VidPrevtyn Beta: Periodic safety update report assessment

10 November 2022 to 9 May 2023

This document consists of:

1. The PRAC assessment report of the VidPrevtyn Beta periodic safety update report (PSUR) covering the period 10 November 2022 to 9 May 2023, and;
2. The VidPrevtyn Beta PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.

EMA/PRAC/516634/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00011035/202305

Active substance(s): SARS-CoV-2, B.1.351 variant, prefusion Spike delta TM protein, recombinant

Period covered by the PSUR: 10/11/2022 To: 09/05/2023

Centrally authorised Medicinal product(s): For presentations: See Annex A	Marketing Authorisation Holder
VidPrevtyn Beta	Sanofi Pasteur

Status of this report and steps taken for the assessment

Current step	Description	Planned date	Actual Date
☐	Start of procedure:	3 August 2023	3 August 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	2 October 2023	2 October 2023
☐	MS/PRAC members and MAH comments	1 November 2023	31 October 2023
☐	PRAC Rapporteur's updated assessment report following comments	16 November 2023	16 November 2023
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	30 November 2023	30 November 2023

Procedure resources	
PRAC Rapporteur	Name: Jana Lukačišinová Tel: Email:
Contact person - PRAC Rapporteur	Name Tel: Email:
Assessor – PRAC Rapporteur	Name Tel: Email: Name Tel: Email:
EMA Procedure Lead	Name Tel: Email:
EMA Procedure Assistant	Name Tel: Email:

Abbreviations:

Ab: Antibody
ADE: Antibody Dependent Enhancement
ADR: Adverse Drug Reaction
AE: Adverse Event
AESI: Adverse Event of Special Interest
ANCA: Antineutrophil Cytoplasmic Antibody
APHP: Assistance Publique Hôpitaux Paris
AR: Adverse Reaction
AS03: Adjuvant System 03
BCCD: Brighton Collaboration Case Definition
BMI: Body Mass Index
CDC: Centers for Disease Control and Prevention
CHMP: Committee for Medicinal Products for Human Use
CI: Confidence Interval
CNS: Central Nervous System
COPD: Chronic Obstructive Pulmonary Disease
CoV-1: Coronavirus-1
CoV-2: Coronavirus-2
CoV-2 preS dTM: CoV-2 Prefusion Spike Delta TM
COVID: Coronavirus Disease
COVID-19: Coronavirus Disease-2019
CT: Computerized Tomography
CTAP: Coronavirus Treatment Acceleration Program
CVD: Cardiovascular Disorders
C-VIPER: Coronavirus Disease-2019 Vaccines International Pregnancy Exposure Registry
CVST: Cerebral Venous Sinus Thrombosis
DART: Developmental and Reproductive Toxicity
DIBD: Development International Birth Date
DLP: Data Lock Point
DRC: Democratic Republic of the Congo
DRCI: Direction de la Recherche Clinique et de l'Innovation
DVT: Deep Vein Thrombosis
EC: European Commission
ECDC: European Centre for Disease Prevention and Control
ECG: Electrocardiogram
ECMO: Extracorporeal Membrane Oxygenation
EEA: European Economic Area
EMA: European Medicines Agency
ESC: Externally Sponsored Collaborative
ESDR: Early Safety Data Review
EU: European Union
EUL: Emergency Use Listing
Fc: Fragment Crystallizable
FDA: Food and Drug Administration
GMT: Geometric Mean Titer

GMTR: Geometric Mean Titer Ratio
GPV: Global Pharmacovigilance
GSK: GlaxoSmithKline
GVP: Good Pharmacovigilance Practices
HCP: Healthcare Professional
HIV: Human Immunodeficiency Virus
IBD: International Birth Date
ICH: International Conference on Harmonisation
ICSR: Individual Case Safety Report
ICU: Intensive Care Unit
IMV: Invasive Mechanical Ventilation
IND: Investigational New Drug
IRR: Incidence Rate Ratio
LMP: Last Menstrual Period
MA: Marketing Authorization
MAAE: Medically Attended Adverse Event
mAb: Monoclonal Antibody
MAH: Marketing Authorization Holder
MedDRA: Medical Dictionary for Regulatory Activities
MHRA: Medicines and Healthcare products Regulatory Agency
MINOCA: Myocardial Infarction with Nonobstructive Coronary Arteries
MRI: Magnetic Resonance Imaging
mRNA: Messenger Ribonucleic Acid
NHP: Non-Human Primates
NIAID: National Institute of Allergy and Infectious Diseases
NOS: Not Otherwise Specified
O/E: Observed Versus Expected
PASS: Post-Authorization Safety Studies
PBRER: Periodic Benefit Risk Evaluation Report
PC: Product Complaint
PF4: Platelet Factor 4
PK: Pharmacokinetic
PRAC: Pharmacovigilance Risk Assessment Committee
PT: Preferred Term
PV: Pharmacovigilance
RA: Regulatory Authority
RMM: Risk Minimization Measures
RMP: Risk Management Plan
ROR: Reporting Odds Ratio
RSI: Reference Safety Information
S: Spike
SAE: Serious Adverse Event
SAR: Serious Adverse Reaction
SARS: Severe Acute Respiratory Syndrome
SDEA: Safety Data Exchange Agreement
SLE: Systemic Lupus Erythematosus
SmPC: Summary of Product Characteristics

SMQ: Standardized MedDRA Queries
suPAR: Soluble Urokinase Plasminogen Activator Receptor
TIA: Transient Ischemic Attack
TTO: Time to Onset
UAE: United Arab Emirates
UK: United Kingdom
UN: United Nation
UNK MFR: Unknown Manufacturer
VAED: Vaccine Associated Enhanced Disease
VAERD: Vaccine Associated Enhanced Respiratory Disease
VE: Vaccine Efficacy
VOC: Variant of Concern
WHO: World Health Organization

Table of contents

1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for SARS-CoV-2, B.1.351 variant, prefusion Spike delta TM protein, recombinant.

2. Assessment conclusions and actions

This is the 1st single assessment of the PSUR for SARS-CoV-2, B.1.351 variant, prefusion Spike delta TM protein, recombinant containing product (Vidprevtyn Beta) covering the period from 10 November 2022 to 9 May 2023.

Vidprevtyn Beta is indicated as a booster for active immunization to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine.

Vidprevtyn Beta is an adjuvanted vaccine composed of the soluble trimeric SARS-CoV-2 recombinant S protein (B.1.351 strain) stabilized in its prefusion conformation and deleted of its transmembrane and intracellular domains. Vidprevtyn Beta is available as solution and emulsion for emulsion for injection. One dose (0.5 mL) contains five micrograms of recombinant SARS-CoV-2 S protein (B.1.351 strain) formulated with adjuvant system 03 adjuvant and is administered intramuscularly.

The International Birth Date (IBD) of Vidprevtyn Beta is 10 November 2022 when it was first authorised in the EU. During this interval period, a marketing authorization was granted in the UK on 20 December 2022. Vidprevtyn Beta is currently marketed in 4 EU member states (AT, FR, IT, PT) and 1 non-EU state (UK) and is approved in a total of 32 countries worldwide.

The MAH provided the exposure data based on administered doses. The total number of doses of Vidprevtyn Beta administered in the EU is approximately 6 920 up to 20 April 2023. The total number of doses in England could be estimated to be approximately 1 630 039 up to 7 May 2023.

During this reporting period, no new signals were identified. However, according to the late-breaking information, one signal on allergic including anaphylactic reactions was opened and the MAH submitted a variation related to hypersensitivity reactions (EMEA/H/C/005754/II/0006). Information about this signal and the outcome of the procedure will be provided by MAH in the next PSUR.

No new safety information was identified by the MAH and no actions were taken for safety reasons during this reporting interval. Nevertheless, a total of 40 cases concerning dizziness in the first days after vaccination were reported, 16 of which were serious of which 9 had a close temporal relationship and simultaneous occurrence of other possible symptoms of reactogenicity. Within the responses to the RSI, the MAH provided an updated review of dizziness from the post-marketing period until 30 June 2023: 50 cases were reported cumulatively. Considering the above as well as the data collected during the clinical trials, the PRAC recommends to update the product information to include dizziness with a frequency rare.

The MAH is requested to assess all AESI listed in the RMP version 1.0 in the next PSUR, including O/E analysis and to determine the range of AESI risk window based on acceptable sources.

Moreover, the MAH should make all efforts to obtain the maximum available information on the reported cases during the follow-ups and to discuss the updated cases in view of new information including causality assessment in next PSURs.

