1. SYNOPSIS

Name of Sponsor/Company	Janssen Biotech Inc
Name of Finished Product	Jcovden
Name of Active Ingredient(s)	Ad26.COV2.S (JNJ-78436735)

Protocol No.: VAC31518COV4001

Title of Study: An Observational Post-Authorization Safety Study to Assess the Safety of Ad26.COV2.S Using Health Insurance Databases in the United States (1.0, 30 June 2025)

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

Sponsor's Responsible Contact: PPD Johnson & Johnson

Keywords: adverse events; cohort design; COVID-19 vaccine; self-controlled risk interval

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Marketing Authorization Holder(s): Janssen Biotech Inc

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Study Center(s): Harvard Pilgrim Health Care Institute; RTI Health Solutions; CVS Health; Carelon Research; Humana Healthcare Research; Optum

Publication (Reference): None

Study Period: Vaccinations were identified in the data sources from 27 February 2021 to 31 December 2021. Data from before this time were used to define eligibility criteria and baseline characteristics; the start date of data availability varied from 01 January 2006 to 01 January 2008, depending on the data source. Follow-up data after 31 December 2021 were used to identify outcomes.

Rationale and Background: Ad26.COV2.S is a monovalent COVID-19 vaccine that was granted emergency use authorization (EUA) in the United States (US) for use in individuals aged 18 years and older on 27 February 2021. During the period of its use in the US, safety concerns with Ad26.COV2.S were identified by the Food and Drug Administration (FDA), such as thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome (GBS), thromboembolic events, myocarditis and pericarditis, and immune thrombocytopenia. This report outlines the results of a post-authorization safety study (PASS) using 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.

Research Question and Objectives: This study aimed to assess the risk of developing prespecified AESIs following administration of Ad26.COV2.S. The primary objective was to assess, in adults aged 18 years and older, the potential association between receipt of 1 dose of Ad26.COV2.S and the occurrence of prespecified AESIs within AESI-specific risk periods, as compared with either 1) individuals exposed to at least 1 dose of BNT162b2 for nonacute events or 2) during a control period within the same individual for acute events.

Study Design: This was a retrospective, non-interventional study conducted in the US to evaluate the occurrence of AESIs after administration of Ad26.COV2.S. The selected AESIs represent a heterogeneous group of outcomes including multiple organ systems, as well as acute and nonacute conditions. Two different study designs were used, depending on whether the AESI was an acute or nonacute event. The primary study design for acute events (i.e., events expected to occur within 60 days of vaccination) was a self-controlled risk interval (SCRI) design conducted in Ad26.COV2.S-exposed individuals in which the relative incidence of each AESI was compared during an AESI-specific postvaccination risk period versus during a control period within the same individual. For nonacute events, a propensity score–matched, active comparator cohort design was used to compare a group of individuals exposed to Ad26.COV2.S with a concurrent comparator group (i.e., individuals exposed to at least the first dose of the primary series of BNT162b2 [Pfizer-BioNTech COVID-19 Vaccine]); nonacute events are not well suited for self-controlled analyses. The active comparator design did not rely on the identification of an unvaccinated comparator group, thus avoiding exposure misclassification bias by underreporting of COVID-19 vaccines in healthcare databases. Additionally, the active comparator cohort design was used as a sensitivity analysis for acute events because the primary SCRI design may have lower statistical power and may be subject to confounding by time-varying confounders (e.g., seasonality).

Setting: This non-interventional study was conducted in individuals who received Ad26.COV2.S to prevent COVID-19 in the setting of routine clinical care and public health practices. Eligible, vaccinated individuals were identified for the study from the time of EUA of Ad26.COV2.S in the US on 27 February 2021 until 31 December 2021, at which time the Advisory Committee on Immunization Practices recommended preferential use of messenger ribonucleic acid (mRNA) vaccines over Ad26.COV2.S. Minimal primary vaccination with Ad26.COV2.S was expected to occur after 2021; thus, no additional index-defining vaccinations with Ad26.COV2.S occurring after this date were included. The study used the data available for research purposes in the Sentinel Distributed Database (SDD) at each Research Partner.

