Janssen Vaccines & Prevention B.V.*

Non-interventional Post-authorization Safety Study - Protocol

An Observational Post-Authorization Safety Study to Assess the Safety of Ad26.COV2.S Using Health Insurance Databases in the United States

Observational Study to Assess the Safety of Ad26.COV2.S

Protocol VAC31518COV4001 Amendment
Amendment 2

Ad26.COV2.S (JNJ-78436735)

* Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor. The sponsor is identified on the Contact Information page that accompanies the protocol.

Status:	Approved
Date:	20 October 2022
Prepared by:	Janssen Vaccines & Prevention B.V.
EDMS number:	EDMS-RIM-225973, 3.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

1. PASS INFORMATION

Title:	**An Observational Post-Authorization Safety Study to Assess the Safety of Ad26.COV2.S Using Health Insurance Databases in the United States**
EU PAS Register No:	Study not yet registered
Active substance (INN common name):	Established name is depicted as COVID-19 vaccine, (Ad26.COV2.S, recombinant)
Pharmaco-therapeutic group (ATC Code):	J07BX03
Medicinal product(s):	Janssen COVID-19 Vaccine
Product reference:	027205
Joint PASS	No
Research question and objectives	This study aims to assess the risk of developing prespecified adverse events of special interest within disease-specific risk periods following the administration of the Ad26.COV2.S vaccine.
Country(-ies) of study	United States
Author	PPD PharmD, MSCE, PPD

2. MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization* Holder:	Janssen Biotech Inc
Address:	Janssen Research and Development, LLC 920 Route 202 South, Raritan, New Jersey, 08869
Contact Details:	PPD PharmD, MSCE; PPD

*EUA granted in the US 27 February 2021; conditional MA granted in the EU 11 March 2021

3. RESPONSIBLE PARTIES

Principal Participating Physician:	Not applicable
Coordinating Physician:	Not applicable
Contact person for this protocol:	PPD PharmD, MSCE
E-mail address of contact person:	PPD

Principal Investigator(s) and Contributors to the Protocol

Name, degree(s)	Job title	Affiliation	E-mail address
PPD		Johnson & Johnson	PPD
		Johnson & Johnson	
		Johnson & Johnson	
		Johnson & Johnson	
		Johnson & Johnson	
		RTI Health Solutions	
		Harvard Medical School & Harvard Pilgrim Health Care Institute	
		Harvard Medical School & Harvard Pilgrim Health Care Institute	
		RTI Health Solutions	
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		RTI Health Solutions	

Data Partner Coordinating Investigators

Name, degree(s)	Job title	Affiliation	E-mail address
PPD	PPD	CVS Health	PPD
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		Humana Healthcare Research	
		Optum	
		Optum	

Note: Data Partner Coordinating investigators have reviewed and contributed to this protocol.

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ADDITIONAL INFORMATION PROVIDED IN ANNEX 1

LIST OF IN-TEXT TABLES AND FIGURES

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AMENDMENTS AND UPDATES

All protocol amendments must be issued by the sponsor and will follow the review and approval process in accordance with local regulations.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**EDMS Nos.**
Amendment 2: Changes to protocol revision (version 3.0)	20 October 2022	EDMS-RIM-225973, 3.0
Amendment 1: Changes to protocol revision (version 2.0)	15 April 2022	EDMS-RIM-225973, 2.0
Protocol Revision (Version 2.0): Changes to the protocol revision (version 1.0)	31 January 2022	EDMS-RIM-494309, 2.0
Protocol Revision (Version 1.0): Changes to the original protocol	28 July 2021	EDMS-RIM-494309, 1.0
Original Protocol	13 April 2021	EDMS-RIM-225973, 1.0

EDMS = electronic document management system; Nos. = numbers; TBD = to be determined.

The changes made to the clinical protocol VAC31518COV4001 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Amendment 2: Changes to Protocol Version 3.0 (Incorporated Into Version 4.0, Dated 20 October 2022)

Overall Rationale: Due to low utilization of the Janssen COVID-19 Vaccine (Ad26.COV2.S, recombinant), the scope of the analyses was reduced to remove the previously planned interim and monitoring analyses, to remove safety analyses associated with second doses of Ad26.COV2.S, and to clarify plans for validation.

Section Number and Name	Description of Change	Brief Rationale
Section 3 Responsible Parties	Updated investigator for Humana	Staff change
Section 5 Milestones	Updated to remove milestones for interim report, second and third monitoring reports	To reflect removal of interim and second and third monitoring analyses
Section 6.2 Overall Rationale for Study	Updated changes to Emergency Use Authorization since last protocol amendment	To make current
Abstract, Section 7 Research Question and Objectives	Modified secondary objective to describe counts and demographics of those individuals who received a second dose of Ad26.COV2.S; removed objective to assess incidence of predefined AESIs after receipt of a second dose of Ad26.COV2.S	Given low utilization and uptake of second doses of Ad26.COV2.S, assessment of incidence of AESIs is no longer feasible
Section 8.1.1 Overview of Study Design and Setting	Removed reference to interim analysis	Interim analysis no longer being conducted
Abstract; Section 8.1.3 Feasibility Assessment (Monitoring Phase)	Modified to reflect only 1 monitoring report to be done; removed interim and additional monitoring reports; removed plan to investigate information on SARS-CoV-2 infection before vaccination	Because additional uptake of Ad26.COV2.S is expected to be minimal following the first monitoring report, the next planned analysis will be for the final analysis

Section Number and Name	Description of Change	Brief Rationale
Section 8.1.3 Feasibility Assessment (Monitoring Phase)	Removed reference to assessing feasibility of calculating proxy SES and describing booster doses during the monitoring phase	Monitoring reports 2 and 3 are no longer planned. Proxy for SES will be included in the final analysis. Boosters will be addressed per the revised secondary objective.
Section 8.3.1 Exposure Assessment	Removed reference that booster doses would be described during the monitoring phase	Monitoring analyses 2 and 3 no longer planned.
Section 8.3.2 Individual Characteristics	Removed reference that frailty would be explored during the monitoring phase	Monitoring analyses 2 and 3 no longer planned. Definition will be included in the SAP.
Abstract; Section 8.3.4.1 Case Ascertainment and Validation Process	Removed requirement that validation would occur only during risk periods following administration of Ad26.COV2.S; clarified options for adjustment of relative risk estimates (whether using SCRI design or an active comparator design)	To allow flexibility for case selection and analysis following chart review at the protocol stage. Details will be provided in the validation plan.
Section 8.3.4.2 Risk Windows	Background rates in Table 1 updated for all outcomes with updated literature	Bring to current.
Abstract; Section 8.7.5.1 Extended Disease-specific Risk Periods; Section 8.1.2 Rationale for Study Design	Removed reference to descriptive time to onset analysis originally planned for the interim analysis to help inform risk windows for final analysis	Interim analysis is no longer being conducted. Alternate risk windows will be selected based on published literature and/or clinical input and will be documented in the statistical analysis plan.
Abstract; Section 8.7 Data Analysis, Table 4; Section 8.7.6 Secondary Analysis of Second Doses of Ad26.COV2.S	Updated to remove incidence of specified AESIs and include counts and descriptions of individuals receiving homologous second doses of Ad26.COV2.S	To align with the revised secondary objective.
Section 8.7.7 Interim Analysis	Section deleted	Interim analysis no longer planned.
Section 12 References	New references added to align with updates to this amendment	Update reference list.
Throughout the document	Minor editorial clarifications, and grammatical, formatting, or spelling changes were made.	Minor clarifications and corrections were made.

Amendment 1: Changes to Protocol Version 2.0 (Incorporated Into Version 3.0, dated 15 April 2022)

Overall Rationale: To address comments and feedback obtained from the Food and Drug Administration (FDA), the comparator group for the active comparator design was changed from recipients of any authorized mRNA vaccine to recipients of BNT162b2. Additional updates were made to clarify planned analyses.

Section Number and Name	Description of Change	Brief Rationale
Section 2 Marketing Authorization Holder(s)	Updated MAH contact	Staff change
Section 3 Responsible Parties	Updated investigator for Humana	Staff change

Section Number and Name	Description of Change	Brief Rationale
Global Update	Changed active comparator from "any mRNA vaccine" to "BNT162b2"	To reflect changes in comparator for active comparator design
Section 5 Milestones	Removed footnote relating to timing of interim report and modified footnote relating to third monitoring report	To reflect that interim analysis will now be run regardless of sample size; thus, planned dates are not contingent on number of events observed; timing and necessity for monitoring report 3 will be assessed once interim results are available
Abstract; Section 8.1.1.2 Cohort Design With Concurrent Active Comparator (Primary Study Design for Non-acute Events and Sensitivity Analysis for Acute Events); Section 8.7.2.1 Propensity Score Matching	Added matching variable (calendar time - within 2 weeks) for the active comparator analysis	To improve comparability of matches in the active comparator design
Abstract; Section 8.1.1.2 Cohort Design With Concurrent Active Comparator (Primary Study Design for Non-acute Events and Sensitivity Analysis for Acute Events); 8.3.2 Individual Characteristics	Removed 2-week calendar time increments from variables to be included in propensity score of the active comparator analysis	To reflect that potential confounding by calendar time will now be addressed through matching
Abstract; Section 8.1.3 Feasibility Assessment (Monitoring Phase)	Indicated that after monitoring query 1, subsequent queries and analyses will limit mRNA vaccinee counts and incidence rates to those vaccinated with BNT162b2	To reflect changes in comparator for active comparator design
Section 8.1.3 Feasibility Assessment (Monitoring Phase)	Added "to be described in monitoring analyses" in front of list of potential confounding factors	To clarify that these factors will be explored during the monitoring query
Section 8.2.2.1 Inclusion/Exclusion Criteria for the Self-Controlled Risk Interval Design	Clarified inclusion/exclusion criteria for SCRI design	Align with planned approach and refer to SAP for more details
Section 8.3.1 Exposure Assessment	Deleted language that active comparator will be limited to first dose only	Align with planned approach to include first and second doses of the primary series for the active comparator vaccine
Abstract; Section 8.3.2 Individual Characteristics	Removed "medications for COVID-19 treatment" as example variable of medication use; removed – "administration of other COVID-19 vaccines" as variable; added observation window for "other vaccines" for SCRI design	To align with the use of an active comparator; and avoid confusion relating to "other COVID-19 vaccines" described in follow-up and clarify how observation for "other non-COVID-19 vaccines" would be handled with SCRI design
Section 8.3.4.2 Risk Windows	Clarified in Table 1 disease-specific washout periods to be used for the active comparator and SCRI design	To align with the use of an active comparator

Section Number and Name	Description of Change	Brief Rationale
Section 8.3.5.2 previously Section 8.3.5.1 Cohort Design with Concurrent Active Comparator	The title ' Cohort Design with Concurrent Unexposed Comparator and Cohort Design with Historical Unexposed Comparator' was changed to 'Cohort Design with Concurrent Active Comparator'	The primary change to the protocol was to change from an unexposed comparator to an active comparator
Section 8.7.1.2 previously Section 8.9.1.1 Cohort Design with Concurrent Active Comparator	The title ' Cohort Design with Concurrent Unexposed Comparator and Cohort Design with Historical Unexposed Comparator' was changed to 'Cohort Design with Active Comparator'	The primary change to the protocol was to change from an unexposed comparator to an active comparator
Section 8.3.5.1 SCRI Design and Section 8.3.5.2 Cohort Design with Concurrent Active Comparator	The order of these Sections was changed from Section 8.3.5.1 Cohort Design with Concurrent Unexposed Comparator and Cohort Design with Historical Unexposed Comparator to Section 8.3.5.1 SCRI Design and vice versa	For a better flow of information
Abstract; Section 8.3.5.2 Cohort Design with Concurrent Active Comparator	Revised end of follow-up criteria	To clarify that switching of brands is an end of follow-up criterion regardless of brand of index vaccination
Section 8.3.5.2 Cohort Design with Concurrent Active Comparator	Clarified rationale for sensitivity analyses to assess risk of AESIs after a single first dose only and after both doses of the active comparator	To clarify that these sensitivity analyses will be performed to address differential lengths of follow-up between the Ad26.COV2.S-exposed and comparator cohorts
Section 8.4.2 HealthCore	Updated data source description for HealthCore	To provide additional details
Section 8.7 Data Analysis, Table 4	Re-organized table	Updated to follow order presented in protocol
Abstract; Section 8.7.1.2 Cohort Design With Active Comparator	Removed specific methods for estimation of incidence rate ratios and 95% CI for active comparator design	Methods for estimation of incidence rate ratios will be specified in the statistical analysis plan
Abstract; Section 8.7.1 Main Summary Measures	Removed “meta-analysis” as a potential method to pool results across data sources	Method for pooling results across data sources will be provided in the statistical analysis plan
Section 8.1.1.2 Cohort Design With Concurrent Active Comparator (Primary Study Design for Non-acute Events and Sensitivity Analysis for Acute Events); 8.7.2.1 Propensity Score Matching; Section 8.9 Limitations of the Research Methods	Removed “time-specific” from descriptions of estimation of propensity scores	To align with updated approach to account for potential confounding by calendar time through matching
Section 8.7.5.2 Alternate follow-up criteria for active comparative design based on BNT162b2 dose (for non-acute events)	Removed end of follow-up criteria for date of any COVID-19 vaccination that is not Ad26.COV2.S and for date of any index comparator mRNA vaccine	For clarity, to remove duplicative information that is already covered by other exclusion criteria

Protocol Revision (Version 2.0): Changes to Protocol Version 1.0 (Incorporated Into Version 2.0, dated 31 January 2022)

Overall Rationale: To address comments and feedback obtained from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The protocol changed the comparator group from unexposed to an active comparator group to minimize the concerns of misclassification of exposure. Additionally, the protocol has added a secondary objective to describe the incidence of AESIs after receipt of second dose of Ad26.COV2.S.