The benefit-risk balance of Vidprevtyn Beta remains unchanged in its approved indications.

3. Recommendations

Based on the PRAC Rapporteur review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing SARS-CoV-2, B.1.351 variant, prefusion Spike delta TM protein, recombinant remains unchanged but recommends that the terms of the marketing authorisation(s) should be varied as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

In view of available data on dizziness from clinical trials, spontaneous reports, including in some cases a close temporal relationship, the PRAC considers a causal relationship between SARS-CoV-2, B.1.351 variant, prefusion Spike delta TM protein, recombinant and dizziness is at least a reasonable possibility. The PRAC concluded that the product information of products containing SARS-CoV-2, B.1.351 variant, prefusion Spike delta TM protein, recombinant should be amended accordingly.

Precise scope:

Update of section 4.8 of the SmPC to add the adverse reaction dizziness with a frequency rare. The Package leaflet is updated accordingly.

The following changes to the product information of medicinal products containing SARS-CoV-2, B.1.351 variant, prefusion Spike delta TM protein, recombinant are recommended (new text **underlined and in bold,** deleted text ~~strike-through~~):

Summary of Product Characteristics

- Section 4.8

The following adverse reaction should be added under the SOC Nervous system disorders with a frequency rare:

Dizziness

Package Leaflet

- 4. Possible side effects

Rare

- **Dizziness**

4. Issues to be addressed in the next PSUR or as a post-authorisation measure (PAM) or as part of a subsequent RMP update

The MAH(s) should also address the following issues in the next PSUR:

Data analysis and presentation:

1. For **literature screening,** the MAH should focus only on the scientific literature concerning vaccines of the same or similar platform.

2. The MAH is requested to follow the "List of AESI intended to be collected and closely monitored in the post marketing setting" in the RMP version 1.0. **All AESI** (including acute septic arthritis, rheumatoid arthritis, type 1 diabetes mellitus, heart failure, stress cardiomyopathy, arrhythmias, anosmia and ageusia) should be presented in the section "Requests based on the core-RMP guidance" of the submitted PSUR. Assessment should be provided including O/E analysis. For AESI omitted within this PSUR submission, cases reported during the current and next PSUR period should be included.
3. **Risk window:**
   The MAH is requested to:
   i) extent the primary risk window of **myocarditis/pericarditis** for purposes of O/E analysis to 28 days as is stated in the protocol V2.2 for Rapid safety assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources, ENCEPP;
   ii) extend the primary risk window of **acute liver injury** for purposes of O/E analysis to 180 days in next PSURs in line with the protocol V2.2. for Rapid safety assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources, ENCEPP;
   iii) extend the primary risk window of **acute respiratory distress syndrome** for purposes of O/E analysis to 6 weeks according to the SPEAC AESI Case Definition Companion Guide for ARDS (Version 1.0);
   iv) extend the primary risk window of **thrombosis with thrombocytopenia syndrome** to 28 days in line with the protocol V2.2. for Rapid safety assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources. The MAH is requested to revise or remove the secondary risk window;
   v) revise the risk window of **microangiopathy and thrombotic microangiopathy** for purposes of O/E analysis;
   vi) complete the risk window of **acute pancreatitis, subacute thyroiditis and Kawasaki disease, rhabdomyolysis** for purposes of O/E analysis;
   vii) correct the secondary risk window of **narcolepsy** in line with the protocol V2.2. for Rapid safety assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources, ENCEPP;
   viii) extend the primary risk window of **AKI and glomerulonephritis** for purposes of O/E analysis to 180 days in line with the protocol V2.2. for Rapid safety assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources, ENCEPP;
   ix) harmonise the risk window of **thrombotic thrombocytopenic purpura** with the risk window determined for immune thrombocytopaenia.
4. The MAH should take into account the character of the reactions and the non-serious cases should be described in detail when appropriate.
5. The MAH is requested to discuss neuropathies/polyneuropathies, demyelinating disorders incl. MS, optic neuritis and seizures under the section of neurological AESI.
6. The MAH is requested to discuss myasthenia gravis under the section of immune mediated AESI and fibromyalgia under the section of musculoskeletal AESI together with rhabdomyolysis.
7. All AESI should be presented in one integrated overview and not split according to the origin of the request (EMA, MHRA, RMP).
8. The terms immune thrombocytopenic purpura and autoimmune thrombocytopaenia fall under the term immune thrombocytopaenia and should be discussed in the section of immune thrombocytopaenia.
9. The MAH is requested to provide the review of the missing cases and discuss ischaemic and haemorrhagic stroke separately.

10. The MAH is requested to provide a review of 6 stroke cases which were not assessed in the current PSUR.
11. The MAH is requested to provide a detailed description how the causal assessment between VidPrevtyn Beta and vaccination failure is performed.

Follow-up process:

12. Generally, the MAH **is requested to make a maximum effort in order to obtain all available information about the reported cases during the follow-ups** and to discuss the updated cases in view of the new information including causality assessment. **This is of utmost importance for fatal cases. Newly obtained information should be presented.**
13. The MAH is requested to provide a description how case follow-ups are processed depending on seriousness and listedness of the AEs.

Targeted follow up request:

14. The MAH is requested to submit a re-evaluation of **all cases reporting 'Allergic and anaphylactic reactions'** with an outcome as ongoing or not recovered, once further information (on the patient's underlying disease conditions, past medical and drug history, concurrent illnesses, and concomitant medications) is available.
15. The MAH is requested to make an effort to obtain the follow-up information for the following cases and discuss the updated information:

i) **Case** [redacted] **concerning myocarditis;**
ii) **case** [redacted] **reporting respiratory arrest, seizures and anaphylaxis;**
iii) **case** [redacted] **reporting myocardial infarction with nonobstructive coronary arteries** including clinical course, results of the performed examinations and diagnosis;
iv) **case** [redacted] **of cerebral venous sinus thrombosis**;
v) **case** [redacted] **concerning stroke** including the results of CT/MR and other relevant examinations and tests.
vi) **case** [redacted] **concerning gout**
vii) **case** [redacted] **concerning single organ cutaneous vasculitis** including the results of biopsy, additional laboratory tests, information about possible involvement of other organs, information about concomitant medications and/or other comorbidities.
viii) **case** [redacted] **reporting retinal haemorrhage;**
ix) **case** [redacted] concerning dizziness including information about examinations, laboratory test, diagnosis and treatment provided during hospitalisation.
x) **case** [redacted] **concerning dizziness, unsteadiness, memory loss and hospitalisation**
xi) **fatal case** [redacted]

5. PSUR frequency

☒No changes to the PSUR frequency

The current **6**-month frequency for the submission of PSURs should remain unchanged.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

VidPrevtyn Beta (COVID-19 vaccine (recombinant, adjuvanted)) is a recombinant protein vaccine derived from the SARS CoV-2 prefusion Spike (S) delta TM (CoV-2 preS dTM) (B.1.351 strain). VidPrevtyn Beta is an adjuvanted vaccine composed of the soluble trimeric SARS-CoV-2 recombinant S protein (B.1.351 strain) stabilized in its prefusion conformation and deleted of its transmembrane and intracellular domains. The combination of antigen and adjuvant enhances the magnitude of immune response, which may contribute to protection against COVID-19.

VidPrevtyn Beta is available as solution and emulsion for emulsion for injection. The volume after mixing one vial of antigen solution (2.5 mL) with one vial of adjuvant emulsion (2.5 mL) allows for delivery of 10 doses of vaccine (0.5 mL per dose). One dose (0.5 mL) of VidPrevtyn Beta contains five micrograms of recombinant SARS-CoV-2 S protein (B.1.351 strain) formulated with adjuvant system 03 (AS03) adjuvant for booster vaccination and is administered intramuscularly.

VidPrevtyn Beta is approved as a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults who have previously received a messenger ribonucleic acid (mRNA) or adenoviral vector COVID-19 vaccine.

In individuals 18 years of age and older, VidPrevtyn Beta is administered intramuscularly as a single dose of 0.5 mL at least four months after a previous COVID-19 vaccine. COVID-19 vaccine (recombinant, adjuvanted) may be given once as a booster to adults that have received prior vaccination series with either mRNA or adenoviral vector COVID-19 vaccines.

No dose adjustment is required in elderly individuals ≥ 65 years of age and the vaccine is not indicated in paediatric population.

This is the 1st single assessment of PSUR submitted for VidPrevtyn Beta (COVID-19 vaccine (recombinant, adjuvanted)), the covered period of this PSUSA is from 10 November 2022 to 09 May 2023.

