JANSSEN BIOTECH, INC.
(A PHARMACEUTICAL COMPANY OF JOHNSON & JOHNSON)

COVID-19 Vaccine Ad26.COV2.S

VAC31518 (JNJ-78436735)

ADDENDUM TO JANSSEN'S BRIEFING MATERIALS (DATED 07 OCTOBER 2021) FOR VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE
MEETING DATE: 15 OCTOBER 2021

TABLE OF CONTENTS

TABLE OF CONTENTS **2**

LIST OF ABBREVIATIONS **3**

1. RATIONALE FOR THIS ADDENDUM **4**

2. INFORMATION ON ONGOING SAFETY EVALUATIONS **4**
2.1. Encephalitis and Acute Disseminated Encephalomyelitis (ADEM) 4
2.2. Acute Hepatic Failure 5
2.3. Flares of Autoimmune Disorders 5
2.4. Thromboembolic Events 6
2.5. Vasculitis 7
2.6. Transverse Myelitis 7
2.7. Cardiomyopathy 7
2.8. Immune Thrombocytopenia 8
2.9. Myocarditis and Pericarditis 8

3. REFERENCES **10**

LIST OF ABBREVIATIONS

Abbreviation	Definition
Ad26	adenovirus type 26
ADEM	acute disseminated encephalomyelitis
COVID-19	coronavirus disease-2019
DVT	deep vein thrombosis
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HLT	high-level term
ITP	immune thrombocytopenia
mRNA	messenger ribonucleic acid
PE	pulmonary embolism
PMR	polymyalgia rheumatica
PT	preferred term
RWD	real-world data
SARS-CoV(-2)	severe acute respiratory syndrome coronavirus(-2)
SCCS	self-controlled case series
TTO	time to onset
US	United States
VTE	venous thromboembolism

1. RATIONALE FOR THIS ADDENDUM

This addendum provides an update on the ongoing safety signals for the COVID-19 Janssen vaccine (Ad26COV2.S) in addition to the briefing material submitted to FDA on 07 October 2021 in which Janssen is requesting EUA (EUA 27205) for the administration of a homologous booster for recipients of single-dose of the Janssen COVID-19 vaccine. Information related to the ongoing safety evaluations are provided in Section 2.

2. INFORMATION ON ONGOING SAFETY EVALUATIONS

The sponsor has a robust safety surveillance system and continually reviews all sources of data, including but not limited to spontaneous post-marketing reports (including direct reports to the sponsor and health authority databases [such as VAERS]), real-world data (RWE) (eg, sequential rapid-cycle analytics utilizing administrative healthcare claims data and/or electronic health records, [EHR]), literature and clinical trials data for potential new safety signals. Given intrinsic limitations, spontaneous report data alone are not sufficient to establish a causal association between an event and Ad26.COV2.S. For any potential new safety signal, the sponsor systematically reviews available pre-clinical, clinical, spontaneous reports and real-world data which continue to accrue at a rapid pace. The following describes ongoing evaluations of reported events where a causal association with vaccination has not been established.

As of 31 August 2021, an estimated of 33.5 million doses of Ad26.COV2.S have been administered globally (US 14.3, EEA 13.6, Others 5.6 million[1]). The data from the Phase 3 double-blind phase of the randomized, placebo-controlled trials are provided and the cutoff dates are as follows:

- VAC31518COV3001 (referred to as COV3001) - 09 July 2021
- VAC31518COV3009 (referred to as COV3009) - 25 June 2021.

2.1. Encephalitis and Acute Disseminated Encephalomyelitis (ADEM)

Encephalitis, including cases of ADEM, was reported in the post marketing setting.

As of 31 August 2021, 36 cases (approximately 1.07 per million doses administered) reporting Encephalitis events (Standardised MedDRA query [SMQ]: Noninfectious encephalitis [narrow]) were reported from post-marketing sources. Of the cases reporting sex, 57% concerned females. Among cases with latency information, reported TTO was within 1 week in 48.5% (16/33) cases, and within 2 weeks in.81.8% (27/33) cases. The median and mean TTO was 8 and 9 days, respectively.