Section Number and Name	Description of Change	Brief Rationale
Section 3; Responsible Parties, Section 4; Abstract	Updated main author affiliated with Harvard Pilgrim Health Care Institute and added contributor to protocol for Janssen.	Staff change for main author at Harvard Pilgrim Institute and contributor for Janssen
Section 3; Responsible Parties	Revised data partner coordinating investigators	Staff change for principal scientist at HealthCore to Janssen and other staff changes
Section 5; Milestones	Updated milestones to reflect start of data collection for monitoring phase, added milestones for 3 monitoring reports, updated interim report date	Clarification for start of data collection and timing for monitoring reports and interim report given refresh schedules for data partners
Abstract, Section 6.1; Background	Section updated, and text added	To make current and reflect current regulatory and safety information
Abstract, Section 7; Research Questions and Objectives	Changed comparator group from unexposed to exposed to a comparator mRNA COVID-19 vaccine	To minimize the issue of misclassification of exposure due to vaccinations that may not be captured in health plan data
Abstract, Section 7; Research Question and Objectives	Added secondary objective to assess the incidence of AESIs after receipt of second dose of Ad26.COV2.S	Per CBER request
Abstract, Section 7; Research Question and Objectives, Section 8; Research Methods	Changed all instances of "unexposed comparator" to "comparator mRNA COVID-19 vaccine" or "active comparator"	To reflect change in comparator
Abstract; Endpoints, Section 7; Research Question and Objectives (Endpoints), Section 8.3.4.2; Risk Windows (Table 1)	Made the following updates to the list of endpoints: added thrombocytopenia, acute myocardial infarction, and 3 composite endpoints (venous thrombosis, arterial thrombosis, and stroke) and specified 1-42 days as the risk window for thrombocytopenia and 1-28 days as the risk window for composite outcomes	Additional events of special interest
Abstract; Study Design, Sections 8.1.1; Overview of Study Design and Setting, 8.1.1.1; Self-controlled Risk Interval Design (Primary Study Design for Acute Events), 8.1.1.2 Cohort Design with Concurrent Active Comparator (Primary Study Design for Non-acute Events and	Specified that a cohort design with active comparator will be primary design for non-acute events and sensitivity analysis for acute events.	Change in study design to add active comparator

Section Number and Name	Description of Change	Brief Rationale
Sensitivity Analysis for Acute Events, 8.1.2; Rational for Study Design, 8.3.5.1; SCRI Design, Figure 1)		
Section 8.1.1.2; Cohort Design With Concurrent Active Comparator (Primary Study Design for Non-acute Events and Sensitivity Analysis for Acute Events) - Figure 2 Cohort Study Design	Updated the figure	Change in study design to active comparator
Section 8.1.1; Overview of Study Design and Setting,	Revised description of selection of comparator cohort: active mRNA vaccine with reference date first dose in primary series;	Change in study design to active comparator
Abstract, Section 8.1.1.2; Cohort Design With Concurrent Active Comparator (Primary Study Design for Non-acute Events and Sensitivity Analysis for Acute Events)	Changed time-specific propensity score matching to propensity score (PS) matching with calendar time as variable, changed matching ratio to 1:4 (Janssen to mRNA)	Change in study design to active comparator
Abstract, Sections 8.1.1; Overview of Study Design and Setting, 8.1.1.2 (section deleted), 8.1.2; Rational for Study Design, 8.2.2.1; Inclusion/Exclusion Criteria for the Self-Controlled Risk Interval Design, 8.3.5.1; SCRI Design, 8.7; Data Analysis (Table 4), 8.7.1.1; Self-controlled risk interval design, 8.7.1.2; Propensity Score Methods, 8.7.5; Sensitivity Analysis	Deleted all instances referring to or describing historical cohort.	Because of the change to active comparator, a historical comparator cohort is no longer needed
Abstract; Monitoring Phase, Section 8.1.3; Feasibility Assessment	Added description of plans for monitoring to abstract and revised details to describe the planned analyses in the Monitoring phase to accommodate the active comparator design, assessment of history of SARS-CoV-2 infection and feasibility of proxy for socioeconomic status (SES)	Align with Monitoring Phase and additional requests from CBER
Section 8.2.2; Population Selection Criteria	Revised inclusion criteria for exposed cohort, active comparator cohort and exclusion criteria for active comparator cohort. Revised to not exclude any	Change in study design to active comparator

Section Number and Name	Description of Change	Brief Rationale
	AESIs before reference date in overall cohort, instead exclude from outcome-specific analyses Revised Exclusion criterion 3 (exclude persons aged < 18 years) Deleted Exclusion criterion 4 (to not identify exposed individuals during the time when Ad26.COV2.S was paused in the US)	Age range: timing change in Ad26.COV2.S age indication would not fall in range of data availability for current study Include exposures during pause: calendar time variables in PS model will account for this
Section 8.3.1; Exposure Assessment	Added text about Ad26.COV2.S vaccine booster; primary analyses will include only first dose; booster doses to be described in monitoring analyses	Based on booster availability since last protocol version, CBER request
Section 8.3.1; Exposure Assessment	Describe assessment of mRNA comparator vaccine, only consider first dose of primary series of mRNA vaccines in primary analyses to be comparable with single-dose primary series of Ad26.COV2.S	Change in study design to active comparator
Abstract, Section 8.3.2; Individual Characteristics	Added PS variables: calendar time at reference date as 2-week time indicators history of COVID-19 testing as well as proxy for SES if feasible	Change in study design and allow for controlling for SES
Section 8.3.4.2; Risk Window (Table 1)	Modified disease-specific windows and risk period for some outcomes	Align with FDA BEST protocol and/or Janssen assessments as part of pharmacovigilance activities
Section 8.3.5.2; Cohort Design with Concurrent Active Comparator	Revised criteria for end of follow-up, added text to describe follow-up criteria given 2-dose mRNA series	Change in study design to active comparator
Section 8.4;	Additional description of data sources provided	Updated CVS Health (Aetna) count and description of Humana
Section 8.5; Study Size	Table 2 revised to reflect precision rather than power, sample relative risk estimates decreased because of expected lower relative risks with active comparator than with unexposed comparator	Recommendation from European regulators and because of change to active comparator design
Section 8.7; Data analysis, Table 4	Revised summary of analyses to reflect new design and new secondary and sensitivity analyses	Change in study design to active comparator
Section 8.7.1.2 Cohort Design with Active Comparator	Added Kaplan Meier curves of AESI in risk periods in matched cohorts and added descriptive analysis to describe individuals who develop SARS-CoV-2 after vaccination but prior to outcome	Change in study design to active comparator
Section 8.7.2.1; Propensity Score Matching	Removed PS estimation in sequential time blocks to 1 overall PS model accounting for 2-week periods of time in the models. Added indicators for occurrence of AESI in disease-specific washout periods	Change in study design to active comparator

Section Number and Name	Description of Change	Brief Rationale
Section 8.7.3; Stratified Analyses	Added stratification by prior history of thrombotic events and/or thrombocytopenia, prior history of specific event more than a year before start of follow-up, and prior history of COVID infection	Based on requests from European regulators
Section 8.7.4; Exploratory Analyses	Section deleted	Historical comparators will no longer be used so exploratory analyses are not needed
Section 8.7.5; Sensitivity Analyses	Revised to specify sensitivity analyses based on comparisons of Ad26.COV2.S to receiving only 1 dose of comparator mRNA vaccine, and to receiving both doses of mRNA vaccine;	Change in study design to active comparator
Section 8.7.5.2; Alternate follow-up criteria for comparative analysis based on mRNA dose for non-acute events cohort design	Added Figures 4 and 5	Change in study design to active comparator
Section 8.7.6; Secondary Analysis of Second Doses of Ad26.COV2.5	Section added to address new secondary objective. To describe second doses of Ad26.COV2.S or third doses of mRNA received and to estimate incidence rates of AESI after second dose of Ad26.COV2.S	Second doses approved after Version 1 protocol was written
Section **Error! Reference source not found.**; Interim Analysis	Revised to give purpose of interim analysis	Based on regulatory feedback to produce more timely results and expected timing of data accrual
Section 8.8; Quality Control	Removed Figure (previously Figure 4)	Text describes process sufficiently
Section 8.9; Limitations	Revised based on study design changes. Addition limitation of booster dose due to code availability	Change in study design to active comparator; availability of booster vaccine
Section 9	Updated Protection of Humans section to comply with data partner recommendations	Text was added to clarify that only aggregate-level data would be returned to the coordinating center for analysis

Protocol Revision (Version 1.0): Changes to Original Protocol (Incorporated Into Version 1.0, dated 28 July 2021)

Overall Rationale: The protocol changed the comparator group from an unexposed to an active comparator group to minimize the concerns of misclassification of exposure. Additional endpoints were added following review of the FDA BEST protocols and further changes were made to align the outcome definitions.

Section Number and Name	Description of Change	Brief Rationale
Abstract, Section 7 Research Questions and Objectives	Added the endpoint: the incidence of cardiac inflammatory disorders (including myocarditis and pericarditis) or sensorineural hearing loss within 1-21 days in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with a comparator mRNA COVID-19 vaccine or during a control window within the same individual	Additional events of special interest were added following review of FDA BEST protocols and aligned outcome definitions.
	Updated the endpoint (additions in bold): the incidence of: - **thromboembolic events:** microangiopathy, disseminated intravascular coagulation, deep vein thrombosis, pulmonary embolism, **cerebral vein thrombosis, peripheral thrombosis,** hemorrhagic or non-hemorrhagic stroke, acute myocardial infarction, coronary artery disease (including acute myocardial infarction), **thrombosis with thrombocytopenia within 1-28 days in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with a comparator mRNA COVID-19 vaccine or during a control window within the same individual.**	
	Updated the endpoint (additions in bold and deletions in strike through)): the incidence of encephalitis (including acute demyelinating encephalomyelopathy and meningoencephalitis), Guillain Barré Syndrome, Bell's palsy, immune thrombocytopenia, thrombocytopenia, and transverse myelitis ~~and sensorineural hearing loss~~ within 1-42 days in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with a comparator mRNA COVID-19 vaccine or during a control window within the same individual.	
Abstract: Study Design; Section 8.1.1 Overview of Study Design and Setting	Deleted North America and added United States	Clarified the geography to be specific to the United States given the participating research partners.

Section Number and Name	Description of Change	Brief Rationale
Abstract: Main Statistical Methods	Modified the statement from: Cohort design with concurrent unexposed comparator (primary study design for non-acute events and sensitivity analysis for acute events) and cohort design with historical unexposed comparator (sensitivity analysis for non-acute events) To: Cohort design with concurrent active comparator (primary study design for non-acute events and sensitivity analysis for acute events)	The primary change to the protocol was to change from an unexposed comparator to an active comparator.
Section 5 Milestones	The milestone: End of data extraction is changed to End of data collection	This statement better reflects the nature of secondary data collection.
Section 8.3.4.1 Case Ascertainment and Validation Process	Updated the case ascertainment and validation process for PPV threshold process	Updated to reflect the initial plans for validation of outcomes.
Section 8.3.4.2 Risk Windows	Updated the Table 1 (AESI-Specific Risk Windows and Background Incidence Rates)	This table was modified to align with the modifications of the outcomes.
Section 8.3.4.3 Control Windows (SCRI Design)	Deleted the Section and moved the control period definitions to Section 8.3.5.1 SCRI Design	Modified to improve protocol organization
Section 8.3.5.1 SCRI Design		
Section 8.6 Data Management	Figure 3 (Workflow) was updated and text describing Figure 3 was updated	For better clarity
Section 8.7.1.2 previously Section 8.9.1.1 Cohort Design with Concurrent Active Comparator	Added the statement ' To assess the impact of potential exposure misclassification in the concurrent unexposed comparator cohort design, quantitative bias analysis will be considered.'	The primary change to the protocol was to change from an unexposed comparator to an active comparator.
Section 8.7.2.2 previously Section 8.9.2.2 Demographic and Baseline Characteristics	Added the statement ' The number of patients in the exposed cohort will be reported by number of Ad26.COV2.S doses received (1, 2, 3 or more doses), and among patients receiving 2 or more doses, the amount of time between doses and demographic characteristics will be reported.'	Added to provide additional characterization of exposure
Section 8.9.4 Exploratory Analyses	Updated the exploratory analyses process	Modified given the primary protocol changes to an active comparator
Section 12 References	Added a reference	To support the text in the body of the protocol

4. ABSTRACT

Protocol Title: An Observational Post-Authorization Safety Study to Assess the Safety of Ad26.COV2.S Using Health Insurance Databases in the United States 20 October 2022)

Sponsor's Responsible Epidemiologist: PPD PharmD, MSCE, Associate Director Epidemiology (Main Author)

NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

SARS-CoV-2 has spread rapidly and globally since its emergence, causing coronavirus disease-2019 (COVID-19). The World Health Organization (WHO) declared that the outbreak constituted a public health emergency of international concern on 30 January 2020 and declared the outbreak to be a pandemic on 11 March 2020.

On 27 February 2021, the United States (US) Food and Drug Administration (FDA), on recommendation by the Vaccines and Related Biological Products Advisory Committee (VRBPAC), granted an Emergency Use Authorization (EUA) for the Ad26.COV2.S vaccine for use in individuals 18 years of age and older based on the totality of scientific evidence available demonstrating that the benefits of the vaccine outweigh the risks. On 20 October 2021, the FDA authorized the use of a single booster dose of Janssen COVID-19 Vaccine as a homologous booster at least 2 months after completion of the primary vaccination, and as a heterologous booster following completion of a primary vaccination with another authorized or approved COVID-19 vaccine. On 19 November 2021, the FDA formally amended the EUA for Janssen COVID-19 Vaccine (Ad26.COV2.S) to authorize the vaccine as a single booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine (ie, as a heterologous booster dose) in individuals aged 18 years and older. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was updated to state that data support the effectiveness of a booster dose when administered at an interval of longer than 2 months after primary vaccination with the Janssen COVID-19 Vaccine. On 14 December 2021, based on reports to the Vaccine Adverse Events Reporting System (VAERS), a passive surveillance system, the FDA revised the EUA Fact Sheet based on evidence of an increased risk of thrombosis with thrombocytopenia syndrome (TTS) with onset of symptoms approximately 1 to 2 weeks after administration of the Janssen COVID-19 Vaccine. On 05 May 2022, the FDA further revised the EUA, limiting use of the Ad26.COV2.S vaccine "to individuals 18 years of age and older for whom other authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine" (US FDA 2022).

Through this protocol, the sponsor plans to conduct a large observational, post-authorization safety study (PASS) aiming to characterize the safety profile of Ad26.COV2.S to inform the scientific community on serious adverse events that could be associated with the use of Ad26.COV2.S.

Research Question and Objectives

This study aims to assess the risk of developing prespecified adverse events of special interest (AESIs) following administration of Ad26.COV2.S.

Objectives

- The primary objective for this study is to assess, in adults aged 18 years and older, the potential association between the occurrence of predefined AESIs and vaccination with Ad26.COV2.S within disease-specific risk periods in individuals exposed to the first dose of Ad26.COV2.S vaccine, as compared with either 1) individuals exposed to at least the first dose of BNT162b2 vaccine for non-acute events or 2) for acute events during a control window within the same individual.

Endpoints

The primary analysis endpoints for this study are to estimate:

- the incidence of anaphylaxis **within 0-2 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual.
- the incidence of generalized convulsion, arrhythmia, acute kidney failure or acute hepatic failure **within 1-14 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual.
- the incidence of cardiac inflammatory disorders (including myocarditis and pericarditis) or sensorineural hearing loss **within 1-21 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual.
- the incidence of:
  - thromboembolic events: microangiopathy, disseminated intravascular coagulation, deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, peripheral thrombosis, hemorrhagic or non-hemorrhagic stroke, acute myocardial infarction, coronary artery disease (including acute myocardial infarction), thrombosis with thrombocytopenia **within 1-28 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual
  - heart failure, or stress cardiomyopathy **within 1-28 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual
  - composite endpoints **within 1-28 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual
    - venous thrombosis, including pulmonary embolism and deep vein thrombosis
    - arterial thrombosis, including coronary artery disease and non-hemorrhagic stroke
    - stroke, including non-hemorrhagic and hemorrhagic strokes
- the incidence of encephalitis (including acute demyelinating encephalomyelopathy and meningoencephalitis), Guillain Barré Syndrome, Bell's palsy, immune thrombocytopenia, thrombocytopenia, and transverse myelitis **within 1-42 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual.
- the incidence of autoimmune thyroiditis, acute aseptic arthritis, multiple sclerosis (including optic neuritis), and Type 1 diabetes mellitus **within 1-365 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine.

Secondary Objective

- The secondary objective for this study is to describe the number of individuals who received a second dose of Ad26.COV2.S as well as their baseline demographics.

Study Design

This is a retrospective observational study using health insurance claims databases in the US. Eligible individuals will be included in the study from the time of EUA of Ad26.COV2.S in the US, and the study will end at the last date of data availability in each of the databases.

The study design will depend on whether the AESI is an acute or non-acute event. The primary study design for acute events (events expected to occur within 60 days of vaccination) will be a self-controlled risk interval design (SCRI) conducted in the Ad26.COV2.S exposed cohort. For non-acute events, a cohort design will be used to compare individuals exposed to Ad26.COV2.S with concurrent active comparators (individuals exposed to at least 1 dose of BNT162b2 [Pfizer-BioNTech COVID-19 vaccine]). The cohort design with a concurrent active comparator will also be used to assess acute events in sensitivity analyses.

Self-controlled risk interval design (primary study design for acute events)

The SCRI design will compare the risk of the AESIs in a postvaccination risk window to a postvaccination control window within the same individual, in a cohort of individuals vaccinated with Ad26.COV2.S.

Individuals will be followed from the start of the risk window to the end of the control window.

