One claim for Pfizer/BioNTech vaccine with > 18 days of follow-up following first vaccination date and no claims for any other vaccine. • One claim for Moderna vaccine with > 25 days of follow-up following first vaccination date and no claims for any other vaccine. • One claim for J&J vaccine with ≤14 days of follow-up following first vaccination date and no claims for any other vaccine.

Table 3. Patient Characteristics and Vaccine Utilization variable definitions

Variable	Role	Data source(s)	Operational definition
Age	Patient Characteristics	HealthVerity Vaccine Data	The number of years between the index date and the patient birth year. If multiple birth years are reported for the same HealthVerity ID, the maximum birthyear will be used. Age will be reported in the following categories: 16 – 17, 18 – 29, 30 – 39, 40 – 49, 50 – 64, 65 – 74, 75 – 84, and 85+. Adolescents age 12-15 will also be reported as data accumulates over monthly data cuts. Continuous statistics including mean, standard deviation (SD), median (Q1-Q3),

Table 3. Patient Characteristics and Vaccine Utilization variable definitions

Variable	Role	Data source(s)	Operational definition
			minimum, and maximum, will also be summarized.
Sex	Patient Characteristics	HealthVerity Vaccine Data	Sex will be reported as Male ('M'), Female ('F'), and Unknown
US Geographic Region	Patient Characteristics	HealthVerity Vaccine Data	US geographic region will be derived from the patient state and categorized into the following: Northeast – Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, Pennsylvania Midwest – Indiana, Illinois, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota South – Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, Texas West – Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Nevada, Wyoming, Alaska, California, Hawaii, Oregon, Washington Other – Puerto Rico
Payer/insurance coverage on index date	Patient characteristics	HealthVerity Vaccine Data	Payer on index date will be reported as the following categories: Commercial, Medicaid, Medicare, Unknown, or missing. If multiple payers are reported on the index date, those will be captured under an ad-hoc "Multiple" category.
Vaccine Administration Setting	Patient characteristics	HealthVerity Vaccine Data	Vaccine administration setting will be determined based on the reported place of service for the claim. Prescription claims will be assumed to have occurred in the Pharmacy setting. The most common settings will be reported.
Conditions that place or may place patients at risk of Severe COVID-19 (6 months prior)	Patient Characteristics	HealthVerity Vaccine Data	Baseline comorbid conditions that place or may place patients at risk of Severe COVID-19 infection will be assessed in the 6 months prior to index vaccination. The ICD-10-CM, ICD-10 Procedure Coding System (ICD-10-

Table 3. Patient Characteristics and Vaccine Utilization variable definitions

Variable	Role	Data source(s)	Operational definition
			PCS), Current Procedural Terminology (CPT-4), and Healthcare Common Procedure Coding System (HCPCS) codes used to identify these conditions are based on the Sentinel COVID-19 Natural History Master Protocol (https://www.sentinelinitiative.org/methods-data-tools/methods/master-protocol-development-covid-19-natural-history)
Prevention seeking behavior (at baseline)	Patient Characteristics	HealthVerity Vaccine Data	These variables will be assessed during the 12 month baseline period: Telephone or Telehealth visits defined as a claim with any of the following procedure codes (G2012, G2010, G2061-G2063; 99205-99205, 99212-99215, 99421-99423, 99441-99443, G0425-G0427, G0406-G0408) COVID-19 laboratory tests defined as a claim with any of the following CPT-4 codes (87635, 86318, 86328, 86769, 87426, 86408, 86409, 86413) Flu vaccinations defined as a claim with the following procedure codes (90653-90664, 90666-90668, 90724, 90470, 90672, 90673, 90685-90688) The cumulative proportion of IC and non-IC subjects receiving their first dose of COVID-19 vaccine, by month, starting from December 2020 until most recent data.
Acute Respiratory Infection Hospitalization (at baseline)	Patient Characteristics	HealthVerity Vaccine Data	Any inpatient claim that occurs in the 12 month baseline period with a diagnosis of J00–J06, J09–J18, J20–J22 will be reported
Follow-up time	Patient Characteristics	HealthVerity Vaccine Data	The number of days between the index date and the earliest of the following: end of the study or end of continuous insurance enrollment
IS drugs use	Patient Characteristics	HealthVerity Vaccine Data	The proportion of subjects with IC conditions and usage of IS drugs for >14 days during the baseline period will be reported, as well as use within 14 days and 28 days within receipt of the first vaccine dose. IS drugs exclude low-dose [<60mg/day] prednisone.