1 unique PSUR was submitted, VidPrevtyn Beta is a centrally authorised product.

Product	Formulation, pharmaceutical forms & strengths	MAH	IBD/ EUBD	Interval period	Cumulative period
Vidprevtyn Beta	Solution and emulsion for emulsion for injection, one dose (0.5 mL) contains 5 micrograms	Sanofi Pasteur	10/11/2022	10/11/2022-09/05/2023	10/11/2022-09/05/2023

The MAH did not propose any changes to the product information.

1.2. Worldwide marketing authorisation status

VidPrevtyn Beta was first authorised in EU on 10 November 2022. In the EU, VidPrevtyn Beta has been marketed in Austria, France, Italy and Portugal.

During the period covered by this report, a MA for COVID-19 vaccine (recombinant, adjuvanted) was granted in Great Britain on 20 December 2022.

It is approved in a total of 32 countries.

Approved posology: COVID-19 vaccine (recombinant, adjuvanted) is administered intramuscularly as a single dose of 0.5 mL at least four months after a previous COVID-19 vaccine. COVID-19 vaccine (recombinant, adjuvanted) may be given once as a booster to adults that have received prior vaccination series with either mRNA or adenoviral vector COVID-19 vaccines. No dose adjustment is required in elderly individuals ≥ 65 years of age. COVID-19 vaccine (recombinant, adjuvanted) is not indicated in paediatric population.

Rapporteur assessment comment:

The information is acknowledged.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

No actions were taken during the reporting interval for safety reasons related to either investigational uses or marketing experience by the MAH, sponsors of clinical trial(s), Regulatory Authorities (RAs), data monitoring committees, or ethics committees that had a significant influence on the risk-benefit profile of the approved medicinal product; and/or an impact on the conduct of a specific clinical trial(s) or on the overall clinical development program.

Rapporteur assessment comment:

No actions were taken for safety reasons during the reporting period.

1.3.2. Changes to reference safety information

The EU summary of product characteristics (SmPC) for COVID-19 vaccine (recombinant, adjuvanted), version 1.0 dated 10 November 2022 was the reference safety information (RSI) valid at the beginning of the PBRER period.

No safety related changes were made in the RSI during the period covered by this report.

Rapporteur assessment comment:

No safety related changes were made in the RSI during the period covered by this report.

1.3.3. Estimated exposure and use patterns

MAH / Product	[redacted] trials (subjects)	Exposure post-marketing experience	
	Cumulative	Cumulative	Interval
Vidprevtyn Beta	2949	1 636 959	1 636 959

Clinical Trials

The cumulative exposure to COVID-19 vaccine (recombinant, adjuvanted), in interventional clinical trials sponsored by the MAH is estimated to be 17 132 participants. Cumulative exposure to COVID-19 vaccine (recombinant, adjuvanted), is displayed as SARS-CoV-2 preS dTM monovalent and bivalent.

Table 1 - Estimated cumulative participant exposure to SARS-CoV-2 recombinant protein monovalent and bivalent vaccines in all Phases 1 to 3 clinical studies

Treatment	Number of Participants
One injection	
SARS-CoV-2 preS dTM Monovalent D614	2148
SARS-CoV-2 preS dTM Monovalent B.1.351	2949
SARS-CoV-2 preS dTM Bivalent D614+B.1.351	676
Placebo	1061
Two injections	
SARS-CoV-2 preS dTM Monovalent D614	7636
SARS-CoV-2 preS dTM Bivalent D614+B.1.351	6057
Placebo/Placebo	10 783
Total:	
SARS-CoV-2 preS dTM Monovalent and Bivalent	17 132
Placebo	11 844

Data as of 09-May-2023 from ongoing studies: VAT00001, VAT00002, and VAT00008.
VAT00002 and VAT00008 participants may choose to receive 1 booster injection after a primary series vaccination.
VAT00008 placebo participants may choose to receive a primary series vaccination (if unvaccinated) or 1 booster injection (if vaccinated) after meeting specific criteria.
Participants who received more than one treatment are counted in each of the treatments, as received injections.

As of 09 May 2023 (DLP), a total of 2949 participants received the monovalent beta B.1.351 booster vaccine.

Post-marketing experience

Exposure data based on administered doses when available have been retrieved from publicly available data sources such as national or international COVID-19 vaccination trackers. For EU/ European Economic Area (EEA) countries, administered doses are retrieved from the European Centre for Disease Prevention and Control (ECDC) Vaccine Tracker.

The number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered per European country and age group as of 20 April 2023 is presented below in table 2:

Table 2 - Number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in European Union by country and age group through 20 April 2023

Country	Europe								Total
	Unknown	0-17	18-24	25-49	50-59	60-69	70-79	80+	
AUSTRIA	0	0	12	93	49	50	37	21	262

Country	Europe								Total
	Unknown	0-17	18-24	25-49	50-59	60-69	70-79	80+	
FRANCE	6456	0	0	0	0	0	0	0	6456
ITALY	0	0	0	46	16	42	18	10	132
PORTUGAL	0	0	1	21	14	17	14	3	70
Total	6456	0	13	160	79	109	69	34	6920

For the United Kingdom (UK), COVID-19 vaccine (recombinant, adjuvanted) administered doses are received directly from the Department for Business, Energy, and Industrial Strategy from the UK government. Of note, COVID-19 vaccine (recombinant, adjuvanted) doses administered in Scotland, Wales and North Ireland are not included. The number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in England per age group as of 07 May 2023 are presented in Table 3.

Table 3 - Number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in England per age group as of 07 May 2023

Country	UK									Total
	Unknown	0-17	18-29	30-39	40-49	50-59	60-69	70-79	80+	
	9	5	128	264	636	1971	13 046	653 305	960 675	1 630 039

UK: United Kingdom.

The total number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered is approximately 1 636 959 up to 07 May 2023.

Post-approval use in special populations

The MAH does not have access to exposure regarding use in special populations from the IBD of COVID-19 vaccine (recombinant, adjuvanted) through the DLP of the PBRER except for elderly population as more than 99.8% of the exposure in England is in elderly population which represents 1 627 026 doses administered (60 years and older (Department for Business, Energy, and Industrial Strategy from the UK government).

Use in the pregnancy and breast-feeding is being studied in non-interventional studies with study ID VAT00012 and VAT00007 (not yet initiated). No exposure in these studies. In addition, feasibility of the study VAT00006 has been re-assessed. It has been considered that VAT00006 is no longer an option, and it has been cancelled. The rationale of this decision has been included in an Answers to Questions document submitted to European Medicines Agency (EMA) through a procedure (EMEA/H/C/005754/MEA/001). According to the review timetable, the Committee for Medicinal Products for Human Use (CHMP) outcome is expected on 20 July 2023.

Use in the immuno-compromised subjects is being studied in externally sponsored collaborative (ESC) studies with study ID VAT00027, VAT00028 and in non-interventional study ID VAT00007 (not yet

initiated). Cumulative exposure in these studies is 32 participants.

Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders [CVD]) and Use in subjects with autoimmune or inflammatory disorders is being studied in non-interventional studies with study ID VAT00007 (not yet initiated). No exposure in this study.

Use in elderly:

In the UK, country where most doses were administered, the local recommendation is targeting the population aged 75-year-old and above. Thus, most of the post-marketing cases are reported in the older population with approximately 86% of cases reported in 70-year-old and above. Safety data presented in this PBRER can be considered as reflecting the safety data in this age group.

Rapporteur assessment comment:

1 636 959 doses were administrated during the covered period. Out of those, 6920 doses were administrated in EU and 1 630 039 doses in England, mostly in elderly due to local recommendations. Of note, the doses administered in Scotland, Wales and North Ireland are not included in the PSUR which is not further justified. The MAH is requested to provide information why the exposures in Scotland, Wales and North Ireland were not included in the PSUR. ***RSI***

Immuno-compromised subjects are studied in 3 studies (VAT00027, VAT00028, VAT00007) with cumulative exposure of 32 participants.

No exposure was observed in pregnant and breast-feeding women, in frail subjects with unstable health conditions and co-morbidities and in subjects with autoimmune or inflammatory disorders.

1.3.4. Data in summary tabulations

Total number of cases and ADRs received from post-marketing data sources by each MAH

MAH/Product	Interval cases	Cumulative cases	Interval adverse reactions	Cumulative adverse reactions
VidPrevtyn Beta	519-	519-	1 227	1 227

A total of 902 cumulative SAEs were reported from MAH-sponsored clinical trials.

A total of 1227 cumulative ARs have been reported, all of which were reported during the present reporting period for COVID-19 vaccine (recombinant, adjuvanted).