Cohort design with concurrent active comparator (primary study design for non-acute events and sensitivity analysis for acute events)

For the cohort design with a concurrent active comparator, the incidence of AESIs will be compared between 2 vaccine cohorts that will be defined based on their exposure to Ad26.COV2.S or BNT162b2:

- **Exposed cohort**: individuals will have received at least 1 dose of Ad26.COV2.S administered according to US recommendations (Biologic License Application [BLA] approval or EUA). The reference date for the exposed cohort will be the first date of receipt of the vaccine.
- **Active comparator cohort**: individuals will have been vaccinated with BNT162b2 at any time on or after the start of the study observation period. The reference date of the comparator cohort will be the calendar date of the first dose in the primary series of BNT162b2. Individuals will be matched by propensity scores (PS) and calendar time (within 2 weeks) at the reference date using a 1:4 ratio of exposed to comparator within the Data Partner distributed database, if feasible; the matching ratio will be dependent on the findings of the relative uptake of vaccinations identified during feasibility assessments and monitoring.

COVID-19 vaccines were first administered to priority populations at high risk of severe disease or exposure, including older adults or those with comorbidities. Therefore, information on the presence of comorbidities within 1 year prior to the reference date and older age will be collected and included in the PS models. Additional covariates to be included are listed under Variables.

Cohorts will be defined utilizing existing secondary healthcare data sources. One year of medical and pharmacy insurance enrollment prior to the reference date will be required to determine whether individuals meet the study criteria and to define baseline characteristics. Data on the occurrence of an AESI will be extracted within the 1 year after the reference date.

Follow-up will begin on or the day after the reference date; follow-up time will end at the earliest of the following: date of first diagnosis of AESI, death, disenrollment from the health plan, administrative end of the study (eg, end of available data), end of duration of the risk period specific to the AESI (up to 1 year after the reference date), date of any COVID-19 vaccine that is not the index vaccine, or date of receipt of

an additional or booster dose beyond the authorized primary series (ie, a second dose of COVID-19 in the Ad26.COV2.S cohort or a third dose of COVID-19 vaccine in the BNT162b2 cohort).

Feasibility assessment (monitoring phase)

At study initiation, counts of Ad26.COV2.S vaccine exposures and any mRNA vaccine exposures, including primary vaccination series, baseline characteristics, and the number of AESIs, will be monitored from each database to confirm the feasibility of implementing the planned final analysis in the available data sources for specific AESIs. The crude incidence rate for each AESI in the risk intervals following vaccination for first-dose Ad26.COV2.S vaccinees and first dose of any mRNA vaccinees will be calculated for each individual AESI after excluding individuals with prior evidence of that AESI before cohort entry in specified time windows.

The observation period for the monitoring analysis will start on the launch date of Ad26.COV2.S in the US (27 February 2021).

Setting and Study Population

For the SCRI design, eligibility criteria will be applied separately for analysis of each AESI. Individuals over the age of 18 years at the reference date will be included if they have received a first dose of Ad26.COV2.S vaccine during the study period, experienced the AESI during the risk or control period, and have at least 1 year of continuous medical and prescription drug coverage prior to the date of vaccination until the end of the AESI-specific control interval.

For the active comparator cohort design, individuals over the age of 18 years at the reference date who have at least 1 year of continuous medical and prescription drug coverage for at least 1 year prior to the reference date, and who have not been found to be vaccinated with any COVID-19 vaccine prior to the reference date will be eligible for the overall study cohorts. Each AESI will be analyzed separately. For the analysis of each AESI, individuals with AESI-specific exclusion criteria will be excluded, and analyses will be done in the AESI-specific subcohort.

Variables

Exposure to the Ad26.COV2.S vaccine or BNT162b2 vaccine will be identified using recorded procedure or pharmacy dispensing codes for COVID-19 vaccines (eg, National Drug Code, Current Procedural Terminology, Healthcare Procedure Coding System codes). Where existing linkages with vaccination registries are available within the appropriate Data Partner research databases, the vaccine registry data also will be used to assess exposure.

Population characteristics will be identified based on medical, pharmacy and procedure codes, and insurance enrollment information. The following variables will be used to characterize the study population and will be included in PS models for the cohort design:

- Demographic characteristics (at reference date) such as age, sex, race/ethnicity (if feasible, as determined during the monitoring phase of the study), and a proxy for socioeconomic status (SES), if feasible, calculated using geographic information at least as granular as a patient's 5-digit ZIP code, and geographic location (eg, state or census region)
- Pregnancy status (at reference date)
- Frailty
- 1-year medical history (at reference date)
  - Comorbidities such as cancer, chronic kidney disease, heart conditions, COPD, asthma, sickle cell disease, immunocompromised states, obesity, Down syndrome, and Type 2 diabetes

- Healthcare utilization (eg, mean number of emergency department visits, inpatient visits)
- Medication use (eg, drug class utilization)
- Previous history of COVID-19 (evidence of either of the following):
    - Diagnosis codes for COVID-19 (yes/no)
    - SARS-CoV-2 positive laboratory result from NAAT, antigen or serology tests if available (evidence of a positive test, yes/no)

- Vaccinations:
    - Administration of other COVID-19 vaccine doses from the reference date of the exposed and active comparator cohorts until the end of the follow-up period (to be used to describe primary series completion or receipt of booster doses, and as censoring criteria; not to be included in propensity score models)
    - Administration of certain vaccines, such as influenza vaccine, any pneumococcal vaccine, any shingles vaccine, or any human papillomavirus (HPV) vaccine from 1 year prior to the reference date
    - Other vaccinations received concurrently with the Ad26.COV2.S vaccine or BNT162b2 vaccine

Evaluation of Safety Outcomes

Within Janssen, a list of AESIs has been created based on current knowledge of the Ad26.COV2.S vaccine and potential risks related to adeno platform vaccine. AESIs will be identified, with a date of diagnosis, using predefined validated algorithms (as possible), based on diagnosis codes (with procedure and/or pharmacy dispensing codes and/or limited to specific medical care settings if applicable to the outcome). Data will be collected on the following AESIs using claims algorithms within disease-specific risk interval periods following the administration of Ad26.COV2.S or BNT162b2:

- Nervous system: encephalitis (including acute demyelinating encephalomyelopathy and meningoencephalitis), Guillain-Barré Syndrome, transverse myelitis, Bell's palsy, Multiple sclerosis, (including optic neuritis), sensorineural hearing loss, generalized convulsion (with and without epilepsy)
- Immune system: autoimmune thyroiditis, immune thrombocytopenia, thrombocytopenia, Type 1 diabetes mellitus, acute aseptic arthritis, anaphylaxis
- Cardiac system: cardiac inflammatory disorders (including myocarditis and pericarditis), microangiopathy, heart failure, stress cardiomyopathy, acute myocardial infarction, coronary artery disease (including acute myocardial infarction), arrhythmia
- Blood and lymphatic system: deep vein thrombosis (DVT), pulmonary embolism (PE), disseminated intravascular coagulation, non-hemorrhagic stroke, hemorrhagic stroke, composite outcome of venous thrombosis (including PE and DVT), composite outcome of arterial thrombosis (including coronary artery disease and non-hemorrhagic stroke), composite outcome of stroke (including non-hemorrhagic and hemorrhagic strokes), cerebral venous thrombosis, peripheral thrombosis, thrombosis with thrombocytopenia
- Renal system: acute kidney failure
- Hepatic system: acute hepatic failure

Case validation to confirm the algorithm and/or disease diagnosis and date of onset may be conducted on AESIs that are judged likely to be misclassified based on clinical expert opinion, prior validation studies (if available), and researchers familiar with the data sources, including the Data Partners. Review of medical records or chronological listing of diagnosis, procedure, and pharmacy dispensing codes in health insurance

claims profiles by clinicians may be conducted, depending on the AESI. For outcomes selected for validation, a strategy for sampling events for validation will consider the rarity of the event.

For the SCRI design, control periods will be the same length as the risk period and the exact timing that control periods will begin will be defined in the statistical analysis plan (SAP). A buffer period may be included between the risk and control periods when the risk period is uncertain. For the cohort design, follow-up will depend on the length of the outcome-specific risk windows.

Data Sources

This study will be conducted using health plan data held by Data Partners that participate in the FDA's Sentinel System, including CVS Health (Aetna), HealthCore (Anthem), Humana, and Optum. These Data Partners update their quality-checked data 3 to 4 times per year; some are updating more frequently with fresher data (ie, shortened data lags) to support FDA-initiated COVID-19 analyses. The study will use the most up-to-date standardized and curated data source available within each Data Partner.

All study data will be accessed with procedures compliant with US subject confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Where appropriate, as required by local regulations, this study will be undertaken only after the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) has given full approval of the final protocol, any applicable amendments, and the sponsor has received a copy of this approval.

Study Size

Subject to the feasibility assessment, a minimum target sample size of 100,000 individuals in the exposed cohort and 400,000 individuals in the active comparator concurrent cohorts will be included in the comparative cohort study.

Main Statistical Methods

Self-controlled risk interval design (primary study design for acute events)

For the SCRI design in the Ad26.COV2.S exposed cohort, incidence rates of each AESI during the risk period will be compared with the incidence rates in exposed cohort during the control period using a conditional Poisson regression model to estimate incidence rate ratios and 95% confidence intervals (CIs).

Cohort design with concurrent active comparator (primary study design for non-acute events and sensitivity analysis for acute events)

For comparisons of Ad26.COV2.S vaccinees versus BNT162b2 vaccinees, matching on PS and calendar time (within 2 weeks) will be implemented to ensure comparability between the 2 exposure groups on observed covariates. The PS is the predicted probability of an individual being classified in the Ad26.COV2.S exposed cohort versus the comparator BNT162b2 cohort, given a set of observed covariates.

The baseline covariates used to fit the PS model will be those described under Variables.

The propensity to be vaccinated with Ad26.COV2.S will be estimated using logistic regression with vaccination received as the dependent variable and all baseline covariates as independent variables. Individuals receiving BNT162b2 will be matched on PSs to individuals receiving Ad26.COV2.S.

All analyses will be summarized by cohort and by data sources. Demographic and baseline characteristics of the individuals at the reference date will be described in the matched analytic cohort. For continuous/ordinal variables the number of observations, mean, standard deviation, minimum, and maximum will be described. For categorical variables, the number and percent per category will be summarized. Balance of characteristics between the exposure groups will be evaluated with absolute standardized differences.

For the cohort design, incidence rates for each AESI will be calculated by dividing the number of events by the follow-up person-time in propensity score-matched exposure cohorts, and cumulative incidence curves will be estimated by exposure group. Incidence rate ratios and 95% CIs will be estimated with Poisson regression models or another appropriate method to be specified in the SAP. The risk difference will be computed as the difference between the incidence rate in the Ad26.COV2.S-exposed cohort and the incidence rate in the active comparator, BNT162b2 exposed, cohort. Incidence rate ratios will be pooled across data sources using a random-effects model or another appropriate method to be specified in the SAP.

Sensitivity analyses

For events with uncertain risk windows, SCRI analyses with extended risk periods will be considered as sensitivity analyses.

Secondary analyses

To address the secondary objective, the number of individuals in the exposed cohort will be reported by the number of Ad26.COV2.S doses received. Among individuals receiving 2 doses of Ad26.COV2.S, the amount of time between doses and the demographic characteristics for those individuals will be reported.

5. MILESTONES

The initial planned dates for key milestones in this study are outlined below.

Milestone:	Planned Date:
Start of data collection[a]	Q1 2022
Monitoring report	Q3 2022
Data extraction (querying) for final study report[b]	Q2-Q3 2023
End of data collection[c]	Q1 2025
Final report to FDA	Q3 2025

[a] Start of data collection is the planned date for starting data extraction for the monitoring phase.
[b] Data sources have a 6-12 month lag for data incorporation; thus, data extraction (querying) Q2-Q3 2023 will include data through ~ Q2-Q3 2022.
[c] End of data collection is the planned date that the analytical dataset (the minimum set of data required to perform the statistical analyses for the primary objective) is completely available. This includes time to conduct analyses following chart validation.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADEM	Acute disseminated encephalomyelitis
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
BLA	Biologic License Application
CDC	Center for Disease Control
CHI	Comprehensive Health Insights
CI	Confidence interval
CMA	Conditional marketing authorization
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
DRB	Designated Regulatory Body
EDMS	electronic document management system
EEA	European Economic Area
EMA	European Medicines Agency
EUA	emergency use authorization
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act
HIPAA	Health Insurance Portability and Accountability Act
HPHCI	Harvard Pilgrim Health Care Institute
HPV	Human papilloma virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
mRNA	Messenger ribonucleic acid
MedDRA	Medical Dictionary for Regulatory Activities
NAAT	Nucleic acid amplification test
NIST	National Institute of Standards and Technology
NNH	Number needed to harm
PASS	Post-authorization safety study
PPV	Positive predictive value
PRISM	Post-licensure rapid immunization safety monitoring
PRO	patient-reported outcome(s)
QA	Quality assurance
RNA	Ribonucleic acid
S	spike protein
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus(-2)
SAS	Statistical Analysis System
SCDM	Sentinel Common Data Model
SCRI	Self-Controlled Risk Interval
SES	socioeconomic status
SPEAC	Safety Platform for Emergency vACcines
UK	United Kingdom
US	United States
VRBPAC	Vaccines and Related Biologics Products Advisory Committee
WHO	World health organization

Definition of Term(s)

Acute event	event expected to occur within 60 days of vaccination
Non-acute event	events expected to occur > 60 days after vaccination
Registry	An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves 1 or more predetermined scientific, clinical, or policy purposes
Study	The term “study” indicates the collection of data for research purposes only. The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed.
Retrospective observational study	A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information from the individual, although this may be required to address specific questions. Studies/Programs/Related Research Activities with only 1 visit can be considered prospective or retrospective bearing in mind this definition and the source of information
Post-Authorization Safety Study (PASS)	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures
Washout period	The disease-specific period of time required prior to COVID-19 vaccination will be defined to more plausibly identify incident cases
Buffer period	The period of time required between risk and control periods to minimize the residual risk attributable to the vaccine
Algorithm	A procedure for solving a mathematical problem (finding the greatest common divisor) in a finite number of steps that frequently involves repetition of an operation. A medical algorithm includes decision tree approaches to healthcare treatment, medical diagnosis, or medical prescription
Primary series	A complete initial COVID-19 vaccination defined as 2 mRNA vaccine doses or at least 1 dose of Ad26.COV2.S vaccine within labeling guidelines

6. BACKGROUND AND RATIONALE

6.1. Background

SARS-CoV-2 Virology and COVID-19 Disease Burden

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) Beta coronavirus (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020, Wu 2020). It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019 (Li Q 2020). Early epidemiological investigations suggested that the majority of early cases were linked to a food market, with patients infected through zoonotic or environmental exposure, followed by the subsequent spread of infection by human-to-human transmission among close contacts (Li Q 2020). However, there is some controversy about the initial origin of the virus (Cyranoski 2020). Genomic sequencing was performed on bronchoalveolar lavage fluid samples collected from patients with viral pneumonia admitted to hospitals in Wuhan, which identified a novel RNA virus from the family Coronaviridae (Lu 2020, Wu 2020). Phylogenetic analysis of the complete viral genome revealed that the virus, SARS-CoV-2, is part of the subgenus Sarbecovirus of the genus Betacoronavirus, and is most closely related (approximately 88% identity) to a group of severe acute respiratory syndrome (SARS)-like coronaviruses previously sampled from bats in China (Lu 2020).

As of 21 December 2021, 275,614,347 cases and 5,364,386 deaths from COVID-19 have been reported worldwide. In the US, approximately 51,102,357 cases and 807,974 deaths have been reported (Johns Hopkins CSSE 2021).

Ad26.COV2.S Vaccine

Ad26.COV2.S (also known as Ad26COVS1, VAC31518, JNJ-78436735) is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 (Ad26) vector, constructed to encode the SARS-CoV-2 Spike (S) protein, stabilized in its prefusion conformation.

The S protein is the major surface protein of coronaviruses. Different animal models have been used for the evaluation of candidate vaccines against SARS-CoV, and the common conclusion that has emerged is that the viral S protein is the only significant target for neutralizing antibodies (Buchholz 2004, Sui 2005, Zhang 2004, Zhou 2004) and the only viral protein that can elicit protective immunity in animal models (Berry 2004, Bisht 2004, Bukreyev 2004, Subbarao 2004, Yang 2004).