Clinical study data from 2 large, double-blind, randomized, placebo-controlled trials have shown no imbalance in rates between Ad26.COV2.S and placebo for Encephalitis (including ADEM). In study COV3001, there were 3 participants with events of interest in the Ad26.COV2.S group (N=

[1] Estimates of exposure are based upon the number of administered doses reported from Centers for Disease Control and Prevention (CDC) for the United States (US), European Centre for Disease Prevention and Control (ECDC) for European Economic Area (EEA) countries, Korea Disease Control and Prevention Agency (KDCA for South Korea, and Ministério da Saúde for Brazil.

21,894) and 3 participants in the placebo group (N=21,882) during the entire double-blind period. In study COV3009, there were no participants with events of interest in the Ad26.COV2.S group (n=15,705) and 2 participants with events of interest in the placebo group (n=15,588) during double-blind period in study COV3009.

Current Sponsor Position and Risk Mitigation Activities:

Based on the review of the totality of data from post marketing cases in the sponsor's safety database and clinical study data, there is insufficient evidence to establish a causal relationship between Ad26.COV2.S and this event. The sponsor will continue to monitor this event through ongoing pharmacovigilance activities.

2.2. Acute Hepatic Failure

Acute hepatic failure was reported in the post marketing setting.

As of 24 August 2021, 28 cases (approximately 0.8 per million doses administered) from post-marketing sources, including spontaneous and solicited cases have been reported. Ten cases concerned males, 15 females, and 3 did not report the sex. The age range was 27 to 78 years. The mean and median TTO was 17.8 days and 14 days, respectively.

In study COV3001, 3 events of interest in the Ad26.COV2.S group (N= 21,894) and 3 events in the placebo group (N=21,882) during the entire double-blind period. In study COV3009, there were 3 events of interest in the Ad26.COV2.S group (N = 15,705) and no events in the placebo group (N= 15,588) during the entire double-blind period. In an open-label study COV3012, 2 cases of acute hepatic failure were reported and both cases were assessed as unrelated to Ad26.COV2.S by the investigators.

Current Sponsor Position and Risk Mitigation Activities:

Based on the review of the totality of data from post marketing cases in the sponsor's safety database and clinical study data, no new safety concern was identified for acute hepatic failure. The sponsor will continue to monitor this event through ongoing pharmacovigilance activities.

2.3. Flares of Autoimmune Disorders

Events related to flares of autoimmune disorders have been reported in the post marketing setting. There is also literature available about newly diagnosed or flares of autoimmune diseases following vaccination with mRNA-based vaccines against SARS-CoV-2 (psoriasis, cutaneous lupus erythematosus, and IgG4 related nephritis) and Astra-Zeneca vaccine AZD1222 (minimal change disease) (Morlidge 2021, Masset 2021, Krajewski 2021, Niebel 2021).

As of 31 August 2021, 224 cases (approximately 6.6 cases per million doses administered) from post marketing sources, including spontaneous and solicited cases have been reported. The majority (77%) of the cases were reported in females. In cases reporting age, the range was 18 to 76 years, and the mean and median ages were 50 years and 52 years, respectively.

In study COV3001, there were 18 participants (0.1%) who reported events of immune-mediated or autoimmune disorders in the Ad26.COV2.S group (n=21,894) compared with 16 participants

(0.1%) in the placebo group (n=21,882). In study COV3009, there were 9 participants (0.1%) who reported events of immune-mediated or autoimmune disorders in the Ad26.COV2.S group (n=15,705) and in the placebo group (n=15,588).

Current Sponsor Position and Risk Mitigation Activities:

Based on the review of the totality of data from post marketing cases in the sponsor's safety database and clinical study data, no new safety concern was identified for autoimmune disorders. The sponsor will continue to monitor this event through ongoing pharmacovigilance activities.

2.4. Thromboembolic Events

Thromboembolic and thrombotic (venous) events (VTEs) are Events of Interest and are included as an Important Potential Risk in Pharmacovigilance Plan for Ad26.COV2.S.