Participant Population and Study Size: The source population for this study was the total population aged 18 years and older available to the Research Partners (i.e., CVS Health, Carelon Research, Humana Healthcare Research, and Optum) for research studies and enrolled in the health plan with medical and prescription drug coverage for at least 1 day from 27 February 2021 to 31 December 2021. All eligible individuals in each data source meeting the eligibility criteria were included in the study.

For the SCRI design, individuals who received Ad26.COV2.S as their first dose of any COVID-19 vaccine were identified; they were eligible for the AESI-specific analyses study if they had sufficient enrollment in the data source and experienced an incident AESI within AESI-specific risk or control periods after vaccination. The sizes of the AESI-specific analyses (combined across all Research Partners) ranged from 2 (cerebral venous sinus thrombosis [CVST]) to 3,012 (thrombocytopenia). There was low statistical power for rarer AESIs.

For the active comparator cohort design, individuals who received Ad26.COV2.S or BNT162b2 as their first dose of any COVID-19 vaccine were identified, and they were eligible for inclusion in AESI-specific cohorts if they had sufficient baseline enrollment and did not have a previous occurrence of the AESI. Recipients of Ad26.COV2.S and BNT162b2 were matched using propensity scores in a fixed 1:4 ratio within 2-week intervals of calendar time. There were 417,126 eligible Ad26.COV2.S recipients before matching. Even after applying AESI-specific exclusion criteria and matching, there were over 200,000 Ad26.COV2.S recipients in each AESI-specific cohort, with over 300,000 for most AESIs.

Variables and Data Sources: This study was conducted using health plan claims data held by 4 large national insurers that participate in the FDA's Sentinel System whose data contribute to the SDD, including CVS Health (Aetna), Carelon Research (Elevance Health), Humana Healthcare Research, and Optum. Study variables were identified in the existing data recorded in the participating data sources. Where possible, validated algorithms were used to identify key variables.

Exposure to Ad26.COV2.S (and BNT162b2 for the active comparator cohort analyses) was identified using procedure codes, pharmacy dispensing codes, or state or local immunization registry records (where available).

The occurrence of AESIs was identified, with a date of diagnosis, using predefined algorithms based on recorded diagnosis codes (along with procedure and/or pharmacy dispensing codes and/or limited to specific medical care settings, if applicable to the outcome). The 30 acute AESIs included nervous and central nervous systems events (i.e., encephalitis [including acute disseminated encephalomyelitis (ADEM) and meningoencephalitis], GBS, transverse myelitis, Bell's palsy, sensorineural hearing loss, generalized convulsions without epilepsy [narrow], generalized convulsions with or without epilepsy [broad]), immune system events (i.e., immune thrombocytopenia, thrombocytopenia, anaphylaxis), cardiac system events (i.e., myocarditis/pericarditis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease [including acute myocardial infarction], acute myocardial infarction, arrhythmia), blood and lymphatic system events (i.e., deep vein thrombosis [DVT], pulmonary embolism [PE], disseminated intravascular coagulation, nonhemorrhagic stroke, hemorrhagic stroke, CVST, peripheral arterial thrombosis, co-occurring thrombosis with thrombocytopenia [TwT], composite venous thrombosis [including PE and DVT], composite arterial thrombosis [including coronary artery disease, nonhemorrhagic stroke], composite stroke [including nonhemorrhagic and hemorrhagic stroke]), renal system events (i.e., acute kidney failure), and hepatic system events (i.e., acute hepatic failure). The 4 nonacute AESIs included nervous and central nervous system events (i.e., multiple sclerosis, including optic neuritis) and immune system events (i.e., autoimmune thyroiditis, type 1 diabetes mellitus, arthritis [broad definition]).

The baseline characteristics of included individuals were described, and these characteristics were included as variables in propensity score models as potential confounders for the cohort design. Such variables included demographic characteristics, clinical characteristics and comorbidities (e.g., frailty, history of COVID-19, conditions associated with higher risk for severe COVID-19, autoimmune disorders, history of each AESI), and healthcare utilization.

Statistical Methods: These analyses were conducted using a distributed network, where analytic programs were developed centrally by the data coordinating center and distributed to the participating Research Partners to run locally. Results were returned to the data coordinating center, where they were aggregated across sites to preserve the privacy of each participating Research Partner.