Ad26.COV2.S encodes a membrane-bound full-length S protein derived from a SARS-CoV-2 clinical isolate (Wuhan, 2019, whole genome sequence NC_045512), with 2 amino acid changes in the S1/S2 junction that knock out the furin cleavage site, and 2 proline substitutions in the hinge region.

Safety concerns have been identified from post-authorization safety surveillance data in Vaccine Adverse Events Reporting System (VAERS), which include thrombosis with thrombocytopenia syndrome (TTS) and Guillain-Barré syndrome and have been added to the Fact Sheets. Potential

emerging safety concerns currently under evaluation include thromboembolic events (TEEs), myocarditis and pericarditis, and immune thrombocytopenia (ITP). (FDA Briefing Document 2021)

6.2. Overall Rationale for the Study

On 27 February 2021, the United States (US) Food and Drug Administration (FDA)on recommendation by the Vaccines and Related Biological Products Advisory Committee (VRBPAC), granted Emergency Use Authorization (EUA) for the Ad26.COV2.S vaccine for use in individuals 18 years of age and older based on the totality of scientific evidence available demonstrating that the benefits of the vaccine outweigh the risks (US FDA 2021). On 20 October 2021, the FDA authorized the use of a single booster dose of Janssen COVID-19 Vaccine as a homologous booster at least 2 months after completion of the primary vaccination, and as a heterologous booster following completion of a primary vaccination with another authorized or approved COVID-19 vaccine. On 19 November 2021, the FDA formally amended the EUA for Janssen COVID-19 Vaccine to authorize the vaccine as a single booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine (ie, as a heterologous booster dose) in individuals aged 18 years of age and older. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was updated to state that data support the effectiveness of a booster dose when administered at an interval of longer than 2 months after primary vaccination with the Janssen COVID-19 Vaccine. (US FDA 2021) On 14 December 2021 based on reports to the Vaccine Adverse Events Reporting System (VAERS), a passive surveillance system, the FDA revised the EUA Fact Sheet based on evidence for an increased risk of TTS with onset of symptoms approximately 1 to 2 weeks after administration of the Janssen COVID-19 Vaccine. On 05 May 2022, the FDA further revised the EUA, limiting use of the Ad26.COV2.S vaccine "to individuals 18 years of age and older for whom other authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine" (US FDA 2022).

On 11 March 2021, The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended conditional marketing authorization for the Ad26.COV2.S vaccine. On 22 April 2021, a new warning on thrombocytopenia and coagulation disorder was added and the adverse drug reaction (ADR) thrombosis in combination with thrombocytopenia was added. On 9 July 2021, a contraindication was added for individuals with a history of Capillary Leak Syndrome (CLS). On 23 July 2021, Guillain-Barré Syndrome was added as an ADR with frequency of rare. On 3 September 2021, diarrhoea and paraesthesia as ADRs with uncommon frequency and hypoesthesia, lymphadenopathy, vomiting, and tinnitus as ADRs with rare frequency. On 1 October 2021, the EMA requested to add a new warning on immune thrombocytopenia (ITP), and to add dizziness and ITP to the list of ADR with frequencies of uncommon and not known, respectively. On 11 October 2021, the EMA revised the labeling to include venous thromboembolism as an ADR. On 16 December 2021, the EMA authorized a booster dose (second dose) of 0.5 mL of COVID-19 Vaccine, which may be administered

intramuscularly at least 2 months after the primary vaccination in individuals aged 18 years and older. Additionally, a booster dose of the COVID-19 Vaccine Janssen (0.5 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another approved COVID-19 vaccine in the EU.

This protocol outlines a Post-Authorization Safety Study (PASS) as a retrospective, observational, propensity-scored matched cohort study utilizing health insurance claims and electronic health records to assess the risk of prespecified adverse events of special interest (AESIs) following vaccination with Ad26.COV2.S.

7. RESEARCH QUESTION AND OBJECTIVES

This study aims to assess the risk of developing prespecified AESIs following administration of Ad26.COV2.S.

Objectives

- The primary objective for this study is to assess, in adults aged 18 years and older, the potential association between the occurrence of predefined AESIs and vaccination with Ad26.COV2.S within disease-specific risk periods in individuals exposed to the first dose of Ad26.COV2.S vaccine, as compared with either 1) individuals exposed to the first dose of BNT162b2 vaccine for non-acute events or 2) for acute events during a control window within the same individual.

Endpoints

The primary analysis endpoints for this study are to estimate:

- the incidence of anaphylaxis **within 0-2 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine, or during a control window within the same individual
- the incidence of generalized convulsion, arrhythmia, acute kidney failure or acute hepatic failure **within 1-14 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine, or during a control window within the same individual
- the incidence of cardiac inflammatory disorders (including myocarditis and pericarditis) or sensorineural hearing loss **within 1-21 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual
- the incidence of
  - thromboembolic events: microangiopathy, disseminated intravascular coagulation, deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral vein thrombosis, peripheral thrombosis, hemorrhagic and non-hemorrhagic strokes, acute myocardial infarction, coronary artery disease (including acute myocardial infarction), thrombosis with thrombocytopenia **within 1-28 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual

  - heart failure, and stress cardiomyopathy **within 1-28 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual
  - composite endpoints **within 1-28 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine or during a control window within the same individual
    - venous thrombosis, including PE and DVT
    - arterial thrombosis, including coronary artery disease and non-hemorrhagic stroke
    - stroke, including non-hemorrhagic and hemorrhagic strokes
- the incidence of encephalitis (including acute demyelinating encephalomyelopathy and meningoencephalitis), Guillain Barré Syndrome, Bell's palsy, immune thrombocytopenia, thrombocytopenia, and transverse myelitis **within 1-42 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine, or during a control window within the same individual.
- the incidence of autoimmune thyroiditis, acute aseptic arthritis, multiple sclerosis (including optic neuritis), and Type 1 diabetes mellitus **within 1-365 days** in individuals vaccinated with the Ad26.COV2.S vaccine and in corresponding individuals vaccinated with the BNT162b2 vaccine.

Secondary Objective

- The secondary objective for this study is to describe the number of individuals who received a second dose of Ad26.COV2.S as well as their baseline demographic characteristics.

8. RESEARCH METHODS

8.1. Study Design

8.1.1. Overview of Study Design and Setting

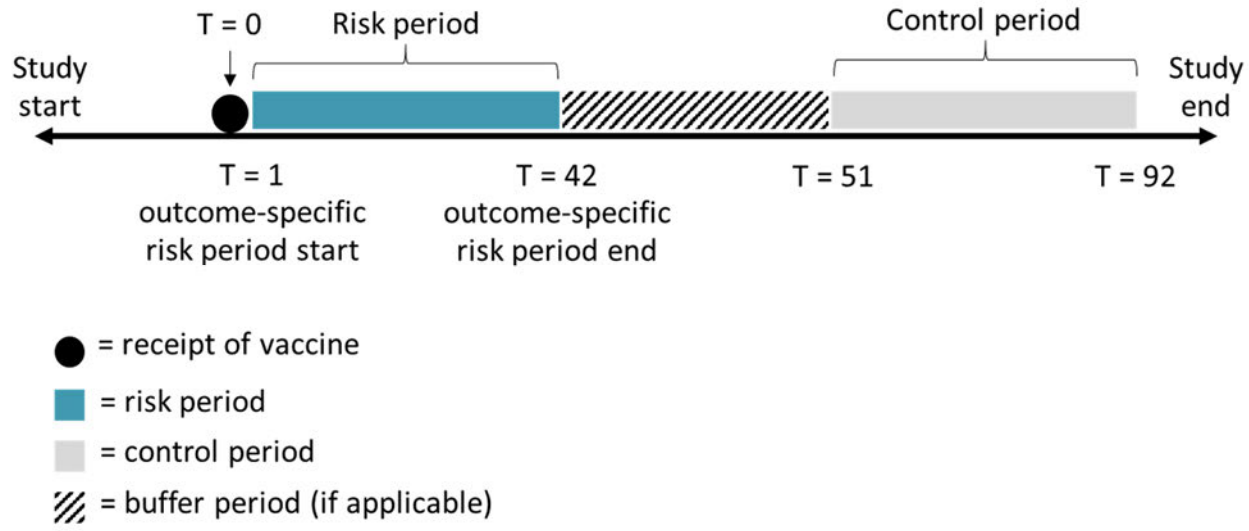
This is a retrospective observational study using health insurance claims databases in the US. Eligible individuals will be included in the study from the time of EUA of the Ad26.COV2.S vaccine in the US, and the study will end at the last date of data availability in each database.

The study design will depend on whether the AESI is an acute or non-acute event. The primary study design for acute events (events expected to occur within 60 days of vaccination) will be a self-controlled risk interval (SCRI) design conducted in the Ad26.COV2.S exposed cohort. For non-acute events, a cohort design will be used comparing individuals exposed to Ad26.COV2.S with concurrent active comparators (individuals exposed to at least the first dose of the primary series of BNT162b2 [Pfizer-BioNTech COVID-19 vaccine]). In sensitivity analyses, a cohort design with a concurrent active comparator will be used to assess acute events.

8.1.1.1. Self-controlled Risk Interval Design (Primary Study Design for Acute Events)

The SCRI design will compare the risk of the AESIs in a postvaccination risk window to a postvaccination control window within the same individual, in a cohort of individuals vaccinated with Ad26.COV2.S (Figure 1). The use of a postvaccination control window (rather than a prevaccination control window) avoids bias due to healthy user vaccinee effect. To account for the possibility that increased risks of AESIs might extend beyond the risk interval, the risk and control windows may be separated by buffer periods for events that do not have well established risk intervals in the literature (to be defined in the statistical analysis plan [SAP]).

Figure 1: Self-Controlled Risk Interval Design



8.1.1.2. Cohort Design With Concurrent Active Comparator (Primary Study Design for Non-acute Events and Sensitivity Analysis for Acute Events)

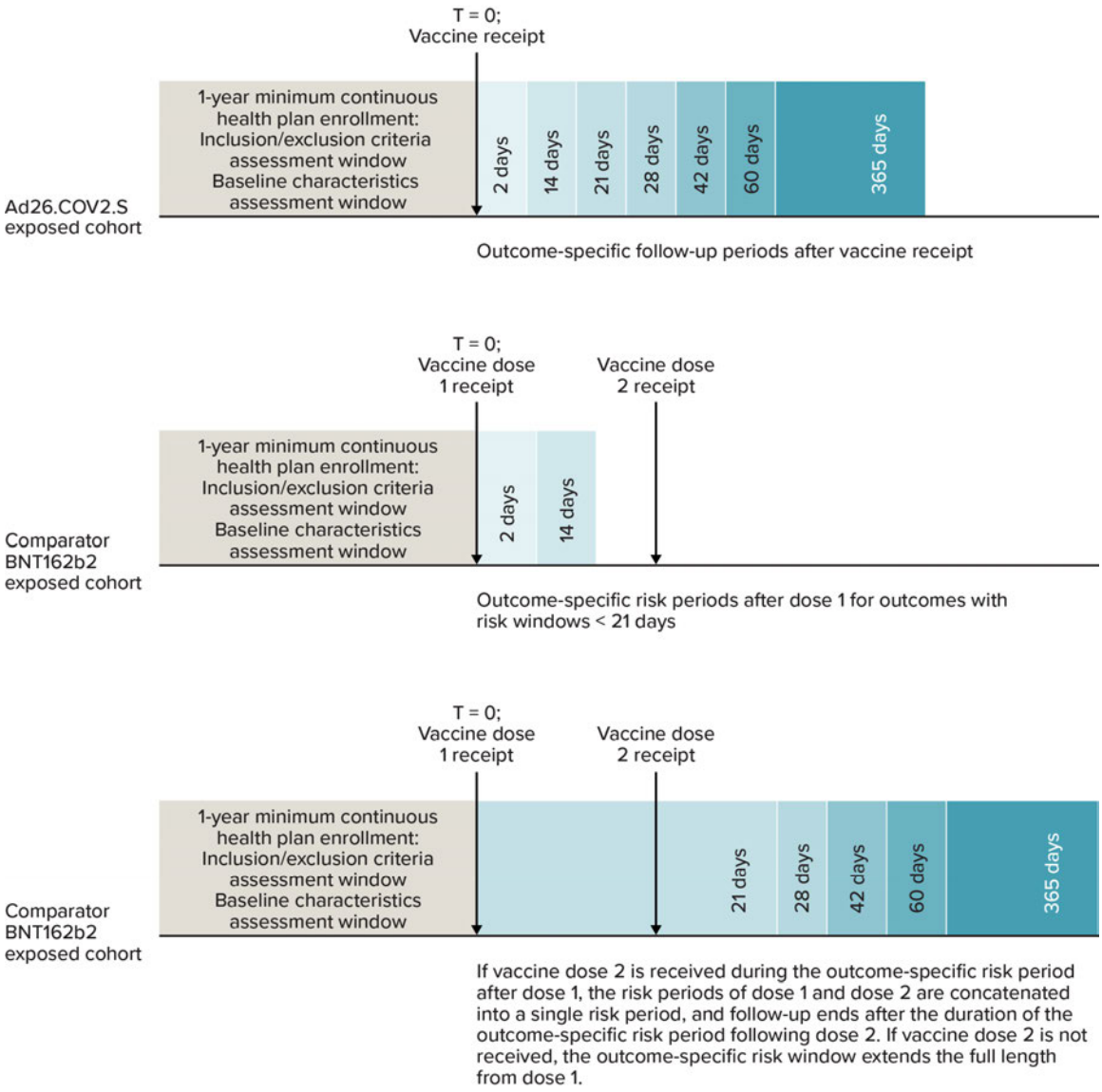
For the cohort design, the incidence of AESIs will be compared between the 1-dose Ad26.COV2.S exposed cohort and the 2-dose BNT162b2 comparator cohort (Figure 2):

- **Exposed cohort**: individuals will have received at least 1 dose of Ad26.COV2.S administered according to US recommendations (BLA approval or EUA). The reference date will be the first date of receipt of Ad26.COV2.S.
- **Active comparator cohort:** individuals will have been vaccinated with at least 1 dose of the primary series of BNT162b2 at any time on or after the start of the study observation period. The reference date of the comparator cohort will be the calendar date of the first dose in the primary series of BNT162b2. Individuals will be matched by propensity scores (PS) and calendar time (within 2 weeks) at the reference date using a 1:4 ratio of exposed to comparator within the Data Partner distributed database, if feasible; the matching ratio will be dependent on the findings of the relative uptake of vaccinations identified during feasibility assessments and monitoring.

COVID-19 vaccines were first administered to priority populations at high risk of severe disease or exposure, including older adults or those with comorbidities. Therefore, information on the presence of comorbidities within 1 year prior to the reference date and older age will be collected and included in the PS models. The covariates for the propensity score models, to be assessed up to the reference date, are described in Section 8.7.2.1.

Cohorts will be defined utilizing existing secondary healthcare data sources. One year of medical and pharmacy insurance enrollment prior to the reference date will be required to determine whether individuals meet the study criteria and to define baseline characteristics. Data on the occurrence of AESI will be extracted within the 1 year after the reference date.

Figure 2: Cohort Study Design



Outcome-specific risk windows:

- 2 days: anaphylaxis.
- 14 days: generalized convulsion, arrhythmia, acute kidney failure, acute hepatic failure.
- 21 days: cardiac inflammatory disorders, including myocarditis and pericarditis, and sensorineural hearing loss.

- 28 days: microangiopathy, disseminated intravascular coagulation, DVT, pulmonary embolism, hemorrhagic and non-hemorrhagic stroke, acute myocardial infarction, coronary artery disease (including acute myocardial infarction), heart failure, stress cardiomyopathy, venous thrombosis composite endpoint, arterial thrombosis composite endpoint, stroke composite endpoint.
- 42 days: encephalitis (including acute demyelinating encephalomyopathy and meningoencephalitis), Guillain Barré Syndrome, Bell's palsy, immune thrombocytopenia, thrombocytopenia, transverse myelitis.
- 365 days: autoimmune thyroiditis, acute aseptic arthritis, multiple sclerosis (including optic neuritis), Type 1 diabetes mellitus.