As of 24 August 2021, 2,598 cases (approximately 77.4 per million doses administered) reporting VTE were retrieved from post marketing sources. Among the cases in which sex was reported, 56.6% were females. Among the patients where age was reported, 1 concerned a 17-year-old (off-label use), 309 (13%) were in the age range of 18 to 35 years, 647 (27%) were in 36 to 50 years, 801 (34%) were in 51 to 64 years, and 614 (26%) were ≥65 years. In 226 cases, the age was not reported. The mean and median TTO was 18.5 days and 13 days, respectively.

The results of the most recent sequential, rapid-cycle RWD analytics utilizing US Health Verity marketplace health claims database (n=416,754 persons exposed to Ad26.COV2.S) indicate a slightly increased risk (relative risk of 1.4- 1.5) of Pulmonary Embolism (PE) within the 28-, 42- and 90-day risk windows using the self-controlled case series (SCCS) design. A slightly increased risk (relative risk around 1.3) of PE was observed within the 42- and 90-day risk windows, as well as with all available post-exposure time at risk, using the comparative cohort design. No increased risk was observed for Deep Vein Thrombosis (DVT), in any risk window or with either design. A slightly increased risk (relative risk of 1.17-1.33) of VTE (composite endpoint [DVT or PE]) within the 90-day risk window was observed using both SCCS and comparative cohort designs. Across these analyses, the upper bound of the 95% confidence interval (CI) was lower than 2, indicating that it is unlikely that any true risk of PE or VTE composite following Janssen vaccine Ad26.COV2.S would exceed a relative risk of 2.

While the RWD analytics specification was robust including SCCS and comparative cohort designs, it needs to be interpreted cautiously as part of routine and interim pharmacovigilance activity considering important limitations and further assessment with more complete outcome ascertainment and replication with additional RWD sources is needed to confirm any finding.

For information related to VTEs reported in clinical studies COV3001 and COV3009, please refer to Section 4.2.2.9 of the Briefing Material for the VRBPAC meeting on 15 October (submitted to the FDA on 07 October 2021).

Current Sponsor Position and Risk Mitigation Activities:

Based on the review of the totality of data from post marketing cases in the sponsor's safety database, clinical study data and real-world data, there is insufficient evidence to establish a causal

relationship between Ad26.COV2.S and thromboembolic events. The sponsor will continue to monitor these events through ongoing pharmacovigilance activities including post-authorization safety studies (PASS).

2.5. Vasculitis

Cases of vasculitis have been reported in the postmarketing setting.

As of 31 August 2021, 61 cases with PT Vasculitis (approximately 1.8 cases per million doses administered) from post marketing sources, including spontaneous and solicited cases have been received by the sponsor. There was no significant difference between the ratio of males to females; and in cases reporting age, the range was 17 to 94 years, and the mean and median ages were 51.8 years and 55.5 years, respectively. Time to onset (TTO) from the administration of Ad26.COV2.S was within 1-2 weeks in 82.3% of the events. The median TTO was 8 days.

There were no cases of vasculitis reported in the 2 large, double-blind, randomized, placebo-controlled studies COV3001 and COV3009.

Current Sponsor Position and Risk Mitigation Activities:

Based on the review of the totality of data from post marketing cases in the sponsor's safety database and clinical study data, there is insufficient evidence to establish a causal relationship between Ad26.COV2.S and this event. The sponsor will continue to monitor this event through ongoing pharmacovigilance activities.

2.6. Transverse Myelitis

Transverse Myelitis was reported in the post marketing setting.

As of 24 August 2021, 39 cases (approximately 1.16 per million doses administered) from post marketing sources, including spontaneous and solicited cases have been received by the sponsor. The male: female ratio of reported cases was comparable, and mean and median TTO were 18.8 days and 14 days, respectively.

In the clinical studies (COV3001 and COV3009) no events of transverse myelitis have been reported in the Ad26.COV2.S group.

Current Sponsor Position and Risk Mitigation Activities:

Based on the review of the totality of data from post marketing cases in the sponsor's safety database and clinical study data, there is insufficient evidence to establish a causal relationship between Ad26.COV2.S and this event. The sponsor will continue to monitor this event through ongoing pharmacovigilance activities.

2.7. Cardiomyopathy

Cardiomyopathy was reported in the post marketing setting.