A total of 19 cumulative ARs have been reported, all of which were reported during the present reporting period for an unknown manufacturer (UNK MFR).

Rapporteur assessment comment:

A total of 902 cumulative SAEs were reported from the MAH sponsored clinical trials and 1227 ADRs cumulatively have been reported during the reporting interval from post-marketing experience.

The MAH provided a review of reported cases separated into 3 sections, i.e., Requests based on the core-

RMP guidance, Additional requests from EMA, and the Requests of MHRA. However, the current ordering is very confusing. It is not clarified by the MAH, why all AESI stated in the list of AESI in the RMP version 1.0 are not included in the section "Requests based on the core-RMP guidance" and why several AESI are not discussed in PSUR at all. Please see section 2.3 for a detailed assessment and PRAC Rapp's request to the next PSUR.

A new important safety information was identified by the Rapp regarding the ADR of dizziness. A total of 40 cases concerning dizziness were reported during the covered period as well as cumulatively. 16 (40%) of all these cases were reported as serious and 24 cases as non-serious. The MAH provided the individual review of the serious cases only, even though dizziness is usually non-serious, subjective, temporary, self-limited, short-term reaction and most cases being reported as non-serious can be expected.

However, in all described cases, dizziness occurred in the first days after vaccination with VidPrevtyn Beta. Moreover, the Rapp concluded that 9 serious cases are probably related to VidPrevtyn Beta especially based on the close time relationship and simultaneous occurrence of other possible symptoms of reactogenicity. Please see section 2.3.2.3. for the PRAC Rapp's assessment of serious cases of dizziness.

The PRAC Rapporteur considers a causal relationship between VidPrevtyn Beta and dizziness is at least a reasonable possibility. Dizziness should be included in the product information. The MAH is requested to propose a frequency of this new adverse reaction based on the available data.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Clinical trials

Completed clinical trials

During the reporting interval of this PBRER, no clinical trials have been completed.

Ongoing clinical trials

VAT00001

A parallel group, Phase I/II, first in human, placebo controlled, dose ranging, multi-center study with a Sentinel Safety Cohort and Early Safety Data Review (ESDR) to assess immunogenicity and safety of SARS-CoV-2 recombinant protein vaccine formulations (two antigen formulations [high or low dose] with either AF03 or AS03 as adjuvants, or no adjuvant for the high antigen dose formulation) and injection schedule (one or two injections) in healthy adults 18 years of age and older. All vaccination in the study occurred prior to the review period. The safety follow-up period of the study has been completed. No safety issue was identified during the long-term safety follow-up. The clinical study report is currently under development.

VAT00002

A Phase II randomized, modified double-blind, multicenter, dose finding study has been conducted in adults 18 years of age and older to evaluate the safety, reactogenicity, and immunogenicity of two injections of 5 µg, 10 µg, or 15 µg of the CoV2 preS dTM (D614) vaccine, adjuvanted with AS03. Interim data from this Phase II study was used to decide on progression to Phase III and to select an antigen

dose formulation for further clinical development evaluating the vaccines when used as a late booster. Supplemental cohorts were tested as part of VAT00002 Phase II/III study to address various prime boost options (the Monovalent B.1.351 [Beta variant] formulation was used in the Supplemental Phase III Cohort 2).

- Supplemental Phase III Cohort 1 to evaluate the safety and immunogenicity of a booster dose of the parental strain (Monovalent D614) vaccine among adults previously vaccinated with a primary series of mRNA (Pfizer/BioNTech or Moderna) or adenovirus-vectored vaccines (Janssen or AstraZeneca).
- Supplemental Phase III Cohort 2 to evaluate the safety and immunogenicity of a booster dose of a variant vaccine (Monovalent B.1.351 [Beta variant] or Bivalent [D614/B.1.351]) in adults previously primed with mRNA or adenovirus-vectored vaccines.
- In addition, available and willing individuals previously primed with the adjuvanted recombinant protein vaccine (different formulations) as part of the Phase II Original Cohort were enrolled into the Supplemental Phase III Cohort 2 and randomized to a booster dose of the parental strain booster vaccine or Monovalent variant booster vaccine.
- Selection of the 5 µg dose was based on the immunogenicity results in non-naive participants of the original cohort of VAT00002.
- All vaccination for the Original Phase II cohort (primary series) occurred prior to the review period. The safety follow-up of the Original Cohort was completed prior to the review period. No related SAEs and no AESI reported in the original cohort. No safety issue was identified for the Original Cohort following completion of the safety follow-up.
- Vaccination for the Supplemental Cohorts in the Phase III portion of the VAT00002 study occurred prior to the review period. Overall, no safety concerns were identified, nor any specific risk group identified for whom safety was of concern. Among participants receiving booster vaccine, there was a favourable safety profile. The safety profile was consistent across booster formulations. No safety issues were identified in subgroups (defined by age or the presence of a high-risk medical condition). These safety data were supportive of the use of the vaccine as a booster, regardless of priming vaccine. The safety data were consistent with and further supports the safety profile established with the primary series formulation seen in the VAT00002 Phase II Original Cohort and other studies.

VAT00008

This is a phase III randomized, modified double-blind, placebo-controlled, multi-stage, multi-center, multi-country study being conducted to assess the efficacy, safety, and immunogenicity of two CoV2 preS dTM-AS03 vaccines (Monovalent [original variant first identified in Wuhan; D614] and Bivalent; D614/B.1.351) in adults 18 years of age and older with two stages as a primary series and open-label extension to assess immunogenicity, safety, efficacy of a Monovalent (B.1.351) booster dose of SARS-CoV-2 adjuvanted recombinant protein vaccine.

- For stage 1, 10 µg antigen Monovalent D614 adjuvanted vaccine is evaluated against placebo. This antigen dose level selection mitigates the risk of having lower antibody (Ab) titers against variants that would be circulating at the time of the efficacy study with potential to result in lower observed vaccine efficacy (VE) for the Monovalent D614 vaccine.

- For stage 2, five µg (D614 component) + five µg (B.1.351 component) antigen dose (Bivalent [D614/B.1.351] adjuvanted vaccine) is evaluated against placebo. It is reasonable to expect that similar homologous responses would be elicited by the B.1.351 component of the bivalent vaccine. Thus, by design, the inclusion of the B.1.351 antigen with the D614 antigen in the bivalent vaccine mitigates the risk of lower Ab responses against circulating variants anticipated with the Monovalent D614 vaccine.
- A booster extension: all participants enrolled in Stages 1 and 2 are offered a Monovalent (B.1.351) booster dose if they are eligible and if they consent to receive it. A safety follow-up of 12 months after booster administration is implemented (unsolicited AE, medically attended adverse event [MAAE], SAE, and adverse event of special interest [AESI]).

No safety concern was raised from the VAT00008 study for the monovalent or bivalent vaccine formulations.

There was no new clinically important information arising from studies ongoing during the reporting interval.

Long-term follow-up

No significant safety findings have been identified during the reporting interval in the long-term follow-up in studies VAT00002 and VAT00008.

Rapporteur assessment comment:

3 clinical trials (VAT00001, VAT00002, VAT00008) were ongoing during the covered period. No study has been completed. VAT00001, Phase I study, is the first in human study, two antigen formulations were studied with the adjuvant AF03, AS03 or without any adjuvant. No safety issue was identified during the safety follow-up and the clinical study report is currently under development. VAT00002, Phase II study evaluated three antigen (D614) formulations with the adjuvant AS03. 5 microgram formulation was selected based on the result of the study for the assessment in the phase 3. In the VAT00002 Phase II/III study supplemental cohorts were studied to address booster options. Supplemental Phase III Cohort 1 evaluated the parental strain (monovalent antigen D614) and Supplemental Phase III Cohort 2 evaluated the monovalent Beta variant antigen (B.1.351) or bivalent vaccine (antigens D614/B.1.351). All vaccinations were made before the covered period and no safety issue was identified. VAT00008 Phase III study evaluated 10 microgram monovalent antigen D614 in stage 1 and bivalent formulation (5 microgram D614 antigen + 5 microgram B.1.351 antigen) in stage 2. In the booster extension of the study monovalent B.1.351 antigen was evaluated. No important safety issue was identified.

1.3.5.2. Non-interventional studies

During the reporting interval, one non-interventional study was ongoing.

VAT00012: This is an international, non-interventional, post-marketing cohort study designed to collect prospective safety data among women vaccinated with a COVID-19 vaccine during pregnancy or within 30 days prior to the first day of the last menstrual period (LMP).