Table 3. Patient Characteristics and Vaccine Utilization variable definitions

Variable	Role	Data source(s)	Operational definition
COVID-19 supportive medication use	Patient Characteristics	HealthVerity Vaccine Data	The use of medications considered supportive for COVID-19 will be assessed in the 12-month baseline period including remdesivir, dexamethasone, doxycycline, norepihephrine, methylprednisolone, lopinavir/ritonavir, eculizumab, sarilumab, tocilizumab, losartan, azithromycin, hydroxychloroquine, siltuximab, colchicine, and convalescent plasma. Codes used to identify these treatments will be based on the Sentinel COVID-19 Natural History Master Protocol
Other baseline medication use	Patient Characteristics	HealthVerity Vaccine Data	Medications for pre-existing conditions per the Sentinel COVID-19 Natural History Master Protocol (eg, angiotensin converting enzyme inhibitors (ACE), angiotensin-receptor blockers (ARB)).
Vaccine utilization	Patient Characteristics	HealthVerity Vaccine Data	Patterns of uptake. The proportion of IC and non-IC patients who are partially and fully vaccinated with BNT162b2 (or any other vaccines), at different calendar months and follow-up periods (eg, 7 days post dose 2, 14 days post dose 2). Mean, median, minimum, and maximum time between receipt of the first and second dose of BNT162b2 (or any other vaccine)

Table 4. Breakthrough Cases Definition

Variable	Role	Data source(s)	Operational definition
Breakthrough SARS-CoV-2 infection	Outcome	HealthVerity Vaccine Data	Among patients who meet the definition of fully vaccinated, a breakthrough SARS-CoV-2 infection will be defined by evidence of a claim with a diagnosis code of U07.1 that occurs >14 days after the second vaccination date. The first claim with a diagnosis of COVID-19 after this time will be used to assess mean and median time from the second dose until the breakthrough case

Table 5. COVID-19 Healthcare resource use and Costs definitions

Variable	Role	Data source(s)	Operational definition
Emergency department (ED) visit	Outcome	HealthVerity Vaccine Data	An outpatient claim with a place of service = 23 that occurs after the breakthrough COVID-19 diagnosis date or at the same time/episode of care
Outpatient Hospital Visit	Outcome	HealthVerity Vaccine Data	An outpatient claim with a place of service = 22 or 19 or a standard billing code that begins with '13' that occurs after the breakthrough COVID-19 diagnosis date or at the same time/episode of care
Other Outpatient Visit (not ED, not hospital-based)	Outcome	HealthVerity Vaccine Data	An outpatient claim that does not meet the definition for an ED visit or Outpatient hospital visit.
Hospitalization	Outcome	HealthVerity Vaccine Data	A record from the chargemaster data with encounter type of Inpatient OR a series of claims (separated by no more than 2 days) with a place of service = 21 or standard billing codes that begin with '11' or '12' that occur after the breakthrough COVID-19 diagnosis or at the same time/episode of care 1st admission and readmissions will be differentiated.
Intensive Care Unit (ICU)	Outcome	HealthVerity Vaccine Data	A claim with a procedure code indicative of ICU utilization during a hospitalization that occurs after the breakthrough COVID-19 diagnosis or at the same time/episode of care 1st admission and readmissions will be differentiated.
Invasive Mechanical Ventilation (IMV) / Extracorporeal Membrane Oxygenation (ECMO)	Outcome	HealthVerity Vaccine Data	A claim with a procedure code indicative of IMV/ECMO utilization during a hospitalization that occurs after the breakthrough COVID-19 diagnosis or at the same time/episode of care Includes both 1st admission and readmissions.
Inpatient Death	Outcome	HealthVerity Vaccine Data	Death that occurs on or after the date of the breakthrough COVID-19 diagnosis. The date of death will be assumed to be the same as the date of the last recorded encounter in the database.

Table 5. COVID-19 Healthcare resource use and Costs definitions

Variable	Role	Data source(s)	Operational definition
			Death information is available from the Charge Description Master (CDM) data and is provided as year-month of death only. Time to death will also be explored.
Length of Stay (LOS)	Outcome	HealthVerity Vaccine Data	Length of stay (LOS) associated with different types of hospitalization treatments mentioned above (eg, ICU), applicable for first index hospitalization and/or readmissions.
Costs	Outcome	HealthVerity Vaccine Data	Non-zero costs associated with any of the previously listed Outpatient and Inpatient encounters (but death). Charges may be assessed in sensitivity analyses to interpret the cost data.

8.4. Data sources

The HealthVerity database contains the largest all-payer (commercial, Medicare, and Medicaid) collection of US healthcare administrative data that links patients' journeys across inpatient admissions, outpatient visits, laboratory visits, and pharmacy services, including COVID-19 tests and vaccinations. Electronic medical records, including Veradigm data, are integrated with the administrative claims data from multiple sources to capture a relatively complete summary of patients' clinical history, including comorbid conditions and other risk factors that may predispose individuals to infections and complications, and use of healthcare resources. With monthly updates available, this data source provides a nearly real-time longitudinal view of patients' journeys across multiple sites of care. All data sets contained within the HealthVerity database are secured and encrypted and all patient information is deidentified. Thus, the data source is fully compliant with the Health Insurance Portability and Accountability Act (HIPAA).