Note that follow-up time for the primary analysis will end upon receipt of a booster dose of Ad26.COV2.S or a booster dose of any COVID-19 vaccine.

8.1.2. Rationale for Study Design

The AESIs included in this study are considered as potential safety risks following administration of Ad26.COV2.S. The selected AESIs represent a heterogeneous group including multiple organ systems, and acute and chronic conditions (Section 8.3.4).

The SCRI design has been selected as the primary design for acute events (ie, AESIs expected to occur within a disease risk period of 60 days) because it only includes vaccinated individuals, which avoids misclassification of unexposed status due to incomplete capture of vaccinations in health insurance claims databases. Because it uses each individual as its own control, the SCRI design avoids potential confounding by factors that do not vary with time. To account for the possibility that increased risks of AESIs might extend beyond the risk interval, the risk and control periods may be separated by buffer periods for events that do not have well established risk intervals in the literature (to be defined in the SAP). Although most AESIs are age-dependent, an age bias is not anticipated because the follow-up period is short compared with the age effect on the incidence of AESIs. However, because the SCRI design generally has less statistical power and for some AESIs, may be subject to confounding by other time-invariant confounders such as seasonality (a proxy for respiratory infections), a cohort design with an active comparator (BNT162b2 exposed) will be used in sensitivity analyses of acute events.

Because the SCRI design is not appropriate for non-acute events, the cohort design with an active comparator (BNT162b2 exposed) will be used to assess these types of events (ie, AESIs expected to occur within a disease risk period of more than 60 days; see Table 1). BNT162b2 has been selected as the active comparator because it is the most commonly used COVID-19 vaccine in the US, and as such should be representative of COVID-19 vaccinees and provide sufficient numbers for all comparisons.

Disease-specific risk periods have been defined for all AESIs, regardless of acute or non-acute; however, these risk periods are based on currently available evidence (eg, from experience with other marketed vaccines or knowledge of COVID-19) and may not be strictly applicable to the Ad26.COV2.S vaccine (Table 1). For this reason, alternative risk periods will be considered in sensitivity analyses for outcomes that do not have a well-defined risk periods (to be defined in the SAP).

8.1.3. Feasibility Assessment (Monitoring Phase)

A feasibility assessment, including monitoring of vaccine uptake, will be conducted for each participating data source to confirm the feasibility of implementing the planned final analysis in the available data sources. The monitoring phase will start after the launch date of Ad26.COV2.S in the US (27 February 2021). Participating data sources will be consulted on a regular basis (depending on data update schedules) from Ad26.COV2.S vaccination launch and over a period of at least 18 months.

The monitoring phase will include the following objectives:

- To assess vaccine utilization among the Ad26.COV2.S and mRNA COVID-19 vaccine–exposed populations across different geographical areas and to identify confounding factors that will be used as PS modeling covariates in the cohort design. Potential confounding factors to be described in monitoring analyses (where available) are age, overall healthcare utilization, preventive healthcare utilization, medication utilization, race/ethnicity, and presence of comorbidities.
- To survey the Data Partners to assess possible linkage to vaccine registries in different US states and assess, if possible, based on ongoing linkage activities between Departments of Public Health and Data Partners, potential under-reporting of exposure.
- To monitor the number of AESIs in individuals exposed to Ad26.COV2.S and mRNA COVID-19 vaccines in the available data resources.

8.2. Setting and Study Population

8.2.1. Study Setting

This study will be conducted using health plan claims data held by 4 large national insurers that participate in the FDA's Sentinel System, including CVS Health (Aetna), HealthCore (Anthem), Humana, and Optum. Further information on the data sources used in this study can be found in Section 8.4. The study period will begin on 27 February 2021, the day Ad26.COV2.S was authorized for emergency use in the US, although data from before 27 February 2021 will be used to define patient characteristics and vaccine history.

8.2.2. Population Selection Criteria

8.2.2.1. Inclusion/Exclusion Criteria for the Self-Controlled Risk Interval Design

For analyses of acute outcomes, individuals will be included in SCRI analyses if the following criteria are met. Note that the eligibility criteria will be applied separately for analysis of each AESI (Additional details regarding requirements for follow-up during the risk and control windows will be defined in the SAP):

- Received a dose of Ad26.COV2.S vaccine during the study period as their first dose of any COVID-19 vaccine
- Experienced the AESI during a risk period (as defined in Table 1) or control period (to be defined in the SAP)

- Did not experience the specific AESI during the pre-event washout period (as defined in Table 1)
- Have at least 1 year of continuous health plan enrollment with medical and prescription drug coverage prior to the reference date and an earliest coverage date on or before 11 December 2020 (to maximize the ability to identify the first COVID-19 vaccine administered during the study period)
- Aged 18 years or older at the reference date

8.2.2.2. Criteria for Exposed and Active Comparator Cohorts

The inclusion and exclusion criteria for each cohort are listed in the subsections below. For both the exposed (Ad26.COV.2.S) and comparator (BNT162b2) cohorts, individuals will be identified at their first observed COVID-19 vaccine dose during the study period, with the date of the dose being the reference date.

While at least 1 year of enrollment in the data plan before the reference date will be required for individuals to be included in the study, if greater than 1 year of baseline data are available for individuals, all available baseline data will be used to define outcome-specific washout periods for some chronic conditions, such as Type 1 diabetes.

8.2.2.2.1. Inclusion Criteria for Ad26.COV2.S Exposed Cohort

To enter the exposed cohort individuals must satisfy ALL of the following criteria at the reference date:

1. Have at least 1 year of continuous health plan enrollment with medical and prescription drug coverage prior to the reference date with a required length of the longer of the following periods:
   a. At least 1 year before the reference date
   b. An earliest coverage date on or before 11 December 2020 (to maximize ability to identify the first COVID-19 vaccine administered during the study period)
2. Receive 1 dose of Ad26.COV2.S on the reference date

The reference date for this cohort will be the date of the first dose of Ad26.COV2.S. The exit rules for this cohort are listed in Section 8.3.5.2.

8.2.2.2.2. Inclusion Criteria for Concurrent Active Comparator Cohort

To enter the active comparator cohort, individuals must:

1. Have continuous health plan enrollment with medical and prescription drug coverage prior to the reference date with a required length of the longer of the following periods:
   a. At least 1 year before the reference date; days
   b. An earliest coverage date on or before 11 December 2020 (to maximize ability to identify the first COVID-19 vaccine administered during the study period)
2. Receive the first dose of the primary series of BNT162b2 on the reference date.

The exit rules for this cohort are listed in Section 8.3.5.2.

8.2.2.2.3. Exclusion Criteria for Exposed and Active Comparator Cohorts

Individuals will be excluded from the exposed and active comparator cohorts if:

1. They have been vaccinated with any COVID-19 vaccines at any time prior to the reference date.
2. They had records of more than 1 COVID-19 vaccine brand on the reference date.
3. They are aged < 18 years on the reference date.

Individuals with diagnosis of any of the AESIs in the AESI-specific washout periods prior to the reference date (Section 8.3.4.2) will not be excluded from the overall study population. However, individuals with diagnoses of AESIs in outcome-specific washout periods before the reference date will be excluded from outcome-specific analyses of those AESIs. Washout periods for each AESI are defined in Table 1.

8.3. Variables

8.3.1. Exposure Assessment

Exposure to the Ad26.COV2.S vaccine and the BNT162b2 vaccine will be identified using procedure or pharmacy dispensing codes (eg, National Drug Code, Current Procedural Terminology code, Healthcare Procedure Coding System codes). Where existing linkages with vaccination registries are available within the appropriate Data Partner research databases the vaccine registry data will also be used to assess exposure.

Given the use of a single booster of Ad26.COV2.S vaccine at least 2 months after completion of the single-dose regimen was not authorized until 20 October 2021, for the time period before 20 October 2021, it is not anticipated that many patients will receive more than 1 dose of Ad26.COV2.S vaccine. However, if some patients have a record of more than 1 dose during the study period prior to October 2021, rules based on the time between dose records (to be defined in the SAP) will be used to distinguish between potential coding errors and potentially additional doses (ie, booster doses). Patients with 2 or more doses of Ad26.COV2.S vaccine will be described (see Section 8.7.2.2) but follow-up and AESIs will only be captured after the first dose for the primary analyses (ie, only the first dose will be eligible to be included as a reference date for the primary exposed cohort; follow-up time for the primary analysis will end on the date individuals receive a booster dose of Ad26.COV2.S or a booster dose of any mRNA COVID-19 vaccine).

Exposure to BNT162b2 will also be identified with procedure, pharmacy, and immunization registry data, as available, similarly to Ad26.COV2.S. BNT162b2 is authorized in the US as a 2-dose primary series with additional doses and booster doses authorized for certain groups. Some procedure codes indicate the dose number of BNT162b2, but other procedure codes and NDC codes do not. The dose number of BNT162b2will be inferred from the observed dose number within the claims.

8.3.2. Individual Characteristics

Population characteristics will be identified based on medical, pharmacy and procedure codes, and insurance enrollment information. The following variables will be used to characterize the study population and will be included in PS models for the cohort design (as described in Section 8.7.2.1):

- Demographic characteristics (at reference date) such as age, sex, race/ethnicity (if feasible, as determined during the monitoring phase of the study), and a proxy for SES, if feasible, calculated using geographic information at least as granular as a patient's 5-digit ZIP code and geographic area (eg, state, or census region)
- Pregnancy status (at reference date)
- Indicators of frailty
  - Frailty will be assessed using an index developed by Kim et al. (Kim 2019) To calculate the frailty index, relevant diagnosis and procedure codes will be identified in the 365 days before day 0 (including day 0). Each variable will be assigned variable-specific weights, and the weights will be summed. Cutoff points will be defined in the SAP.
- 1-year medical history (at reference date)
  - Comorbidities such as cancer, chronic kidney disease, heart conditions, COPD, asthma, sickle cell disease, immunocompromised states, obesity, Down syndrome, Type 2 diabetes
  - Healthcare utilization eg, mean number of emergency department visits, inpatient visits
  - Medication use (eg, drug class utilization)
  - Previous history of COVID-19 infection (evidence of either of the following)
    - Diagnosis codes for COVID-19 (yes/no)
    - SARS-CoV-2 positive laboratory result from NAAT, antigen, or serology tests if available (evidence of a positive test, yes/no)
- The ability to identify SARS-CoV-2 positive tests may be limited due to incomplete capture of test results in the Sentinel data sources. Currently, some Data Partners are in the process of incorporating NAAT and antigen tests and results into the data sources. SARS-CoV-2 serology tests and results are not yet available but if captured in the data sources may be provided in the future. The extent of availability of relevant laboratory test results in the Sentinel sites participating in this study will be evaluated during the monitoring phase.
- Vaccinations:
  - Administration of certain vaccines, such as influenza vaccine, any pneumococcal vaccine, any shingles vaccine, or any human papillomavirus (HPV) vaccine during the year before the reference date (for active comparator design) or from 90 days before the reference date and during the risk and control windows (for SCRI design)
  - Other vaccinations received concurrently with the Ad26.COV2.S vaccine or BNT162b2 vaccine
- Indicator variables for previous occurrence of each AESI using all available history before reference date (Table 1).

8.3.3. Study Outcomes

AESIs, as defined in Section 8.3.4.1, will be identified, with a date of diagnosis, using predefined validated algorithms (as possible), based on diagnosis codes (with procedure and/or pharmacy dispensing codes and/or limited to specific medical care settings if applicable to the outcome).

8.3.4. Evaluation of Safety Outcomes

Within Janssen, a list of AESIs has been created based on current knowledge of the Ad26.COV2.S vaccine and potential risks related to adenovirus vaccine platform. Table 1 lists the AESIs to be ascertained in the study with specific risk windows and background incidence rates.

8.3.4.1. Case Ascertainment and Validation Process

The incidence of AESIs following administration of the Ad26.COV2.S vaccine or the BNT162b2 vaccine will be ascertained in claims data using claims algorithms. Case validation to confirm the algorithm and/or disease diagnosis and date of onset may be conducted for high priority AESIs that are judged likely to be subject to misclassification based on clinical expert opinion, prior validation studies (if available), and researchers familiar with the data sources, including the Data Partners. Review of medical records or chronological listings of diagnosis, procedure, and pharmacy dispensing codes in health insurance claims profiles by clinicians may be conducted, depending on the AESI. Where available, Brighton Collaboration definitions or any other clinical definitions from published literature or learned societies will be used as case definitions if medical record review is implemented for the AESI. For outcomes selected for validation, a sampling strategy may be implemented based on the number of algorithm-identified events to select cases that are eligible for case validation. Published validation estimates of the algorithms used may also be considered to inform or adjust relative risk estimates. If the positive predictive value (PPV) of a given AESI is above a prespecified threshold (eg, ≥ 80%), all identified cases in the electronic data will be included in the final analysis. If the PPV is lower than the prespecified threshold (eg, < 80%), then the validation results or published validation estimates will be used to inform or adjust relative risk estimates (eg, complete case analysis for the SCRI design or quantitative bias analysis for the active comparative design) in the electronic data. The PPV threshold for determining whether all cases identified in claims data are to be included in final analysis will be specific to each AESI and will depend on the background rate of each AESI. The sampling strategy, the selection of which high priority AESIs to be validated and the rationale for selection, details on the validation methods, and the plan for integrating the validation results into the final analysis will be described in the data validation plan.

8.3.4.2. Risk Windows

Table 1: AESI-Specific Risk Windows and Background Incidence Rates

Body system	AESI	Disease-specific washout period before administration of Ad26.COV2.S or BNT162b2 for active comparator design	Disease-specific washout period before event for SCRI design	Disease-specific risk period following the administration of Ad26.COV2.S or BNT162b2	Range of adult background rates per 100,000 person-years reported in the external literature[a,b]
Nervous and central nervous system	Encephalitis, including ADEM & meningoencephalitis	180 days	180 days	1-42 days	2-73 (Li X et al. 2021; Baker MA et al. 2013; Ostropolets A et al. 2022; Esposito D et al. 2018)
	Guillain-Barré Syndrome	365 days	365 days	1-42 days	< 1-23 (Baker MA et al. 2013; Li X et al. 2021; Klein NP et al. 2010; Ostropolets A et al. 2022; Esposito D et al. 2018)
	Transverse myelitis	365 days	365 days	1-42 days	< 1-5 (Baker MA et al. 2013; Li X et al. 2021; Klein NP et al. 2010; Ostropolets A et al. 2022)
	Bell's palsy	180 days	180 days	1-42 days	40-174 (Li X et al. 2021; Baker MA et al. 2013; Ostropolets A et al. 2022)
	Multiple sclerosis, including optic neuritis	All available	Not applicable for SCRI	1-365 days	2-29 (Alonso A and Hernán MA 2008; Klein NP et al. 2010; Esposito D et al. 2018)
	Sensorineural Hearing loss	365 days	365 days	1-21 days	12-81 (Alexander TH and Harris JP 2013)
	Generalized convulsions (without epilepsy)	180 days	180 days	1-14 days	25-120 (Kotsopoulos I et al. 2005)
	Generalized convulsions (with epilepsy)	365 days	365 days	1-14 days	14-62 (Kotsopoulos I et al. 2005)