The study population includes two cohorts of pregnant women 18 years of age and older matched by country and gestational age (±two weeks):

- Cohort 1: pregnant women exposed from 30 days prior to the first day of the LMP to end of pregnancy to at least one dose of a COVID-19 vaccine. These participants are enrolled as part of the Coronavirus Disease-2019 Vaccines International Pregnancy Exposure Registry (C-VIPER).
- Cohort 2: pregnant women unexposed to a COVID-19 vaccine during pregnancy. These participants are enrolled through the Pregistry International Pregnancy Exposure Registry with the same methods as those in Cohort 1. Women vaccinated before 30 days prior to the first day of the LMP are eligible for inclusion.

The total duration of the study is five years. Obstetric, neonatal, and infant outcomes will be assessed on an ongoing basis as data become available. Data on pregnancy, neonatal and infant outcomes will be included in the interim reports.

There were no safety or efficacy findings relevant to the benefit-risk assessment identified from the non-interventional study during the reporting interval.

A listing of all MAH-sponsored non-interventional studies completed or ongoing during the reporting period, and with the primary aim of identifying, characterizing, quantifying a safety hazard, confirming the safety profile of COVID-19 vaccine (recombinant, adjuvanted), or measuring the effectiveness of risk management measures is presented in Appendix 4.2.

Rapporteur assessment comment:

One non-interventional study designed to collect prospective data among pregnant women is currently ongoing. 6000 subjects are planned to be enrolled. No subjects were enrolled until 9 May 2023.

1.3.5.3. Information from other clinical trials and sources

VAT00013: An investigator-sponsored, randomized, single-blinded multicenter clinical trial to assess the immunogenicity and safety following a booster dose of the COVID-19 mRNA vaccine original formulation (Pfizer/BioNTech) and two adjuvanted sub-unit vaccines (Monovalent D614 or Monovalent B.1.351) administered in adults who received two doses of Pfizer/BioNTech mRNA original formulation vaccine as a primary vaccination.

VAT00026: This phase 2 clinical trial will evaluate the safety and immunogenicity of an additional dose of prototype and variant (alone or in combination) vaccine candidates in previously vaccinated participants with or without prior SARS CoV-2 infection. The participants should have had a primary series of a Food and Drug Administration (FDA) approved vaccine plus a booster to be eligible for participation in this trial.

VAT00027: This study is an open label, non-randomized pilot study to evaluate the safety and immunogenicity of a dose of the Sanofi-GSK Monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine in kidney transplant recipients with a persistently low SARS-CoV-2 Ab titer.

VAT00028: This is a randomized, multi-site, adaptive, open-label clinical trial comparing the immune response to different additional doses of COVID-19 vaccine in participants with autoimmune disease requiring immunosuppressive medications.

There were no safety or efficacy findings relevant to the benefit-risk assessment in other clinical trials or study sources during the reporting period.

Rapporteur assessment comment: *4 other clinical trials are ongoing. In the study VAT000027 including kidney transplant recipients, subjects are currently being recruited. Other 3 studies are ongoing and additional participants are not currently enrolled. No significant safety issue was identified.*

1.3.5.4. Medication errors

Out of the 18 cases of medication errors reported during the review period, nine (four serious and five non-serious) were reported with AEs (50 %) and nine cases with no reported AEs (50 %).

The most frequently reported PTs within the Medication error SMQ with COVID-19 vaccine (recombinant, adjuvanted) are presented in Table 4.

Table 4 - Most frequently reported medication errors reported during the interval

Medication Error description	PT for Medication Error	Count of events of Medication Error
• Three reporters think a reaction occurred as a result of a mistake made in the administration of the vaccine. One of them reported "May have been too much administered". • A consumer who was on anticoagulant medication when the patient received the vaccine - realized that it is not advised to have this vaccine when taking medication to prevent blood clots. • A nurse suggested the burning pain was caused by the blunt needle. • Another reporter stated, "vaccination administered halfway up deltoid muscle, patient described hitting the bone with the needle".	*Medication error*	6
Patients mistakenly received COVID-19 vaccine (recombinant, adjuvanted) vaccine as their first or second primary dose.	*Product use in unapproved indication*	5
COVID-19 vaccine (recombinant, adjuvanted) was administered less than four months after the previous dose.	*Inappropriate schedule of product administration*	4
• During the reconstitution of the product, the sampling was difficult, the syringe emptied directly during the pressure[a]. • According to a consumer, injection was made in unhygienic situation ("injected directly from a syringe in a clear plastic box containing many already made-up mixtures of supposed injection").	*Product preparation error*	2
• In one case[a], during the reconstitution of the product, the sampling was difficult, the syringe emptied directly during the pressure. Product was administered but incorrect dose administered. A product technical complaint has been initiated. • No more details in the other case reported with "Incorrect dose administered by product.	*Incorrect dose administered/Incorrect dose administered by product*	2

a Same case reported with Incorrect dose administered and Product preparation error.
PT: Preferred Term.

There were no relevant safety findings on patterns of medication errors and potential medication errors identified which would require specific risk minimization measures (RMM) at this time. The information on patterns of medication errors and potential medication errors does not change the overall benefit-risk evaluation of COVID-19 vaccine (recombinant, adjuvanted). No published significant safety findings regarding medication errors have been available during the reporting interval.

Rapporteur assessment comment:

No significant safety finding on pattern of the medication errors was identified. The adverse reactions reported in the cases of medication error are mostly listed ADRs (table not reproduced in the AR).

1.3.5.5. Literature

In accordance with the GVP, the MAH is screening literature articles to search for any new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts when relevant to the medicinal product. If relevant and applicable, information on other active substances of the same class should be considered.

Commencement of literature screening has been determined by the last date of package submission of the MA application(s) for COVID-19 vaccine (recombinant, adjuvanted) (March 2022) and a broad strategy has been applied with search criteria including any COVID-19 vaccine product, irrespective of manufacturer or vaccine technology, and a report of AE(s) without restriction by seriousness or severity as stated in EU Risk Management Plan (RMP) version 1.0 DLP 08 November 2022. In the Responses to Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur Rolling review RMP final assessment report received on 01 October 2021 and in EU RMP version 1.0 DLP 08 November 2022, the following is stated: "as knowledge of the SARS-CoV-2 virus, COVID-19 and vaccines evolves, it is expected that the above strategies will likewise change evolve". Indeed, the MAH would propose to implement a focused strategy with search criteria on protein and/or nano particle and/or adjuvanted COVID-19 vaccine product now that safety profiles of other COVID-19 vaccine platforms are considered stabilized with millions of doses distributed and taken into account that they are closely monitored by their respective MAHs.

During the reporting period, four publications identified from the scientific (including non-clinical) and medical literature, contained relevant safety findings summarized hereafter.

Rapporteur assessment comment:

The MAH proposes to change the search strategy for screening of the scientific literature. Currently, the literature is monitored for any COVID-19 vaccine irrespective of the platform. The PRAC Rapp agrees that the monitoring criteria is too broad, the MAH should focus on the scientific literature concerning the vaccines of the same or similar platform in the next PSURs. ***Next PSUR***

Adverse events of special interest - Myocarditis and pericarditis

Macias Saint-Gerons D, Ibarz MT, Castro JL, Fores-Martos J, Tabares-Seisdedos R. Myopericarditis Associated with the Novavax COVID-19 Vaccine (NVX-CoV2373): A Retrospective Analysis of Individual Case Safety Reports from VigiBase. Drugs Real World Outcomes. 2023 Jun;10(2):263-70.

The authors presented a retrospective analysis of myopericarditis, an AESI, associated with a protein sub-unit vaccine, NOVAVAX® (NVX-CoV2373), reported to the World Health Organization (WHO) global safety database and compared to the rates reported with other COVID-19 vaccines. From 31 703 998 ICSRs, there were 61 812 ICSRs of myopericarditis and 61 were reported for NOVAVAX vaccine. Out of 61 included cases, 45 reported pericarditis, 11 myocarditis, four myopericarditis and one both terms (myocarditis and pericarditis). Most of the cases were reported from Australia (82%). The median age of individuals was 35.5 years old, and most were males (38; 62.3%). Twenty-four (24) reports (39.3%) were considered serious, none of them were fatal. The median induction period for myopericarditis from

vaccination (after the most recent immunization) estimated from 40 ICSRs, was three days. Increased disproportionality for myopericarditis was found for NVXCoV2373 (Reporting Odds Ratio [ROR] 14.47, 95% confidence interval [CI] 11.22–18.67) and mRNA vaccines: BNT162b2 (ROR 17.15, 95% CI 16.88-17.42) and mRNA-1273 (ROR 6.92, 95% CI 6.77-7.08). Higher values were found in males. Disproportionality for the NVX-CoV2373 vaccine was found in the age groups 18-44 and 45-65 years in both sexes, but with higher values in males. Chest pain was the most common co-reported event 43 (70.5%). The adenoviral vector-based vaccine Ad26.COV2.S showed slightly increased disproportionality (ROR 1.83, 95% CI 1.70-1.98), whereas no increased disproportionality was found for ChAdOx1 adenoviral vector-based vaccine. The authors concluded that new NVX-CoV2373 vaccine shows an increased disproportionality for myopericarditis similar to mRNA vaccines.