For the 30 acute AESIs, the primary study design was the SCRI; each acute AESI was evaluated separately in AESI-specific analysis sets consisting of those who experienced an incident AESI during the AESI-specific risk or control periods; the length of the risk periods ranged from 2 days to 42 days. The characteristics of included individuals in each AESI-specific analysis set were described. For each AESI, the relative incidence ratio (RIR) comparing AESI incidence during the risk and control periods was estimated using conditional Poisson regression models; 95% confidence intervals (CIs) were estimated with exact methods. Subgroup analyses estimated RIRs and 95% CIs within clinically relevant subgroups of the AESI-specific analysis sets. Sensitivity analyses evaluated the impact of using shorter risk periods for myocarditis/pericarditis and co-occurring TwT. Quantitative bias analyses (QBAs) evaluated the potential impact of differential outcome misclassification for selected AESIs. As a sensitivity analysis, the acute AESIs were also evaluated with the active comparator cohort design.

Each of the 4 nonacute AESIs was evaluated in an AESI-specific cohort created by applying AESI-specific washout criteria to ensure identification of new-onset events. The active comparator cohort design estimated incidence rate ratios (IRRs) and incidence rate differences (IRDs) with their respective 95% CIs by comparing the incidence of AESIs during follow-up in Ad26.COV2.S recipients with those of matched BNT162b2 recipients.

RESULTS:

Participant Information: For the SCRI analyses, there were 419,647 unique individuals identified in the data sources who received an eligible dose of Ad26.COV2.S and who had sufficient preindex enrollment. After defining AESI-specific analysis sets from this overall group of Ad26.COV2.S recipients, the sizes of the AESI-specific analysis sets were variable; sizes of the analysis sets ranged between CVST (n = 2) and thrombocytopenia (n = 3,012).

For the active comparator cohort analyses, there were 417,126 eligible Ad26.COV2.S recipients and 3,017,983 eligible BNT162b2 recipients identified in the data sources. Among all cohort analyses for all AESIs (both nonacute and acute), the sizes of the Ad26.COV2.S groups in the AESI-specific cohorts (before matching) ranged from 243,089 (arthritis [broad]) to 417,123 (CVST).

Demographics and Baseline Information: For the SCRI analyses overall (i.e., before defining AESI-specific analysis sets), 47.9% of Ad26.COV2.S recipients were female, with a mean age of 53.5 years (standard deviation [SD], 15.9). Approximately half of the Ad26.COV2.S recipients were aged 50 to 74 years. Certain comorbidities and history of AESIs were frequent, with heart conditions, obesity/ overweight, type 1 or 2 diabetes mellitus, depression/bipolar/schizophrenia, and arrhythmia all being present in more than 20% of Ad26.COV2.S recipients. Occurrence of the AESIs of interest before vaccination with Ad26.COV2.S was typically rare, but coronary artery disease, arrhythmia, and composite arterial thrombosis all occurred before vaccination in greater than 10% of Ad26.COV2.S recipients. Each of the AESI-specific analysis sets differed substantially in size and composition, as they were restricted to individuals who experienced the AESI after vaccination.

For the active comparator cohort analyses, the multiple sclerosis–specific cohort was used as an example of the distribution of characteristics before and after matching, as this nonacute AESI had the smallest number of excluded individuals. Before matching, a larger proportion of BNT162b2 recipients than Ad26.COV2.S recipients were identified later in the study period (i.e., September-December 2021). Additionally, although the absolute numbers of COVID-19 vaccine recipients receiving other vaccines on the same day were small, a larger proportion of the BNT162b2 recipients received an influenza vaccine on the same day than Ad26.COV2.S recipients (3.8% vs. 0.3%, respectively). Other demographic and clinical characteristics were generally well balanced between the groups, even before matching. After matching, all characteristics were well balanced. Very similar patterns of covariate balance before and after matching were observed in all other AESI-specific cohorts.

Treatment Information: In both the SCRI and cohort analyses, individuals were identified at the receipt of their first dose of COVID-19 vaccine. In the SCRI analyses, individuals were excluded if they received a second dose of any COVID-19 vaccine before the end of the control period (maximum of 98 days after receipt of dose 1). Across all AESI-specific analysis sets, 1.1% to 1.8% of Ad26.COV2.S-vaccinated individuals were excluded for receiving another dose of any COVID-19 vaccine during the risk, buffer, or control periods.