Body system	AESI	Disease-specific washout period before administration of Ad26.COV2.S or BNT162b2 for active comparator design	Disease-specific washout period before event for SCRI design	Disease-specific risk period following the administration of Ad26.COV2.S or BNT162b2	Range of adult background rates per 100,000 person-years reported in the external literature[a,b]
Immune system	Autoimmune thyroiditis	All available	Not applicable for SCRI	1-365 days	5-97 (Klein NP et al. 2010; Esposito D et al. 2018)
	Immune thrombocytopenia	365 days	365 days	1-42 days	1-56 (Baker MA et al. 2013; Klein NP et al. 2010; Li X et al. 2021; Ostropolets A et al. 2022; Esposito D et al. 2018)
	Thrombocytopenia	90 days	90 days	1-42 days	
	Type 1 diabetes mellitus	All available	Not applicable for SCRI	1-365 days	19-382 (Klein NP et al. 2010; Baker MA et al. 2013; Esposito D et al. 2018)
	Acute aseptic arthritis[c]	All available	Not applicable for SCRI	1-365 days	3-205 (Pennisi M et al. 2019; Esposito D et al. 2018)
	Anaphylaxis	180 days	180 days	0-2 days	7-85 (Lee S et al. 2017; Baker MA et al. 2013; Li X et al. 2021; Ostropolets A et al. 2022; Esposito D et al. 2018)
	Composite endpoint – Cardiac inflammatory disorders, including myocarditis and pericarditis	365 days	365 days	1-21 days	2-54 (Li X et al. 2021; Baker MA et al. 2013; Ostropolets A et al. 2022)
	Microangiopathy	365 days	365 days	1-28 days	
	Heart failure	All available	All available	1-28 days	812-5,020 (Cuthbertson CC et al. 2018)[d]
	Stress cardiomyopathy	365 days	365 days	1-28 days	
	Coronary artery disease, including acute myocardial infarction	All available	All available	1-28 days	41-823 (Manemann 2015)
	Acute myocardial infarction	180 days	180 days	1-28 days	6-1,514 (Li X et al. 2021; Ostropolets A et al. 2022)
	Arrhythmia	All available	All available	1-14 days	9-6,195 (Kjerpeseth LJ et al. 2021)[e]

Body system	AESI	Disease-specific washout period before administration of Ad26.COV2.S or BNT162b2 for active comparator design	Disease-specific washout period before event for SCRI design	Disease-specific risk period following the administration of Ad26.COV2.S or BNT162b2	Range of adult background rates per 100,000 person-years reported in the external literature[a,b]
Blood and lymphatic system disorders	Deep vein thrombosis	180 days	180 days	1-28 days	66-1,206 (Li X et al. 2021; Huang W et al. 2014; Ostropolets A et al. 2022)
	Pulmonary embolism	180 days	180 days	1-28 days	20-427 (Li X et al. 2021; Huang W et al. 2014; Ostropolets A et al. 2022)
	Disseminated intravascular coagulation	180 days	180 days	1-28 days	< 1-203 (Li X et al. 2021; Singh B et al. 2013; Ostropolets A et al. 2022)
	Non-hemorrhagic stroke	180 days	180 days	1-28 days	17-1,523 (Li X et al. 2021; Feigin VL et al. 2015; Ostropolets A et al. 2022)
	Hemorrhagic Stroke	180 days	180 days	1-28 days	13-506 (Li X et al. 2021; Feigin VL et al. 2015; Ostropolets A et al. 2022)
	Cerebral venous thrombosis	180 days	180 days	1-28 days	< 1-1.7 (Coutinho JM et al. 2012)
	Peripheral arterial thrombosis	180 days	180 days	1-28 days	
	Thrombosis with thrombocytopenia syndrome	180 days	180 days	1-28 days	2-362 (Biologics Effectiveness and Safety (BEST) Initiative 2021)
	Composite endpoint – Venous thrombosis (including PE and DVT)	180 days	180 days	1-28 days	108 (Huang W et al. 2014)
	Composite endpoint – Arterial thrombosis (including coronary artery disease and non-hemorrhagic stroke)	180 days	180 days	1-28 days	

Body system	AESI	Disease-specific washout period before administration of Ad26.COV2.S or BNT162b2 for active comparator design	Disease-specific washout period before event for SCRI design	Disease-specific risk period following the administration of Ad26.COV2.S or BNT162b2	Range of adult background rates per 100,000 person-years reported in the external literature[a,b]
	Composite endpoint – Stroke (includig non-hemorrhagic and hemorrhagic strokes)	180 days	180 days	1-28 days	
Renal system	Acute kidney failure	365 days	365 days	1-14 days	20.9 (Liaño F, Pascual J, and Madrid Acute Renal Failure Study Group 1996)
Hepatic system	Acute hepatic failure	All available	All available	1-14 days	0.55 (Bower WA et al. 2007)

ADEM = acute disseminated encephalomyelitis; AESI = adverse event of special interest; CI = confidence interval; DVT = deep vein thrombosis; PE = pulmonary embolism.

[a] 95% CIs not provided for background rate ranges.

[b] Details of rate calculations: Age-stratified rates: Baker, Esposito, Kostopolous, Coutinho; Age- and sex-stratified rates: Li, Ostroplets, Klein, Alexander, Lee, Manemann, Kjerpeseth, Singh; Crude rates: Liaño, Bower; Other: BEST (age- and data source-stratified), Cuthbertson (age-, sex-, and race-standardized, stratified by inpatient/outpatient setting), Huang (age- and sex- standardized), Alonso & Hernán (age-standardized, stratified by sex), Feigen (age-standardized), Pennisi (unknown)

[c] Note that the phenotype implemented was labeled “arthritis” broad, non-specific to aseptic arthritis.

[d] Heart failure rate estimated among individuals aged 65 years and older.

[e] Outcomes restricted to inpatient or fatal atrial fibrillation, 2014.

8.3.5. Follow-Up

8.3.5.1. SCRI Design

Individuals will be followed from the start of the risk window to the end of the control window (Figure 1). Control period definitions will be specific to each AESI and may be the same length or longer than the risk period. Control period definitions, including their placement relative to vaccination and length, will be defined in the SAP, taking into account the rareness and potential seasonality of each AESI. A buffer period may be included between the risk and control periods when the risk period is uncertain as documented in the literature. Postvaccination control windows will be used for the final analyses to avoid healthy vaccinee bias.

8.3.5.2. Cohort Design with Concurrent Active Comparator

Follow-up time for the primary objective evaluating the first dose of Ad26.COV2.S or the primary series of BNT162b2 will start on or the day after the reference date (depending on the specific AESI risk window) and will continue until the earliest of the following:

- date of first diagnosis of the AESI
- end of the duration of the disease-specific risk period (specified in Table 1; up to 1 year after the reference date)
- disenrollment from the health plan
- administrative end of study (eg, end of available data)
- death
- date of any COVID-19 vaccine that is a different brand than the index vaccine
- date of receipt of an additional or booster dose beyond the authorized primary series (ie, a second dose of COVID-19 vaccine in the Ad26.COV2.S cohort or a third dose of COVID-19 vaccine in the BNT162b2 cohort)

The authorized primary series of BNT162b2 consist of 2 doses, spaced 21 days apart. If the AESI-specific risk period after dose 1 of BNT162b2 ends before a second dose is received, follow-up will end at the end of the dose 1 disease-specific risk period. However, a second dose of BNT162b2 may be received during the dose 1 disease-specific risk periods of some AESI. If a second dose is received before the end of the AESI-specific risk period, the risk periods of dose 1 and dose 2 will be concatenated into a single risk period, and follow-up will end after the duration of the disease-specific risk period following dose 2. To address differential lengths of follow-up time between the exposed and comparator cohorts that will arise from including second doses of BNT162b2 in the comparator cohort, modifications of this criteria will be evaluated in sensitivity analyses (Section 8.7.5).

Note that follow-up time will not be censored if a diagnosis of COVID-19 occurs after the initial vaccine dose. Only severe COVID-19 that arises to medical attention will be captured given the nature of the available data. This information will be captured and used in descriptive analyses.

8.4. Data Sources

This study will be conducted using health plan claims data held by Data Partners that participate in the FDA's Sentinel System, including CVS Health (Aetna), HealthCore (Anthem), Humana, and Optum. These Data Partners typically update their quality-checked data 3 to 4 times per year, although some are updating more frequently with fresher data (ie, shortened data lags) to support FDA-initiated COVID-19 analyses. The study will use the most up-to-date standardized and curated data source available within each Data Partners, leveraging the Sentinel Common Data Model (SCDM). These databases capture longitudinal information on vaccines, medical products (dispensed prescriptions, vaccines administered), inpatient and outpatient diagnoses, inpatient and outpatient treatments and procedures, based on billing codes as well as laboratory results.

The average enrollment length for patients across data sources participating in the Sentinel System is similar to other claims databases of members with medical and pharmacy coverage; about 25% of patients have over 3 years of enrollment, and patients with chronic conditions such as diabetes and older members typically have longer than average enrollment periods within these databases. All study data will be accessed with procedures compliant with US subject confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Where appropriate, as required by local regulations, this study will be undertaken only after the IEC/IRB has given full approval of the final protocol, any applicable amendments, and the sponsor has received a copy of this approval.

8.4.1. CVS Health (Aetna)

Aetna, a CVS Health company, is one of the nation's leading healthcare benefits companies, serving 38 million people. Aetna became an FDA Sentinel Data Partner in 2010. Aetna's SCDM captures longitudinal information on dispensed prescriptions, inpatient and outpatient diagnoses, inpatient and outpatient treatments and procedures, and laboratory results. As of December 2020, there were approximately 35 million unique individuals available for research.

8.4.2. HealthCore

HealthCore, Inc., a participant in Sentinel since 2008, is a significant contributor to the Sentinel Collaboration and Sentinel Distributed Database. The HealthCore Integrated Research Database (HIRD) is a broad, clinically rich, and geographically diverse data spectrum of longitudinal medical and pharmacy claims data from commercially-insured health plan members across the US. Member's enrollment, medical care (professional and facility claims), prescription drug use, laboratory test result data, and healthcare utilization, all of which may be tracked for health plan members in the database dating back to January 2006. As of February 2021, there were 79 million unique individuals with medical coverage and approximately 60 million with medical and pharmacy coverage available for research.

8.4.3. Humana

Humana Healthcare Research Inc. (HHR) is a wholly owned health economics and outcomes research subsidiary of Humana Inc. HHR focuses on conducting research on various topics, including treatment effectiveness, drug safety, adherence, medical and pharmacy benefit design, disease management programs, and other healthcare services based on the Humana health plan member population. HHR has been an active collaborator and Data Partner in the FDA Sentinel System and several large national distributed research networks. Humana databases represent geographic coverage for the entire US population and represent over 27 million lives.

8.4.4. Optum Research Database

The Optum Research Database is a proprietary research database that contains eligibility data and medical claims and includes health plan members who are geographically diverse across the US and comprise approximately 3% to 4% of the US population. Optum has curated and quality-checked data formatted to the SCDM available for use and is a longtime participant in the Sentinel System.

8.5. Study Size

8.5.1. SCRI

Table 2 shows the statistical power that can be obtained for a range of relative risks and a range of sample sizes. For example, a sample size of 100 will allow the detection of a relative risk equal to or greater than 2 with 93% statistical power.

Table 2: Detectable Relative Risk and Statistical Power for SCRI Design

Relative Risk	Number of Events in Risk and Control Period	Power
1.5	20	0.142
2	20	0.320
2.5	20	0.495
3	20	0.638
1.5	50	0.292
2	50	0.667
2.5	50	0.881
3	50	0.963
1.5	100	0.519
2	100	0.926
2.5	100	0.994
3	100	1.000
1.5	150	0.692
2	150	0.987
2.5	150	1.000
3	150	1.000
1.5	200	0.812
2	200	0.998
2.5	200	1.000
3	200	1.000

Source: Musondo, 2006.

8.5.2. Cohort

Subject to the feasibility assessment, a minimum target sample size of 100,000 individuals in the exposed cohort will be included in the study. Table 3 shows the probabilities that the upper limit of the 95% CI around the observed relative risk will be less than 1.5, 2.0, 2.5, or 3.0 for various study sizes, incidence rates, and values of the actual relative risk in the population. These calculations assume a matching ratio exposed/ comparator of 1:4.

For example, assuming a total of 100,000 individuals in the exposed cohort and 400,000 in the comparator cohort, each followed for a 60-day risk window, if the incidence rate of the outcome is 50 per 100,000 person-years in the comparator cohort and the actual relative risk in the population is 1.0, the probability that the upper limit of the 95% CI of the observed relative risk will be below 3.0 is 0.805. For the same study size and rate but assuming the actual relative risk in the population is 1.2, the probability that the upper limit of the 95% CI of the observed relative risk will be below 3.0 is 0.714.

Table 3: Probability that upper bound of 95% CI will be below specified relative risks

Actual RR in Population	Number of Exposed Individuals	Incidence Rate in Comparator Individuals (Cases per 100,000 Person-years)	Upper 95% Bound of Relative Risk			
			1.5	2	2.5	3
1.0	50,000	1	0.032	0.037	0.042	0.047
		10	0.051	0.081	0.112	0.143
		50	0.110	0.241	0.383	0.513
		100	0.179	0.428	0.652	0.805
	100,000	1	0.035	0.044	0.052	0.059
		10	0.067	0.122	0.182	0.242
		50	0.179	0.428	0.652	0.805
		100	0.312	0.711	0.914	0.979
	200,000	1	0.040	0.054	0.068	0.081
		10	0.096	0.202	0.318	0.429
		50	0.312	0.710	0.914	0.979
		100	0.548	0.945	0.997	1.000
1.2	50,000	1	0.029	0.034	0.039	0.044
		10	0.039	0.065	0.093	0.123
		50	0.064	0.167	0.298	0.431
		100	0.089	0.290	0.525	0.714
	100,000	1	0.031	0.039	0.047	0.054
		10	0.046	0.092	0.146	0.203
		50	0.089	0.290	0.525	0.714
		100	0.138	0.512	0.816	0.946
	200,000	1	0.033	0.047	0.060	0.073
		10	0.058	0.142	0.248	0.358
		50	0.138	0.512	0.816	0.946

Actual RR in Population	Number of Exposed Individuals	Incidence Rate in Comparator Individuals (Cases per 100,000 Person-years)	Upper 95% Bound of Relative Risk			
			1.5	2	2.5	3
		100	0.233	0.804	0.981	0.999
1.4	50,000	1	0.026	0.032	0.037	0.041
		10	0.029	0.051	0.077	0.105
		50	0.035	0.111	0.223	0.350
		100	0.039	0.179	0.395	0.605
	100,000	1	0.027	0.035	0.043	0.050
		10	0.031	0.068	0.115	0.167
		50	0.039	0.179	0.395	0.605
		100	0.047	0.313	0.668	0.883
	200,000	1	0.027	0.040	0.052	0.065
		10	0.033	0.097	0.187	0.290
		50	0.047	0.313	0.668	0.883
		100	0.060	0.549	0.923	0.994

Source: Rothman, 2015
Note: Calculations assume that each individual contributes a 60-day risk window.