MAH Comment: Based on the study conducted by the authors suggesting an increased disproportionality with the protein sub-unit vaccines. However, a greater risk of hospitalization and death has been observed in association with COVID-19 infection than with the vaccination. This study also had several limitations. The data source for the study was retrieved from spontaneous reports database from which no definitive causal associations can be drawn. Relevant information such as viral testing for myocarditis was lacking from the reports. In addition, the exact mechanism of action for vaccine-induced myopericarditis remains to be elucidated. More evidence from controlled studies is necessary. Myocarditis/ Pericarditis is already an important potential risk for COVID-19 vaccine (recombinant, adjuvanted). Please also refer Section 16.3 and Section 16.4 for details.

Rapporteur assessment comment:

The MAH provided an analysis of the risk of myocarditis/pericarditis with Nuvaxovid concluding that increased disproportionality of myocarditis is similar to mRNA vaccines. The causal relationship of myocarditis/pericarditis with Nuvaxovid was already established with frequency not known. 1 case report of myocarditis was received during the covered period for VidPrevtyn Beta, please see the section 2.3.1.2.

Special population - Patients with kidney transplant receiving immunosuppressive therapy

Nafar M, Mostafaloo N, Firouzan A, Poorrezagholi F, Samadian F, Dalili N, et al. Immunogenicity and Safety of SpikoGen, an Adjuvanted Recombinant SARS-CoV-2 Spike Protein, as a Heterologous Third Booster Dose in Kidney Transplant Patients: A Single-arm Clinical Trial. Clinical Therapeutics. 2022 Dec 1;44(12):1566-76.

The authors assessed the immunogenicity and safety of the SpikoGen® vaccine as a third booster dose in special patient population (43 patients undergoing kidney transplant receiving immunosuppressive therapy) at a referral center for kidney transplantation in Iran. The patients had received their primary vaccination based on an inactivated whole virus platform (Sinopharm) one to three months earlier. SpikoGen is a subunit recombinant S protein vaccine combined with Advax-CpG55.2 TM adjuvant, a microcrystalline polysaccharide particle engineered from delta inulin. The most common local and systemic reported solicited AEs were injection site pain in 19 patients (44.19%) and fatigue in 10 (23.26%), which were largely mild and transient. No SAEs were reported.

MAH Comment: In this article, the authors performed a single-arm, open-label, prospective clinical trial including 43 patients with SpikoGen (adjuvanted recombinant S protein trimer vaccine). The authors

observed that a single booster dose of the vaccine given one to three months after primary vaccination with two doses of Sinopharm vaccine induced positive humoral and cellular immune responses in immunosuppressed patients undergoing renal transplant, thereby achieving S Ab levels predictive of protection. While positive responses are observed, the number of transplant patients was relatively low and there was no control group. In addition, this was a single-center study. Further information would be needed from larger, multicenter studies to extend these results. Use in immunocompromised subjects is a missing information for COVID-19 vaccine (recombinant, adjuvanted). Please refer Section 16.3 and Section 16.4 for details.

Rapporteur assessment comment:

The MAH provided a safety analysis of an adjuvanted recombinant vaccine SpikoGen used as a booster dose in patients with immunosuppression after kidney transplant. The majority of solicited local and systemic adverse events were injection site pain and fatigue and were mostly mild and transient. No serious adverse events were reported. Injection site pain and fatigue are listed adverse reactions of VidPrevtyn Beta.

Special population - Pregnant women

Cole C, Tsakiroglou M, Waitt C. Communication is crucial: Lessons from COVID-19 vaccination and pregnancy. Br J Clin Pharmacol. 2023 Feb;89(2):582-93. (8)

The authors presented findings from the systematic review and meta-analysis concerning pregnancy outcomes following COVID-19 vaccination with BNT162b2, Moderna, ChAdOx1 and Janssen vaccines from multiple studies. No difference in maternal outcomes, neonatal outcomes or AEs and no increased risks in pregnant women or neonates were found in vaccinated women compared to non-vaccinated.

MAH Comment: Based on the systematic review of safety outcomes associated with COVID-19 vaccines, this article summarizes key aspects and outcomes due to COVID-19 vaccination during pregnancy. For a vast majority of the studies, the reported side-effects in pregnant women were similar to the general population and no significant impact on the adverse maternal or fetal outcomes were observed with the vaccines. The various studies and recommendations further affirm that COVID-19 vaccines reduce the risk of hospitalizations and deaths in pregnant women as in the nonpregnant population. The authors highlight the importance of advice and reassurance on the safety of COVID-19 vaccinations in pregnant population for effective benefit-risk communication. Use in pregnant women and while breastfeeding is a missing information for MAH COVID-19 vaccine (recombinant, adjuvanted). Please refer Section 16.3 and Section 16.4 for details.

Rapporteur assessment comment:

The MAH provided an analysis of the systematic review assessing pregnancy outcomes following vaccination with Comirnaty, Spikevax, Vaxzevria and Jcovden with a conclusion that no increased risk in pregnant women and neonates was found.

No case concerning use of VidPrevtyn Beta in pregnant women has been reported yet.

Tormen M, Taliento C, Salvioli S, Piccolotti I, Scutiero G, Cappadona R, et al. Effectiveness and safety of COVID-19 vaccine in pregnant women: A systematic review with meta-analysis. BJOG. 2023 Mar;130(4):348-57.

The authors presented a systematic review and meta-analysis of pregnancy outcomes and risk of pregnancy related complications in COVID-19 vaccinated pregnant population with Pfizer, AstraZeneca, and Jansen vaccines (no protein-based vaccine included in the analysis) and a comparison to unvaccinated population. Administration of a COVID-19 vaccine during pregnancy resulted in a statistically significant reduction in SARS-CoV-2 infection and COVID-19-related hospitalizations, but the certainty of evidence was very low. The effect appeared to be greater for both infection and hospitalizations when considering only fully vaccinated women, although the level of certainty was still very low. Conversely, the difference in Intensive Care Unit (ICU) admissions related to COVID-19 did not reach statistical significance, likely due to the small number of total cases of both vaccinated and unvaccinated women. Nine (9) studies evaluated fetal complications occurring during pregnancy in vaccinated versus unvaccinated women. No significant differences were observed for the following outcomes: pregnancy loss, fetal abnormalities, small for gestational age, intrauterine growth restriction, preterm birth, stillbirth, meconium-stained amniotic fluid, neonatal ICU admission and hypoxic-ischemic encephalopathy between vaccinated and unvaccinated women.

MAH comment: It was concluded that COVID-19 vaccination administered during pregnancy seems to reduce SARS-CoV-2 infection and COVID-19-related hospitalization, with no significant effects on maternal-fetal complications (9). However, the certainty of evidence was low as the data was identified from observational studies. Use in pregnant women and while breastfeeding is a missing information for MAH COVID-19 vaccine (recombinant, adjuvanted). Please refer Section 16.3 and Section 16.4 for details.

Rapporteur assessment comment:

The systematic review of 14 observational studies including above 350 000 women assessed the effectiveness and safety of COVID-19 vaccines (Comirnaty, Spikevax, Vaxzevria and Jcovden) in pregnant women. There were no statistically significant differences between vaccinated and non-vaccinated women in the observed maternal-foetal complications.

No articles on patients vaccinated with protein-based vaccines or COVID-19 vaccine (recombinant, adjuvanted) in pregnant women were identified.

1.3.5.6. Other periodic reports

During the reporting interval this is the only PBRER prepared by the MAH for this product including periodic reports prepared by the contractual partner.

Rapporteur assessment comment:

No other periodic reports were prepared during the covered period.

1.3.6. Lack of efficacy in controlled clinical trials

No new controlled clinical trials indicating a lack of efficacy of COVID-19 vaccine (recombinant, adjuvanted), in the authorized indications, relevant for the benefit-risk evaluation were identified during the reporting interval.