As of 24 August 2021, 23 cases (approximately 0.7 per million doses administered) from post marketing sources, including spontaneous and solicited cases have been received by the sponsor;

65% were reported in men and the age range was 21 to 79 years. The mean and median TTO from the time of vaccination were 22.1 and 13.5 days respectively.

In studies COV3001 and COV3009, there were no events of cardiomyopathy reported in the Ad26.COV2.S groups. Two events were reported in the placebo group in study COV3001.

Current Sponsor Position and Risk Mitigation Activities:

The overall safety information available for Ad26.COV2.S from clinical studies and medical review of post marketing cases has not identified a safety concern for cardiomyopathy. The sponsor will continue to monitor this event through ongoing pharmacovigilance activities.

2.8. Immune Thrombocytopenia

Immune thrombocytopenia (ITP) was reported in the post marketing setting.

As of 24 August 2021, 240 spontaneous cases (approximately 7.1 per million doses distributed) from post marketing sources, including spontaneous and solicited cases have been received by the sponsor. Of these 240 cases, 110 concerned females and 130 males with an age range of 19 to 94 years. The mean and median TTO was 14.3 days and 10 days, respectively.

The results from the most recent sequential, rapid-cycle RWD analyses utilizing US Health Verity marketplace health claims database (n=416,754 persons exposed to Ad26.COV2.S) indicate a slightly increased risk (relative risk of 1.86 to 2.22) of ITP within the 28-, 42- and 90-day risk windows using the SCCS and comparative cohort designs.

While the RWD analytics specification was robust including SCCS and comparative cohort designs, it needs to be interpreted cautiously as part of routine and interim pharmacovigilance activity considering important limitations; further assessment with more complete outcome ascertainment and replication with additional RWD sources is needed to confirm any finding.

No events of immune thrombocytopenia were reported in the Ad26.COV2.S groups in clinical trials.

Current Sponsor Position and Risk Mitigation Activities:

Based on the review of the totality of data from post marketing cases in the sponsor's safety database, clinical study data and real-world data, there is insufficient evidence to establish a causal relationship between Ad26.COV2.S and this event. The sponsor will continue to monitor this event through ongoing pharmacovigilance activities including PASS.

2.9. Myocarditis and Pericarditis

Myocarditis and Pericarditis have been reported in the post marketing setting.

As of 31 August 2021, 135 cases (approximately 4 per million doses administered) reporting cardiac inflammatory disorders, including myocarditis and pericarditis were retrieved from post marketing sources, including spontaneous and solicited cases. The male: female ratio was 2:1 for the cases that sex was reported, and the age ranged from 18 to 76 years. The mean and median TTO for pericarditis and myocarditis was 17.9 days and 8 days, respectively.

During the double-blind phase in COV3001, pericarditis was reported in 1 participant in the Ad26.COV2.S group and no participants in the placebo group. No events of myocarditis were reported in study COV3001 during the double-blind phase period. In the double-blind phase of COV3009, 1 event of pericarditis was reported in each group (Ad26.COV2.S and placebo), 1 event of myocarditis was reported in the placebo group.

Current Sponsor Position and Risk Mitigation Activities:

Based on evaluation of the data, the sponsor does not consider myocarditis and pericarditis as a safety concern at this time. The sponsor will continue to closely monitor these events through ongoing pharmacovigilance activities.

3. REFERENCES

Krajewski PK, Matusiak Ł, Szepietowski JC. Psoriasis flare-up associated with second dose of Pfizer-BioNTech BNT16B2b2 COVID-19 mRNA vaccine. J Eur Acad Dermatol Venereol. 2021;35(10).

Niebel D, Novak N, Wilhelmi J, et al. Cutaneous adverse reactions to covid-19 vaccines: insights from an immuno-dermatological perspective. Vaccines. 2021;9(9):944.

Masset C, Kervella D, Kandel-Aznar C, Fantou A, Blancho G, Hamidou M. Relapse of IgG4-related nephritis following mRNA COVID-19 vaccine. Kidney International. 2021;100(2):465-466.

Morlidge C, El-Kateb S, Jeevaratnam P, Thompson B. Relapse of minimal change disease following the AstraZeneca COVID-19 vaccine. Kidney Int. 2021;100(2):459.