In the active comparator cohort analysis among the Ad26.COV2.S group, approximately 40% received another dose of COVID-19 vaccine after the index date; approximately 9% received a second dose of Ad26.COV2.S, 13% received a dose of BNT162b2, and 17% received a dose of another brand or dose of unspecified brand/valency. Among the BNT162b2 group, approximately 75%-78% received a second dose of BNT162b2.

Outcomes of Interest: For the primary SCRI analyses of the 30 acute AESIs, SCRI analyses of several AESIs resulted in slightly elevated RIR estimates with varying levels of precision. For co-occurring TwT (risk period = 28 days, analysis set n = 138), the RIR was 1.82 (95% CI, 1.27-2.63). For generalized convulsions without epilepsy (narrow) (risk period = 14 days, analysis set n = 206), the RIR was 1.40 (95% CI, 1.05-1.86); for analysis of the broader generalized convulsions outcome (i.e., generalized convulsions with or without epilepsy; risk period = 14 days, analysis set n = 259), the analysis set was larger, but the RIR was slightly attenuated (RIR = 1.25; 95% CI, 0.97-1.61). For myocarditis/pericarditis

(risk period = 28 days, analysis set n = 42), the RIR was 1.33 (95% CI, 0.69-2.61). For PE (risk period = 28 days, analysis set n = 49), the RIR was 1.33 (95% CI, 0.73-2.47). And for Bell's palsy (risk period = 42 days, analysis set n = 162), the RIR was 1.31 (95% CI, 0.95-1.82). The SCRI analysis results for the other AESIs were generally close to or below the null. In subgroup analyses, some differences were observed by age group (e.g., for both generalized convulsions outcomes and myocarditis/pericarditis, the largest RIR estimates were observed in the youngest age groups; for co-occurring TwT, the highest RIR estimates occurred among those aged 40-59 years and among the oldest age group). In the active comparator cohort sensitivity analyses for acute AESIs, incidence varied widely by type of AESI; GBS, microangiopathy, and CVST had incidence rates (IRs) of less than 10 events per 100,000 person-years, whereas sensorineural hearing loss, thrombocytopenia, coronary artery disease, arrhythmia, arterial thrombosis, and acute kidney failure had IRs greater than 1,000 events per 100,000 person-years. Case counts for many AESIs were small, resulting in imprecise IRD and IRR estimates. The IRR estimates were variable, ranging between those observed for peripheral arterial thrombosis (0.75; 95% CI, 0.48-1.18) and CVST (4.22; 95% CI, 0.71-25.28). For most outcomes with increased RIRs observed in the primary SCRI analyses, the active comparator cohort sensitivity analyses were also generally consistent with an increased risk (e.g., co-occurring TwT, both generalized convulsions outcomes, myocarditis/pericarditis, and Bell's palsy).

For the primary active comparator cohort analyses of the 4 nonacute AESIs comparing recipients of Ad26.COV2.S with recipients of BNT162b2, arthritis (broad) was the most frequently occurring nonacute AESI, with IRs above 8,000 events per 100,000 person-years in both vaccination groups; all other AESIs had IRs less than 100 events per 100,000 person-years. For autoimmune thyroiditis, both IRD (−4.34; 95% CI, −19.34 to 10.66) and IRR (0.96; 95% CI, 0.81-1.12) estimates were very close to their respective null values. For arthritis (broad), the IRR estimate was 1.03 (95% CI, 1.01-1.05); because of the high IRs, this translated to an IRD estimate of 271.20 cases per 100,000 person-years (95% CI, 111.16-431.25). For type 1 diabetes mellitus, the IRR estimate was 1.10 (95% CI, 0.74-1.64); because of the very low IRs, this translated to an IRD estimate of 1.50 (95% CI, −4.75 to 7.76). For multiple sclerosis, the IRD estimate was −9.50 (95% CI, −17.70 to −1.30), with an IRR estimate of 0.77 (95% CI, 0.60-0.98). In the subgroup analyses, many IRRs could not be estimated in those defined by concurrent vaccination receipt because of having 0 cases in 1 or both vaccination groups. Due to the small sample sizes in the subgroups, IRR estimates (when they could be estimated) were generally less precise than the overall estimates.