Rapporteur assessment comment:

The information is acknowledged.

1.3.7. Late-breaking information

Since the DLP for this PBRER, the MAH has identified the following new information regarding potentially important safety and efficacy and/or effectiveness:

One signal on allergic including anaphylactic reactions has been opened on 17 May 2023, validated on 14 June 2023. On 26 June 2023, signal of allergic including anaphylactic reactions was confirmed as an identified risk. The weighted cumulative evidence was considered sufficient to support a causal association between COVID-19 vaccine (recombinant, adjuvanted) and allergic including anaphylactic reactions that should be reflected in the RSI.

Regarding anaphylactic reactions, highest levels of certainty for the diagnosis of anaphylaxis (levels 1 and 2 of the Brighton Collaboration Case Definition (BCCD) [10]) were not reached for any case; however anaphylactic reactions could be expected after any vaccination. In addition, the pattern observed of allergic reactions reported after the use of COVID-19 vaccine (recombinant, adjuvanted) (rash, urticaria, rash erythematous, pruritus, swelling face) supports the fact that the signal detected is judged to be of sufficient likelihood to justify verificatory action and moves to full evaluation and further characterize allergic including anaphylactic reactions. Further details regarding this signal will be discussed in the next PBRER interval.

Rapporteur assessment comment:

In August 2023 the MAH submitted a variation of the marketing authorisation related to hypersensitivity reactions. The issue has been assessed in a currently ongoing procedure EMEA/H/C/005754/II/0006. The information about the outcome of the signal and procedure will be provided by MAH in the next PSUR.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Summary of safety concerns at the beginning of the reporting period

Important identified risks	None

Important potential risks	Vaccine-Associated Enhanced Disease including Vaccine-Associated Enhanced Respiratory Disease Myocarditis and Pericarditis
Missing information	Use in pregnancy and while breast-feeding Use in immunocompromised subjects Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders Interactions with other vaccines Long-term safety

2.2. Signal evaluation

There are no signals that were ongoing at the DLP or closed during the reporting interval.

Rapporteur assessment comment:

During the covered period, no signals were detected, validated or closed except the signal of hypersensitivity, which is currently reviewed via separate procedure.

2.3. Evaluation of risks and safety topics under monitoring

Rapporteur assessment comment:

The MAH divided the issues requested to be monitored in 3 sections in the PSUR – Requests based on the core-RMP guidance, Additional requests from EMA and the Requests of MHRA. It is not clear why not all AESI stated in the list of AESI in the RMP version 1.0 are included in the section "Requests based on the core-RMP guidance". The current structure is very confusing. Therefore, all AESI should be presented in one integrated overview and not split according to the origin of the request (EMA, MHRA, RMP) as this makes the data difficult to follow. ***Next PSUR***

In addition, several AESI are not discussed in PSUR at all – acute septic arthritis, rheumatoid arthritis, type 1 diabetes mellitus, heart failure, stress cardiomyopathy, arrhythmias, anosmia and ageusia. The MAH is asked to include the assessment of these AESI in the next PSURs including O/E analysis. In the next PSUR, the cases reported during the current and next PSUR period should be included. ***Next PSUR***

2.3.1. Requests based on the core-RMP guidance

2.3.1.1. Anaphylactic reactions

Based on the MedDRA search criteria SMQ Anaphylactic reaction Algorithmic, a total of five serious case reports of potential anaphylactic reactions were retrieved on the period; none met level 1 or 2 BCCD level for anaphylaxis.

• Case [redacted] reported from an HCP via [redacted] and involving a 93-year-old [redacted] with an unspecified ongoing food allergy experienced back pain, eye movement disorder, respiratory arrest, and erythema a couple of minutes after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient was laid down and recovered 10 mins later with feet elevation. Based on the limited reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 3 for anaphylaxis.

• Case [redacted] was reported from an HCP via [redacted]. A [redacted] with no reported medical history experienced acute anaphylaxis, two min after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient was given adrenaline two times (half an hour apart) and was transferred to a hospital. The patient recovered. The concomitant medications included apixaban; macrogol 3350, potassium chloride, sodium bicarbonate, sodium chloride; furosemide; gabapentin; Hypromellose; omeprazole; paracetamol and cholecalciferol. Further information regarding detailed symptoms, concurrent condition during vaccination, medical history, tolerance of previous vaccinations, and investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. This case was assessed as BCCD level 4 for anaphylaxis.

• Case [redacted] was reported from a consumer via [redacted] A 74-year-old [redacted] with no reported medical history developed dizziness, dyspnea, erythema, miliaria, and asthenia one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient's past vaccination was COVID-19 vaccine Moderna, and past medications included atorvastatin, clopidogrel for cerebrovascular accident and paracetamol for headache. Concomitant medications included lisinopril for blood pressure; pantoprazole for gastroesophageal reflux disease; and venlafaxine for depression. Patient was reported as recovering. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for anaphylaxis.

• Case [redacted] was reported by a consumer via [redacted] and involves a 77-year-old [redacted] with medical history of bronchitis improved after diet, gastritis and ongoing glaucoma who experienced coughing, influenza, headache, flushing and productive cough two days after receiving the vaccine. The patient also experienced fatigue unknown duration after the vaccination. The patient was treated with paracetamol for headache. The patient recovered from coughing and had not recovered from influenza, productive cough, fatigue, flushing and headache. The patient's past medical history of bronchitis could be a confounding factor. Based on the reported information, the role of suspect cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.

• Case [redacted] was reported from a consumer via [redacted] An unknown age [redacted] with no reported medical history developed diarrhea on the day of vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient also developed pruritus, pharyngeal swelling, vaccination site bruising, vaccination site warmth and lymphadenopathy unknown duration after the vaccination. The patient's past vaccinations were not reported. Outcome was reported as not recovered for vaccination site bruising, vaccination site warmth, diarrhea and unknown for pruritus, lymphadenopathy, and pharyngeal swelling.

Based on the minimal information reported, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for anaphylaxis.

In addition to Anaphylactic reactions specific analysis, 17 cases including seven serious and 10 non-serious cases reported swelling face/angioedema based on the MedDRA search strategy for SMQ: "Angioedema" (Narrow); none met BCCD level 1 or 2 for anaphylaxis.

Based on medical review of cumulative data, a signal on Allergic including anaphylactic reactions has been opened on 17 May 2023 and has been validated on 14 June 2023.

Rapporteur assessment comment:

Five cases reporting anaphylaxis were received during the covered period. All cases include only limited information. Two cases were reported by healthcare professionals. In the first case, it is not clear if respiratory arrest occurred. Elevation of the patient's feet is described as the only treatment (BCC Level 4). In the second case, no symptoms of anaphylaxis are described (BCC level 4).

In one consumer case, only dyspnoea is described as a symptom of anaphylaxis (BCC level 4), in the second case the reactions seem to be rather the symptoms of viral infection which appeared two days after vaccination (BCC level 5). In the last consumer case, diarrhoea, pruritus without further specification and pharyngeal swelling are described. The PRAC Rapp disagrees with the MAH´s assessment that this case is of BCC level 4. The case should be assessed as of level 2 certainty, the patient experienced one major respiratory symptom (pharyngeal swelling) and two minor symptoms (pruritus and diarrhoea).

Most reported cases of anaphylaxis and angioedema are of limited information precluding in depth assessment. Generally, the MAH is requested to make an effort in order to obtain maximum available information during the follow-ups and to discuss the updated cases in view of the new information including causality assessment. ***Next PSUR***

The MAH is requested to submit a re-evaluation of all cases reported with 'Allergic and anaphylactic reactions' with an outcome as ongoing or not recovered within the next PSUR, once further information (on the patient's underlying disease conditions, past medical and drug history, concurrent illnesses, and concomitant medications) is available. ***Next PSUR***

In addition, 17 cases of angioedema were received during the reporting period, which are described in the section 2.3.2.2.

In August 2023 the MAH submitted a variation of the marketing authorisation related to hypersensitivity reactions. The issue has been assessed in a separate procedure EMEA/H/C/005754/II/0006, angioedema has been covered by this assessment.

The MAH should continue to present anaphylactic reactions in the PSUR.

2.3.1.2. Myocarditis/Pericarditis

One case of myocarditis was retrieved for COVID-19 vaccine (recombinant, adjuvanted) during the reference period. The serious case report of myocarditis was reported from consumer via [redacted] in an elderly patient of unknown gender two days after vaccination. An 81-year-old and unknown gender patient experienced positional dizziness and myocarditis two days after vaccination with COVID-19

vaccine (recombinant, adjuvanted). At time of reporting, the outcome was not recovered. Further information on patient underlying disease condition, past medical and drug history, concomitant medications, description of the reported symptoms, complementary investigations and results excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for myocarditis.