8.6. Data Management

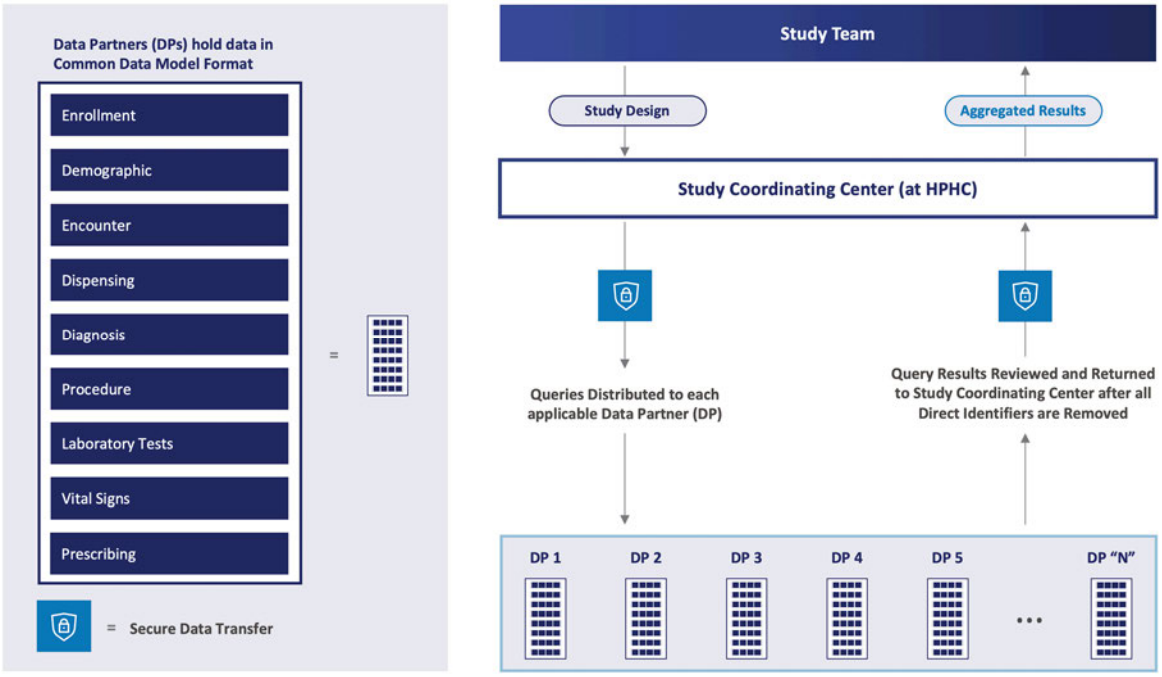
Harvard Pilgrim Health Care Institute (HPHCI), located in Boston, Massachusetts, will serve as the coordinating center for the proposed study. HPHCI staff or contractors will be responsible for writing and distributing Statistical Analysis System (SAS) programs that can be used to evaluate data from the administrative claims databases at participating Data Partners. The distributed network will leverage the SCDM (Sentinel 2021; Curtis 2012) which allows Data Partners to maintain physical and operational control of their data while allowing use of their data to meet the study needs. The HPHCI will maintain a secure distributed querying web-based portal to enable secure distribution of analytic queries, data transfer and document storage. The system will meet all required State and Federal security guidelines for health data (eg, Federal Information Security Management Act [FISMA], HIPAA) and will be specifically FISMA-compliant for FISMA security controls as specified in the National Institute of Standards and Technology (NIST) Special Publication 800-53 (NIST and Joint Task Force Transformation Initiative 2020).

HPHCI brings expertise in conducting multi-site evaluations using disparate electronic healthcare data systems, including extensive work with the Health Care Systems Research Network, the Vaccine Safety Datalink, FDA Sentinel, the National Institutes of Health Care Systems Research Collaboratory, Innovation in Medical Elements Development [IMEDS], the Biologics and Biosimilars Collective Intelligence Consortium, and PCORnet. The HPHCI Coordinating Center has expertise in conducting large-scale multi-site studies using various distributed analytic approaches, form common data models and analytics to common protocols implemented locally, and is well positioned to implement the planned study. In collaboration with RTI Health Solutions, HPHCI will oversee all project activities, including scientific leadership, management of the

partnership, coordination of activities with the Data Partners and other participants, oversight of the project plan and budgets, establishment of secure infrastructure used for collaboration, and training related to use of the SCDM and associated querying tools. The Data Partners will establish and maintain the administrative, hardware, and software capabilities and capacity to respond to data requests in a timely manner. They will also provide data science support with epidemiologic review.

Figure 3 describes the general workflow for the final analysis. Based on the study design developed by the study team, the study coordinating center first submits a computer program designed to meet the needs of the study through a secure portal. Next, the participating Data Partners receive and run the computer program behind their firewalls, using data that is formatted to the SCDM. Following this, the Data Partners review their results and return them to the study coordinating center through a secure portal. Finally, the study coordinating center reviews the results returned by the Data Partners, aggregates the data across the sites and then transfers the aggregated results back to the study team.

Figure 3: Workflow



8.7. Data Analysis

Statistical analyses of each Data Partner's aggregated data will be performed by the coordinating center and will align with analyses described in this study protocol. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections. Additional details will be provided in the SAP. A summary of planned analyses is provided in Table 4.

Table 4: Summary of Planned Analyses

Analysis	Study design for Acute AESIs	Study design for Non-acute AESIs	Risk period Definition of Risk Period	Notes on main purpose of analysis/difference from primary analysis
Primary	SCRI	Cohort: exposed (Ad26.COV2.S) vs. active comparator (BNT162b2)	Disease-specific risk period	NA
Stratified analysis (by comorbidities and by age)	SCRI	Cohort: exposed (Ad26.COV2.S) vs. active comparator (BNT162b2)	Disease-specific risk period	Subgroup analysis
Sensitivity	SCRI	Cohort: exposed (Ad26.COV2.S) vs. active comparator	Extended disease-specific risk period	Incorporates use of alternative disease risk periods
Sensitivity	NA	Cohort: exposed (Ad26.COV2.S) vs. active comparator (BNT162b2)	Disease-specific risk period	Alternate comparison of Ad26.COV2.S to first or second dose of BNT162b2
Sensitivity	Cohort: exposed (Ad26.COV2.S) vs. active comparator (BNT162b2)	NA	Disease-specific risk period	Incorporates use of alternate study design
Secondary	Descriptive analysis of Ad26.COV2.S-exposed individuals in the cohort who have received a second dose of Ad26.COV2.S	Descriptive analysis of Ad26.COV2.S-exposed individuals in the cohort who have received a second dose of Ad26.COV2.S	Disease-specific risk period	Describe counts for and characteristics of individuals receiving 2nd dose of Ad26.COV2.S

AESI = adverse event of special interest; SCRI = self-controlled risk interval; NA = not applicable.
Note: Acute AESIs are events expected to occur within 60 days of vaccination.

8.7.1. Main Summary Measures

The primary analysis will compare the incidence rates of each AESI between risk period and control period (SCRI for acute events) for Ad26.COV2.S exposed individuals, or between Ad26.COV2.S exposed individuals and BNT162b2 exposed individuals (cohort design with active comparator for non-acute events). All analyses will be conducted separately, with PS adjustment, within each data source and pooled across data sources using a random-effects model or another appropriate method to be specified in the SAP.

8.7.1.1. Self-controlled Risk Interval Design

The incidence rate ratio comparing AESI incidence during the risk and control periods will be estimated using conditional Poisson regression models (Whitaker 2006).

8.7.1.2. Cohort Design With Active Comparator

Incidence rates for each AESI will be calculated by dividing the number of cases by the follow-up person-time in each of the matched exposure groups. Incidence rate ratios and 95% CIs will be estimated with Poisson regression modeling or another appropriate method to be defined in the SAP. The risk difference will be computed as the difference between the incidence rate in the exposed cohort and the incidence rate in the comparator cohort.

Daily cumulative incidence will be estimated in each exposure group as 1 minus the Kaplan Meier estimate, and the cumulative incidence curves of the occurrence of AESI over time in the risk periods will be plotted in the matched cohorts to visualize time trends with days since the reference date as the time scale.

The percentage of outcomes that were preceded by a documented SARS-CoV-2 infection (COVID-19 diagnosis code or SARS-CoV-2 positive laboratory test result) after the first dose of either the Ad26.COV2.S or comparator BNT162b2 vaccine will be reported.

8.7.2. Main Statistical Methods

8.7.2.1. Propensity Score Matching

For the cohort designs, matching on calendar time at vaccination (within 2 weeks) and PS will be used to ensure comparability between individuals exposed to Ad26.COV2.S versus BNT162b2. The PS is the predicted probability of an individual being classified in the exposed cohort versus the comparator cohort, given a set of observed covariates. Propensity scores will be estimated with multivariable logistic regression models with Ad26.COV2.S exposure as the dependent variable and baseline covariates as the independent variables. The baseline covariates used to fit the PS model will be the individual characteristics described in Section 8.3.2 and indicators for occurrence of AESI in the disease-washout period described in Section 8.3.4.2.

This large-scale empirical adjustment strategy should address expected confounders that are recorded in the databases, including demographics and comorbidities associated with AESIs. The study will be subject to the limitation that some confounders may be unmeasured or inadequately represented in claims data, including lifestyle behaviors, such as diet and exercise.

8.7.2.2. Demographic and Baseline Characteristics

For the cohort design, disposition will be summarized by cohort and by data sources. Demographic and baseline characteristics of the individuals at the reference date will be described in the matched analytic cohort. For continuous/ordinal variables the number of observations, mean, standard deviation, minimum, and maximum will be described. For categorical variables, the number and percent per category will be summarized. Balance of characteristics between the exposure groups before and after PS matching will be evaluated with absolute standardized differences.

8.7.3. Stratified Analyses

Analyses within the primary study designs (cohort design with active comparator for non-acute events and SCRI design for acute events) will be stratified by the following clinically relevant subgroups:

- select comorbidities (by the presence or absence of comorbidity)
- frailty
- receipt of other vaccinations concurrently with Ad26.COV2.S
- age ([18-39]; [40-59]; [60-79], [80+])
- prior history of thrombotic events and/or thrombocytopenia
- prior history (ever) of specific event more than a year before start of follow-up
- prior history of COVID-19 infection

For the cohort design with active comparator, the original study population before matching will be divided into these subgroups and the PS matching will be repeated in each of the subgroups to create matched exposed and comparator cohorts within the subgroups. The balance of individual characteristics by exposure group will be re-evaluated within each subgroup, and subgroup-specific incidence rate and incidence rate ratios with 95% CIs will be estimated.

8.7.4. Missing Values

Further details of the analysis, including handling of missing data will be described in the SAP.

8.7.5. Sensitivity Analyses

8.7.5.1. Extended Disease-specific Risk Periods

Sensitivity analyses will be performed to assess the risk of AESI within extended disease-specific risk periods for events for which the risk interval is not well known or not currently documented in the vaccine safety literature. These extended disease-specific risk periods will be further described in the SAP.

8.7.5.2. Alternate Follow-up Criteria for Active Comparative Design Based on BNT162b2 Dose (for Non-acute Events)

As described in Section 8.3.5.1, for the primary analysis of non-acute events evaluated using a cohort design, if the disease-specific risk period after dose 1 of the comparator vaccine (BNT162b2) overlaps with the receipt of dose 2, the risk periods for dose 1 and dose 2 will be concatenated together into a single risk period. Sensitivity analyses will be conducted for non-acute events using a cohort design with the active comparator after receiving only a single dose (Figure 4) or after receiving both doses (Figure 5) of the comparator vaccine. Note that sensitivity analysis with the active comparator after receiving only a single dose will be performed only for AESI with risk periods of 21 days or longer (where overlap of the dose 1 risk period with dose 2 of BNT162b2 is expected), as this sensitivity analysis will be identical to the primary analysis if the dose 1 and dose 2 risk periods do not overlap.

Figure 4: Cohort Study Design for Sensitivity Analysis After Only a Single Dose of BNT162b2

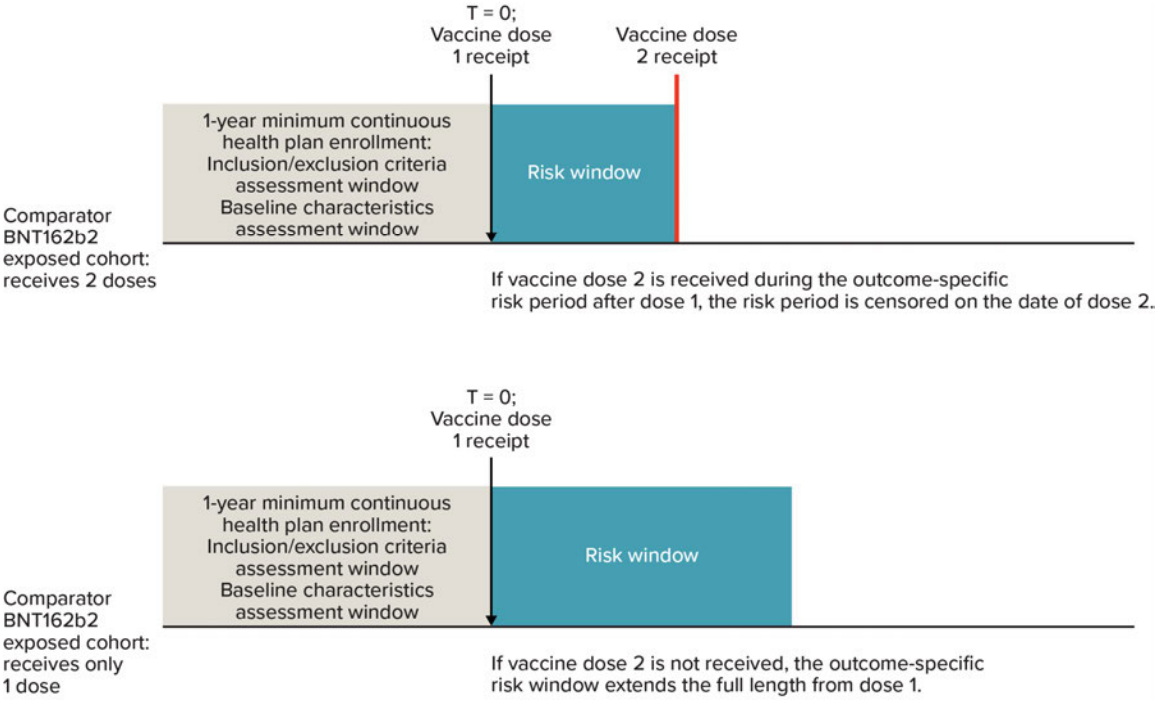
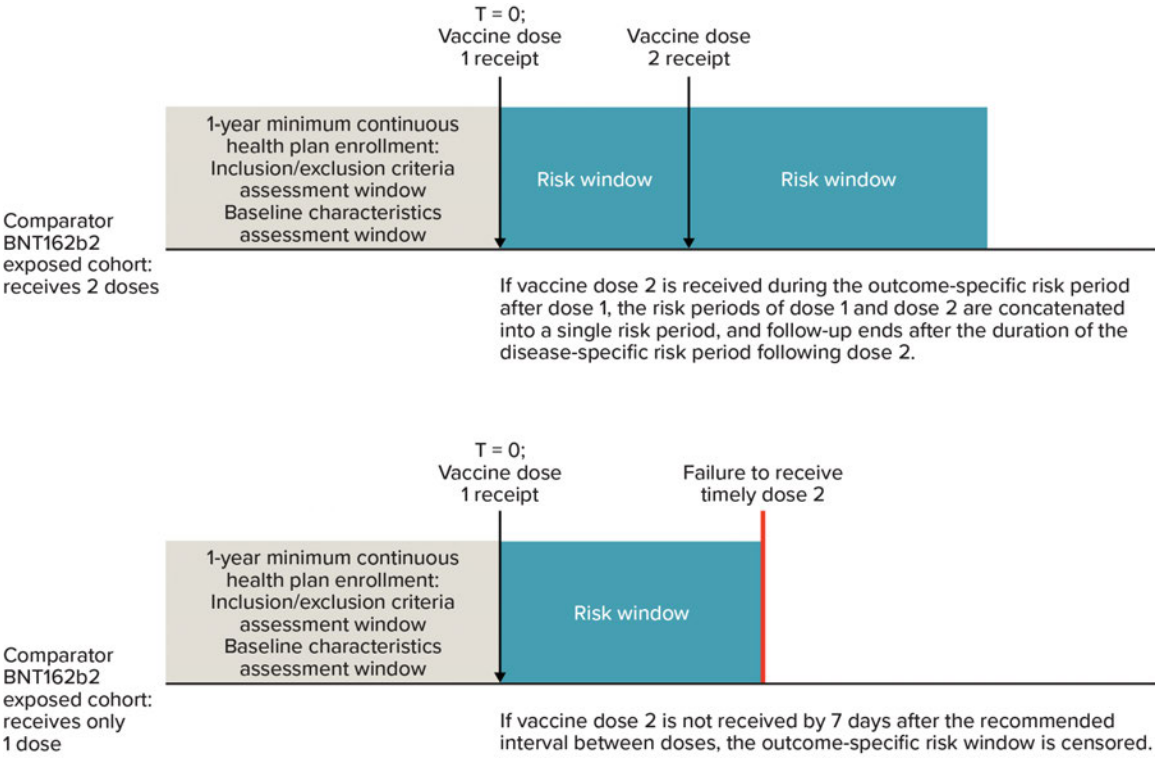


Figure 5: Cohort Study Design for Sensitivity Analysis After Both Doses of BNT162b2



To avoid immortal person-time by defining exposure groups at dose 1 based on receipt of dose 2 after baseline, all comparator vaccine recipients will begin follow-up at dose 1 for both comparisons, and the criteria for stopping follow-up will consist of the following:

- For the comparison of Ad26.COV2.S to receiving only 1 dose of BNT162b2:
  - date of first diagnosis of the AESI
  - end of the duration of the disease-specific risk period after dose 1 (specified in Table 1; up to 1 year after the reference date)
  - disenrollment from the health plan
  - administrative end of study (eg, end of available data)
  - death
  - date of receipt of a second dose of any COVID-19 vaccine (regardless of whether it is part of the primary series or is an additional dose or a booster dose)
- For the comparison of Ad26.COV2.S to receiving both doses of BNT162b2 :
  - date of first diagnosis of the AESI
  - end of the duration of the disease-specific risk period after dose 1 of Ad26.COV2.S or dose 2 of BNT162b2 (specified in Table 1; up to 1 year after the reference date)
  - disenrollment from the health plan
  - administrative end of study (eg, end of available data)
  - death
  - date of any COVID-19 vaccination that is not the same brand as the index COVID-19 vaccine
  - date of receipt of second BNT162b2 dose too early (ie., before day 17, based on CDC guidance [active comparator cohort only]) (Table C, footnote to intervals: Clinical Guidance for COVID-19 Vaccination | CDC 2022)
  - failure to receive a second dose of BNT162b2 by day 28, the recommended interval between dose 1 and 2 (21 days) plus a brief grace period for variation in real-world receipt (active comparator cohort only)
  - date of receipt of an additional or booster dose beyond the authorized primary series (ie, a second dose of COVID-19 vaccine in the Ad26.COV2.S cohort or a third dose of COVID-19 vaccine in the BNT162b2 cohort)

8.7.5.3. Alternate Study Design

For acute events, a sensitivity analysis will be conducted using a cohort design with an active comparator (described in Section 8.1.1.2).