8.5. Study size

The sample size for this study is fixed by the duration of the observation window. No formal sample size computation will be performed. All subjects who meet the inclusion/exclusion criteria will be included in the analyses.

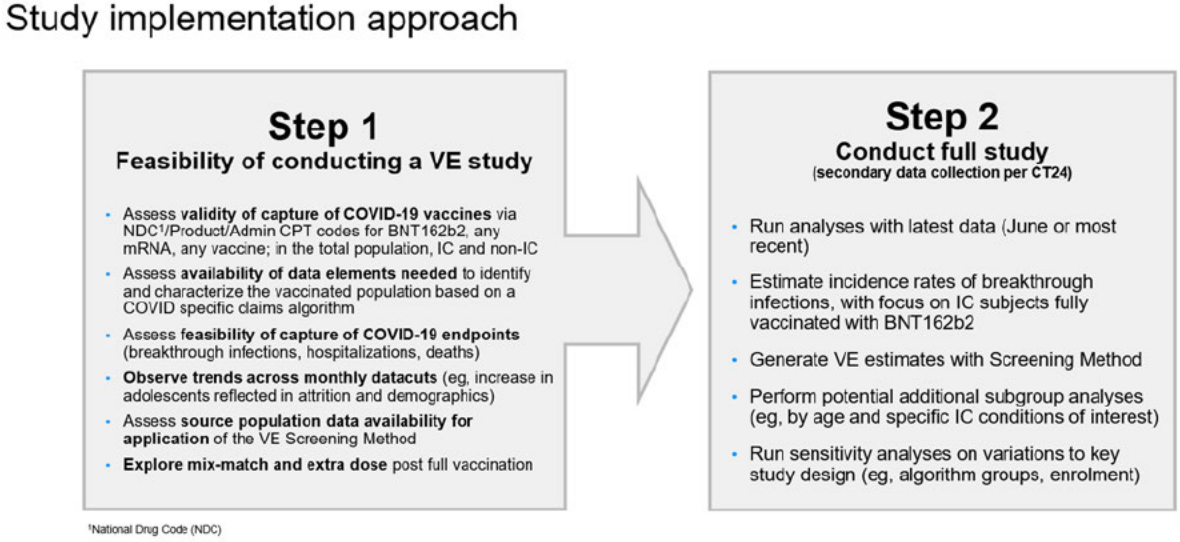
Feasibility analyses confirmed the availability of data to identify vaccinated subjects, subjects with underlying IC conditions, and breakthrough infections. The current study is mainly descriptive in nature. For the exploratory aim, the entire source population available in the HealthVerity database will be included in the analysis.

8.6. Data management

This study will use secondary data collected in the HealthVerity Healthcare database, specifically from the Vaccine and Real-Time Insights and Evidence (RTIE) data sets, which are de-identified and HIPAA compliant. The study will utilize a data cut consisting of data from December 1, 2018 through July 8, 2021 (or the most recent data available).

8.7. Data analysis

Data analyses will follow extensive feasibility analyses aimed at determining whether a full study and the assessment of vaccine effectiveness are feasible, as illustrated below:



Characteristics of the IC, non-IC and total population (IC + non-IC) groups will be described. Descriptive statistics for continuous variables will include N (number of patients), mean, median, standard deviation, Q1, Q3, minimum, and maximum. Categorical variables will be described using frequency counts and percentages.

The incidence rate of breakthrough cases of SARS-CoV-2 infection will be determined based on the following:

- Among fully vaccinated patients, those who have a claim for COVID-19 (ICD-10-CM: U07.1) that occurs on or after >14 days following their second dose of an mRNA vaccine (or 1st dose of Johnson & Johnson) will be considered to have had a breakthrough event. The time from 14 days after the qualifying dose until the breakthrough event will be the person time at risk.

- Among fully vaccinated patients with no evidence of COVID-19 after their qualifying dose, the time from 14 days after the qualifying dose until the end of follow-up will be the person time at risk.

The incidence rate of breakthrough cases of SARS-CoV-2 infection will be calculated as the number of patients who experience the event divided by the observed time at risk, and reported per 100 person years. Poisson 95% confidence intervals will be reported for the incidence rates.

Absolute effect measures such as risk difference between non-IC and IC will be reported. Time period specific effect estimates (eg, at 6 months after vaccination) may be estimated if feasible. The characteristics of the breakthrough infections will be described, including clinical presentation and severity.