Other Analyses: Of the 417,126 Ad26.COV2.S recipients identified in the cohort study, a second dose of Ad26.COV2.S was observed in 37,860 individuals (9%). Relative to the overall population of Ad26.COV2.S vaccinees (represented by the largest AESI-specific cohort for multiple sclerosis), recipients of a second dose received their first dose relatively early in the study period (i.e., March-May 2021) and were slightly more likely to have a condition associated with higher risk for severe COVID-19 (79% vs. 72%, respectively).

Adverse Events/Adverse Reactions: No adverse events (AEs), other than those specifically evaluated in this study, were identified or evaluated. All aggregated results for the safety outcomes are presented in this report, and assessments of causality at the individual case level were not feasible in these data sources.

DISCUSSION AND CONCLUSION:

Discussion: Using various approaches, this study evaluated the potential association between Ad26.COV2.S vaccination and 30 acute and 4 nonacute AESIs. Signals for some of the AESIs (e.g., GBS, co-occurring TwT [described as TTS in the factsheet], myocarditis/pericarditis) have already been recognized through passive surveillance systems and described in the US EUA factsheet for healthcare providers. This PASS evaluated both these and other potential AESIs. Although many estimates were relatively imprecise due to small case counts, consistently elevated, precise effect measure estimates were observed for generalized convulsions and co-occurring TwT. Other studies have also suggested an association between Ad26.COV2.S and TTS or co-occurring TwT.

Analyses of other AESIs yielded estimates that were less precise and occasionally inconsistent across analyses. However, estimates for GBS, transverse myelitis, Bell's palsy, anaphylaxis, myocarditis/ pericarditis, arrhythmia, thrombocytopenia, and PE were generally consistent with a potential increased risk associated with Ad26.COV2.S. These results are largely consistent with other studies in the literature, which have suggested imprecise—albeit numerically elevated—effect measure estimates for these AESIs.

These analyses were performed using large US healthcare databases that include information for individuals from throughout the US and in varying healthcare settings. These results should be generalizable to the US population of insured adults aged 18 years or older who received Ad26.COV2.S during the study period.

This study relied on recorded healthcare information in existing databases to identify the key study variables, including the exposures, AESIs, and individual characteristics. For example, TTS is a recognized outcome of vaccination with Ad26.COV2.S, but for this study, the phenotype of co-occurring TwT (diagnosis of a thrombosis with a diagnosis or laboratory evidence of thrombocytopenia within ± 7 days) was used, as not all the necessary elements to define clinical TTS were routinely available in administrative healthcare databases. Data not recorded or incorrectly recorded in these databases could result in misclassification of study variables. Given the broad list of AESIs evaluated and large heterogeneity in the type of events (e.g., acute vs. long latency conditions), the study used 2 different study designs. Both study designs had advantages, and the 2 designs addressed different study questions. However, both designs are also subject to potential limitations depending on the characteristics of the individual AESIs: the SCRI requires the specification of relevant risk and control periods, and outcomes must meet strict assumptions; the active comparator cohort design is subject to confounding between vaccination groups.

Conclusions: The observed estimates from the PASS for co-occurring TwT, GBS, and myocarditis/ pericarditis were consistent with increased risks previously described in the US EUA healthcare provider factsheet, though the effect measure estimates were occasionally imprecise with wide CIs. This study did not observe an increased risk of immune thrombocytopenia, which had been identified as a risk in the US EUA healthcare provider fact sheet. Additionally, consistently elevated, precise effect measure estimates were observed for generalized convulsions, which was not listed on the factsheet as a potential risk. Analyses of other acute AESIs yielded estimates that were less precise and occasionally inconsistent across analyses, but estimates for transverse myelitis, Bell's palsy, anaphylaxis, arrhythmia, thrombocytopenia, and PE were consistent with a potential increased risk. Thus, an association of these AESIs with Ad26.COV2.S cannot be ruled out by these data. The results for the remaining acute AESIs (encephalitis, sensorineural hearing loss, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, acute myocardial infarction, DVT, disseminated intravascular coagulation, nonhemorrhagic stroke, hemorrhagic stroke, CVST, peripheral arterial thrombosis, composite venous thrombosis, composite arterial thrombosis, composite stroke, acute kidney failure, acute hepatic failure) and all nonacute AESIs (multiple sclerosis, autoimmune thyroiditis, type 1 diabetes mellitus, arthritis [broad]) did not suggest increased risks associated with Ad26.COV2.S receipt.