8.7.6. Secondary Analysis of Second Doses of Ad26.COV2.S

To address the secondary objective, the number of patients in the Ad26.COV2.S exposed cohort will be reported by the number of Ad26.COV2.S doses received (1 or 2 doses), and among patients receiving 2 doses, the amount of time between doses and demographic characteristics will be reported.

8.8. Quality Control

As described in Section 8.6, the distributed network used for this study plans to leverage the SCDM that enables data standardization across Data Partners. Furthermore, each of the participating Data Partners has experience with this data model given its role as an active participant in the Sentinel System. This study will use the same data quality assurance procedures as the Sentinel System and the same curated datasets used by FDA to conduct Sentinel analyses. The quality assurance approach assesses consistency with the SCDM, evaluates adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across Data Partners. Full quality assurance processes and details on the Sentinel data curation approach are documented on the Sentinel website (Sentinel c2010-2018; Sentinel 2017). The data curation approach is consistent with guidance set forth by the FDA in its current recommendations for data quality assurance, specifically, 'Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data' (Guidance), section IV.E 'Best Practices - Data Sources: QA and Quality Control,' published in May 2013 (FDA 2013).

In addition to quality assurance of data elements, HPHCI adopts standard SAS programming quality assurance and quality control processes used by the Sentinel System to check SAS programs and deliverables.

By signing onto this protocol, the investigators agree to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted, and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical and Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

8.9. Limitations of the Research Methods

Given the broad list of potential events that could be associated with the Ad26.COV2.S vaccine and the large heterogeneity in the type of events, acute versus long latency diseases, different study design approaches will be used depending on the type of event. For acute events, the primary study design will be the SCRI design (Baker 2015), which is preferred due to its inherent control for time-constant factors; additionally, because it is restricted to vaccinated individuals, it avoids bias due to misclassification of unexposed individuals due to vaccination outside traditional medical care settings, which may not be captured in health plan data. For non-acute events, the primary study design will be the cohort design with active comparators, which avoids bias due to temporal trends in healthcare utilization for events of interest over time, differential outcome misclassification by exposure group (relieving concern of missing vaccine doses as everyone has recorded vaccine information), and confounding by vaccine hesitancy, healthcare access, or personal health beliefs and behaviors. (Lund 2015)

Experience with other vaccines indicates that safety risks may occur within specific periods postvaccination, for example, the risk of Guillain-Barré syndrome within 6 to 8 weeks after the

swine flu vaccine. However, for most of the AESIs included in this study, the risk windows are not clearly established; theoretical risk periods based on previous experience, mechanistic evidence and biological plausibility are considered. For this reason, a subset of the listed AESIs (to be defined in the SAP) will also be assessed within a larger risk period in sensitivity analyses.

COVID-19 is a complex disease for which people at higher risk of developing severe COVID-19 have been identified (Centers for Disease Control and Prevention, 2020). The proposed propensity score-matched cohort design (primary design for non-acute events) will allow adjustment for observed potential confounders at the time of the reference date, and the SCRI design (primary design for acute events) inherently adjusts for all time-constant factors. The covariates for inclusion in propensity score models for the cohort design will be harmonized across data sources by considering the lowest level of the hierarchical structure (eg, states instead of zip codes). In this observational database study conducted using commercial insurance databases, confounders that can influence vaccine behaviors such as beliefs, educational level, or socioeconomic status cannot be considered because they are either not recorded or incompletely recorded in the data. Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured, unreported, or misspecified confounders in the cohort designs.

A feasibility assessment will be conducted to monitor the number of exposed individuals in each cohort by available potential confounders.

The American Medical Association communicated the approved codes for SARS-CoV2 vaccine products, including the code for Janssen single dose and booster dose vaccine, therefore it is likely that the Ad26.COV2.S vaccine will be identifiable in the data sources. However, uncertainties remain on the capture and identification of the individuals vaccinated with the Ad26.COV2.S vaccine, especially in settings like mass vaccination clinics or other sites in which insurance claims would not be generated. In addition, while the single dose and booster dose have different CPT administration codes, the NDC codes do not distinguish between the 2; dose number will be inferred from the observed order of records in the data. Therefore, depending on the setting in which the vaccine is administered, there may be incomplete capture of all vaccine doses in the data sources.

Algorithms including medical encounters with diagnosis codes and/or claims for procedures or medications will be developed to identify the AESI that may occur in both study cohorts. Where available, published validated algorithms will be used. Case validation to confirm the disease diagnosis and date of onset may be conducted on AESIs that are likely to be misclassified in electronic data. The validation will be based on medical record review or review of claims profiles, depending on the AESI.

9. PROTECTION OF HUMANS

Where appropriate, as required by local regulations, this study will be undertaken only after an IEC or IRB has given full approval of the final protocol and any applicable amendments, and the sponsor has received a copy of this approval (see Annex 1.2).

Personal data collected from individuals included in this study will be limited to those data that are necessary to fulfill the objectives of the study, and must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations (see Annex 1.3). All data will be passively collected through provision of healthcare and collected through administrative claims data to be analyzed retrospectively while maintain data privacy with only aggregate-level data returned to a coordinating center for further aggregation with multiple participating Data Partner organizations.

Confidentiality of individual records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual individuals or physicians. At no time during the study will the sponsor receive individual identifying information.

All study data will be accessed with procedures compliant with US subject confidentiality requirements, including HIPAA.

All study data will be stored on secure password-protected servers throughout the conduct of the study. We will also report only aggregate-level statistics and effect measures to ensure individual's confidentiality.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the sponsor, which will contain summary results collected from the databases that participated in the study. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2012). Communication via appropriate scientific venues will be considered.

Identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating Data Partner) shall be the property of the sponsor as author and owner of copyright in such work.

Further details of publication policies and practices are provided in Annex 1.6.

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ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 1.1: Regulatory Documentation

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, where applicable. A study may not be initiated until any applicable local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before starting the study:

- Protocol and amendment(s), if any, signed and dated by the Data Partner.
- Where appropriate, as required by local regulations, a copy of the dated and signed written IEC/IRB approval of the protocol, amendments, and any recruiting materials.
- Where appropriate, as required by local regulations, a copy of the dated and signed written Designated Regulatory Body (DRB) approval of the protocol, protocol amendments, and any other recruiting materials. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Where appropriate, as required by local regulations, the name and address of the DRB (with a statement that it is organized and operates according to applicable laws and regulations). If a participating Data Partner or a member of the participating personnel is a member of the DRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote or opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Documentation of the qualifications (eg, curriculum vitae) of the participating Data Partners, where appropriate.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first individual:

- Signed and dated clinical trial agreement, which includes the financial agreement

Annex 1.2: Ethics Compliance

Independent Ethics Committee or Institutional Review Board

Before the start of data collection, the participating Data Partner (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, protocol amendments
- Any other written materials to be provided to the individuals
- Participating Data Partner curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)

- Information regarding name of the sponsor, institutional affiliations, other potential conflicts of interest
- Any other documents that the IEC/IRB requests to fulfill its obligation

Where appropriate, as required by local regulations, this study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding those that are purely administrative, with no consequences for data collection), and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the participating Data Partner (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding those that are purely administrative, with no consequences for data collection)
- Revision(s) to any other written materials to be provided to individuals
- If applicable, new or revised individual recruiting materials approved by the sponsor
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB
- Reports of adverse events that are serious, unlisted/unexpected, and temporally associated with the product under study
- New information that may adversely affect the safety of the individuals or the conduct of the study
- Report of deaths of individuals under the participating Data Partner's care
- Notification if a new Data Partner is responsible at the participating site
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding those that are purely administrative, with no consequences for data collection), the amendment and applicable revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At the end of the study, where required by local regulations, the participating Data Partner (or sponsor where required) will notify the IEC/IRB about the study completion.

Annex 1.3: Patient Data Protection

The collection and processing of personal data from individuals included in this study will be limited to those data that are necessary to fulfill the objectives of the study, which must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of individuals confidential.

The individual has the right to request through the participating Data Partner access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Annex 1.4: Record Retention

If a responsible person retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the participating Data Partner relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the participating Data Partner must permit access to such reports.

Annex 1.5: Study Completion/Termination

The final data from the participating site will be sent to the sponsor (or designee) after completion of the final data collection time point at that site.

The sponsor reserves the right to close a participating site for data collection or to terminate the study at any time for any reason at the sole discretion of the sponsor.

A participating site is considered closed when all required documents and study specific supplies have been collected and a site closure assessment has been performed.

The participating Data Partner may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a participating site by the sponsor or participating Data Partner may include but are not limited to:

- Failure of the participating Data Partner to comply with the protocol, requirements of the local health authorities, or the sponsor's procedures
- Inadequate recruitment of individuals by the participating Data Partner

The participating Data Partner should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

Annex 1.6: Use of Information and Publication

All information, including but not limited to information regarding Ad26.COV2.S or the sponsor's operations (eg, patent applications, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the participating Data Partner and not previously published, and any Deliverables generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The participating Data Partner

agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the sponsor's prior written consent.

Any data source created in connection with performance of the study and contained in the Deliverables that can benefit from copyright protection (except any publication by the participating Data Partner as provided for below) shall be the property of the sponsor as author and owner of copyright in such work. “Data Source” means the final, curated and extracted, fully de-identified data and dataset with the Deliverables.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish the primary (multicenter) results of work performed under the study without approval from the participating Data Partner. Data Partner may participate in preparing and submitting said sponsor publication. The participating Data Partner has the right to publish data results of work performed under the study specific to the associated participating site after the primary data are published. If a participating Data Partner wishes to independently publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 30 days (15 days for review of any poster presentation, abstract or other written or oral material which describes the results of the study) before submission for publication or presentation. No publication or presentation shall contain any Personal Information or Confidential Information. If requested by the sponsor in writing, the participating Data Partner will withhold such publication for up to an additional 60 days to allow for the sponsor to file a patent application or to take such other action to protect its proprietary or intellectual property interests. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the participating Data Partner. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, participating Data Partners will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final Deliverables, or the sponsor confirms in writing there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state, among other things, that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Section Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2, 7
1.1.2 The objectives of the study?	☒	☐	☐	7
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (ie, population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	7
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
1.2.3 if applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	Yes	No	N/A	Section Number(s)
2.1 Is the source population described?	☒	☐	☐	8.2
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	8.2
2.2.2 Age and sex?	☐	☒	☐	
2.2.3 Country of origin?	☐	☒	☐	
2.2.4 Disease/indication?	☐	☒	☐	
2.2.5 Co-morbidity?	☐	☒	☐	
2.2.6 Seasonality?	☐	☒	☐	
2.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8.2

Comments:

Section 3: Study design	Yes	No	N/A	Section Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	8.1
3.2 Is the study design described? (eg, cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	8.1
3.3 Does the protocol describe the measure(s) of effect? (eg, relative risk, odds ratio, deaths per 1,000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	8.1, 8.5
3.4 Is sample size considered?	☒	☐	☐	8.5
3.5 Is statistical power calculated?	☒	☐	☐	8.5

Comments:

Section 4: Data sources	Yes	No	N/A	Section Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	8.4
4.1.2 Endpoints? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	8.4
4.1.3 Covariates?	☒	☐	☐	8.4
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3, 8.4
4.2.2 Endpoints? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3, 8.4
4.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle, etc)	☒	☐	☐	8.3, 8.4
4.3 Is the coding system described for:				
4.3.1 Diseases? (eg, International Classification of Diseases (ICD)-10)	☒	☐	☐	8.3, 8.4
4.3.2 Endpoints? (eg, Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	8.3, 8.4
4.3.3 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	8.3, 8.4
4.4 Is the linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	8.4

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (eg, operational details for defining and categorizing exposure)	☒	☐	☐	8.3.1
5.2 Does the protocol discuss the validity of exposure measurement? (eg, precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	8.3.1
5.3 Is exposure classified according to time windows? (eg, current user, former user, non-use)	☒	☐	☐	8.3.1
5.4 Is exposure classified based on biological mechanism of action?	☒	☐	☐	8.3.1
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	8.3.1

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Section Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	8.3.3, 8.3.4
6.2 Does the protocol discuss the validity of endpoint measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	8.3.4.1

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Section Number(s)
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	8.7
7.1.2 Information biases? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	8.1.2, 8.7
7.2 Does the protocol address known confounders? (eg, collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	8.7
7.3 Does the protocol address known effect modifiers? (eg, collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	8.7
7.4 Does the protocol address other limitations?	☒	☐	☐	8.9

Comments:

Section 8: Analysis plan	Yes	No	N/A	Section Number(s)
8.1 Does the plan include measurement of absolute effects?	☐	☒	☐	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	8.7
8.3 Are descriptive analyses included?	☒	☐	☐	8.7
8.4 Are stratified analyses included?	☒	☐	☐	8.7
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	8.7
8.5.2 Effect modifiers?	☒	☐	☐	8.7
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	8.7
8.6.2 Effect modification?	☒	☐	☐	8.7

Comments:

Section 9: Quality assurance, feasibility, and reporting	Yes	No	N/A	Section Number(s)
9.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.8
9.2 Are methods of quality assurance described?	☒	☐	☐	8.8
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	8.8
9.4 Does the protocol discuss study feasibility? (eg, sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.5
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	8.2.1
9.5.2 Any progress report?	☒	☐	☐	5
9.5.3 End of data collection?	☒	☐	☐	8.1.1
9.5.4 Reporting? (ie, interim reports, final study report)	☒	☐	☐	8.7
9.6 Does the protocol include a section to document future amendments and deviations?	☐	☒	☐	
9.7 Are communication methods to disseminate results described?	☒	☐	☐	11
9.8 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 10: Ethical issues	Yes	No	N/A	Section Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	9
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
10.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

MAIN AUTHOR SIGNATURE

I have read this protocol and agree that it contains all necessary details for carrying out this study.

Sponsor's Main Author:

Name (typed or printed): PPD PharmD, MSCE

Institution: Janssen Vaccines & Prevention B.V.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Signature

User	Date	Reason
PPD	02-May-2023 12:31:17 (GMT)	Document Approval
PPD	02-May-2023 12:42:13 (GMT)	Document Approval