The primary analysis will describe results among the non-IC cohort and the IC cohort who are vaccinated with BNT162b2. Subgroup analyses will include results for clinically meaningful subgroups as defined by vaccination type, relevant patient characteristics (eg, age), and each IC condition as listed below:

- HIV/AIDS
- Solid malignancy
- Bone marrow transplant
- Organ transplant (excluding bone marrow)
- Rheumatologic/inflammatory
- Primary Immunodeficiencies
- Other immune condition
- CKD or ESRD
- Hematologic malignancy
- IS drug use: >14 days IS medications (chemotherapy, immuno-modulators (IM), or corticosteroids excluding low-dose [<60mg/day] prednisone – See Drug List) and not falling into any of the above 9 condition groups
- >14 days of anti-metabolite use and not falling into any of the above 10 condition or drug use groups
- More than 1 IC condition

Analyses for younger cohorts (eg, 12-15) will also be conducted, as data accumulates.

For the exploratory aim, the Screening Method will be used to calculate VE for the overall study population of subjects with an IC condition and also stratified VE estimates for the different immunocompromised subject groups, with VE also determined for those subjects with >1 IC condition[26]. We will use the proportion of the population that are vaccinated (PV) and the proportion of subjects with breakthrough SARS-CoV-2 infections that are vaccinated (PCV) to calculate VE using the following formula:

$$VE = (PV - PCV)/[PV(1-PCV)]$$

where PV = the proportion of the population that is vaccinated (ie, vaccination coverage) and PCV = the proportion of subjects with breakthrough SARS-CoV-2 infections that are vaccinated.

Additionally, breakthrough incidence rates and VE will be stratified by age at diagnosis (eg, < 65 and ≥ 65 years of age at index vaccination).

Sensitivity analyses will be conducted to test the robustness of findings by varying key study design aspects (eg, continuous enrolment, IC case definition) and data analysis techniques. Other statistical techniques (eg, matched analyses, multiple regression, propensity scores) may be applied on an exploratory basis after careful examination of potential confounders (eg, age, time from vaccination). Exploratory analyses related to alternate dosing may also be conducted upon feasibility results, and as recommendations from public health authorities evolve. The analyses (entirely or in part) will be conducted over time and updated on a rolling basis as monthly data cuts become available.

While the analyses will be focused on the IC population, analyses will also be conducted (in part or entirely) on the non-IC population, the total (IC + non-IC) population or relevant subgroups (eg, other high-risk conditions, vaccination status) to support the interpretation of findings.

8.8. Quality control

Data in HealthVerity's COVID Healthcare database are collected weekly in an electronic format. HealthVerity employs its foundational product to match patients between different data sources with high accuracy. However, not all data points are available in every data source and as a result, not all variables in the database are completely populated. In addition, the database contains both pre- and post-adjudicated claims and, based on the data source, adjudication may or may not be captured. To maximize data completeness and uniformity, it may be necessary to exclude certain data sources from the analysis due to differences in data structure and content.

8.9. Limitations of the research methods

There are several limitations associated with this study. The healthcare claims data are

collected for billing purposes and may be subject to misclassification, misdiagnosis, and underreporting. While the sensitivity and specificity of the Greenberg algorithm were 87.4% (95% confidence interval (CI), 80.6-92.5%) and 97.6% (95% CI, 95.0-99.9%), we cannot assess the impact that our modifications had on the accuracy of the algorithm to identify immunocompromised patients. While we used the same codes as Patel[25] for HIV, which included HIV only when symptomatic, we cannot be certain about the degree of immunosuppression among patients who had International Classification of Diseases (ICD) codes for symptomatic HIV/AIDS. Further research leveraging Electronic Health Records/ Lab data is warranted to increase sensitivity of capturing symptomatic HIV cases. Due to irregular capture of COVID-19 vaccinations by insurers these results may only be generalizable to a subset of insured individuals. The HealthVerity Census algorithm which links unique patients across disparate data sources may incorrectly assign the same unique identifier to different people or different identifiers to the same person, though this is expected to have negligible impact on the interpretation of results. Additionally, due to the fact that the HealthVerity Data set is comprised of multiple data sources, there may be different levels of missingness for certain variables captured in this analysis.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information

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

9.2. 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.

9.3. Institutional review board (IRB)/Independent ethics committee (IEC)

IRB/IEC review is not required.

9.4. 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). This study will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline

10. 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 (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met

11. 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 (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

N/A

ANNEX 3. ICD-10 CODE LIST

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

IC Condition	ICD-10 Code
Enteritis and colitis	K50-K52
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)

IC Condition	ICD-10 Code
Other immune conditions	
Disorders of immune mechanism	D89
Neutropenia	D70
Functional disorders of neutrophils	D71
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 subject with the ESRD codes above and ≥1 hemodialysis procedure session during the baseline period identified by at ≥1 of the following codes: Z49.31;

IC Condition	ICD-10 Code
	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 subject 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**	
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.