In addition, no increased O/E ratio has been detected for myocarditis/pericarditis.

• Conclusion: Based on medical review of cumulative data supported by O/E analysis, no safety concern has been identified.

Rapporteur assessment comment:

One case of myocarditis was reported during the covered period and also cumulatively. It is a consumer case with limited information, no information about the symptoms, the results of the laboratory tests, virology, ECG, ECHO or MRI and treatment was provided (BCC level of certainty 4). The MAH is requested to follow-up this case in order to obtain all available information and to discuss the updated case in detail in the next PSUR. ***Next PSUR***

In addition, the MAH specified the risk window for O/E analysis as follows: the primary risk window as 1-7 days and the secondary risk window as 1-42 days. The PRAC Rapp does not agree with the MAH´s proposal. The highest risk of myocarditis/pericarditis following mRNA vaccines and Nuvaxovid is within 14 days after vaccination. The proposed primary risk window is too short. The PRAC Rapp proposes to extent the primary risk window to 28 days as is stated in the protocol V2.2 for Rapid safety assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources, ENCEPP. ***Next PSUR***

2.3.1.3. COVID-19 AESI

A total eight case reports of COVID-19 infection were reported, of which two were reported as serious case reports and are detailed below. No fatal outcomes or severe cases were being reported.

Rapporteur assessment comment:

Please refer regarding COVID-19 cases to the section 2.4.1. Important potential risks

2.3.1.4. Dermatological AESIs (including Chilblains, Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis)

No cases reporting these reactions have been identified.

Rapporteur assessment comment:

No cases of Chilblain-like lesions, Erythema multiforme, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis were reported.

The MAH should continue to present dermatological AESIs in the PSUR.

2.3.1.5. Facial paralysis (Bell's palsy)

No case report of facial paralysis (Bell's Palsy) has been reported.

Rapporteur assessment comment: *No cases of facial paralysis were reported. The MAH should continue to present data on facial paralysis in the PSUR.*

2.3.1.6. Hepatic AESIs

No case report of hepatic AESI has been reported.

Rapporteur assessment comment: *No cases of Acute liver injury were reported.* *For the purposes of O/E analysis, the MAH determined the primary risk window as 1-14 days. The PRAC Rapp is of opinion that the proposed risk window is too short and proposes to extend the primary risk window to 180 days in next PSURs in line with the protocol V2.2. for Rapid safety assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources, ENCEPP.* ***Next PSUR*** *The MAH should continue to present hepatic AESI in the PSUR.*

2.3.1.7. Pregnancy related AESIs

There was no reported use in pregnancy.

Rapporteur assessment comment: *No cases of pregnancy related AESI were reported.* *The MAH should continue to present related AESI in the subsequent PSUR.*

2.3.1.8. Respiratory AESIs

Based on the MedDRA search strategy focused on acute respiratory distress syndrome, three serious case reports of respiratory AESIs were identified: one case of respiratory arrest ([redacted]) also reported hypersensitivity manifestations and is presented under Anaphylactic reactions, one case ([redacted]) reported seizures along with respiratory arrest and it is presented below under "Seizures" Section and remaining one case of severe acute respiratory distress syndrome ([redacted]) is presented here.

• Case [redacted] reported by a consumer via [redacted] referred to a 77-year-old [redacted] with medical history of atrial fibrillation, hypertension, and hypercholesterolemia, who experienced SARS-CoV-1 infection (SARS) 14 days after vaccination with COVID-19 vaccine (recombinant, adjuvanted) and SARS-CoV-2 infection (confirmed by test but no test result was provided) 15 days after vaccination. The concomitant medications included apixaban for atrial fibrillation; atorvastatin for blood cholesterol

increased; bisoprolol for heart rate increased; and ramipril for hypertension. Symptoms were extreme coughing, sneezing, runny nose, shortness of breath and difficulty breathing for which the patient was given antibiotics to prevent chest infection. The outcome was reported as not recovered from SARS and recovering from COVID-19. Further information regarding SARS-CoV-2 vaccination history, other risk factors, complementary examination results and time of first symptoms appearance for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed, and a potential vaccination failure cannot be retained. This case was assessed as BCCD level 5 for VAED.

Based on medical review of cumulative data, no safety issue on respiratory AESIs has been identified. In addition, no increased observed versus expected (O/E) ratio has been detected for respiratory AESIs.

Rapporteur assessment comment:

Within respiratory AESI, 2 cases of respiratory arrest and 1 case of ARDS were reported. 2 cases are medically confirmed and 1 case from a consumer. The first HCP case was already discussed in the section 2.3.1.1. Anaphylactic reaction. It is not clear if respiratory arrest occurred. Elevation of the patient´s feet is described as the only treatment (BCC Level 4). In the second HCP case listed which is presented by the MAH in the section of seizures, respiratory arrest and seizures occurred 10 minutes after vaccination with VidPrevtyn Beta. Adrenaline was administered due to anaphylaxis and the patient was intubated and transferred to the emergency room. (BCC Level 4). It is not clear why this case was not discussed as anaphylaxis. The MAH is requested to follow-up the case [redacted] in order to obtain all available information and to discuss the updated case in detail in the next PSUR. ***Next PSUR*** *In the consumer case, a patient experienced SARS-CoV-2 infection two weeks after vaccination with VidPrevtyn Beta (BCC Level 5).*

For the purposes of O/E analysis, the MAH determined the primary risk window of Acute respiratory distress syndrome as 0-14 days. The PRAC Rapp does not agree with the MAH´s proposal. The MAH states that the primary risk window was determined based on the SPEAC AESI Case Definition Companion Guide for ARDS (Version 1.0), however, in the section 4.1.3 Recommendation for duration of surveillance it is specifically stated: "If immunization leads to direct lung injury (via stimulation of innate or adaptive immune mechanisms), ARDS would be expected to occur within 1 to 6 weeks after vaccine administration." The MAH is asked to revise the primary risk window in line with this specification in the next PSURs. ***Next PSUR***

The MAH should continue to present respiratory AESI in the PSUR.

2.3.1.9. Gastro-intestinal disorders

One non-serious case report ([redacted]) of dyspepsia was reported. Based on medical review of this case report, no safety concern has been identified.

Rapporteur assessment comment:

The MAH should continue to present gastro-intestinal AESI in the PSUR.

2.3.1.10. Coronary artery disease

One serious case of myocardial infarction ([redacted]) was reported from an HCP via [redacted] and involving a 78-year-old non-tobacco user[redacted], with ongoing chronic kidney disease, who experienced myocardial infarction one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Diagnosis was myocardial infarction with nonobstructive coronary arteries (MINOCA). There was medical history that relates to previous venous or arterial thromboses. The patient did not confirm or suspect autoimmune or inflammatory disease, including vasculitis. No hemorrhage was identified. As per reporter, this case report was not related to possible blood clots or low platelet counts or possible myocarditis or pericarditis. At time of reporting, the outcome was recovered/resolved. Further information regarding concomitant medication and tolerance, laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for Thrombosis/Thromboembolism.

Based on the medical review of the case report, no safety concern has been identified. In addition, no increased O/E ratio has been detected for coronary artery disease AESI. Refer to Appendix 6.4.2.

Rapporteur assessment comment:

One case reporting myocardial infarction with nonobstructive coronary arteries (MINOCA) was reported during the reporting period. No results of the performed examinations were provided, however, the reporter (HCP) stated that no haemorrhage, blood clots, myocarditis or pericarditis were identified. MINOCA is a syndrome with many causes. Its prevalence ranges between 5 and 25% of all MIs. The prognosis is extremely variable, depending on the causes of MINOCA. Clinical history, echocardiography, coronary angiography, and left ventriculography represent the first-level diagnostic investigations. Nevertheless, additional tests are required in order to establish its specific cause, thus allowing an appropriate risk stratification and treatment. The causes specified in UpToDate are following: Coronary artery spasm, Acute thrombosis at the site of non-obstructive eccentric plaque thrombosis, Spontaneous coronary artery dissection, Takotsubo cardiomyopathy, Coronary microvascular dysfunction, Viral myocarditis and Coronary artery embolism. The MAH is asked to make an effort in order to obtain all available details of the case including clinical course, results of the performed examinations and diagnosis and to discuss the updated case in the next PSUR. ***Next PSUR***

The MAH should continue to present data on coronary artery disease in the PSUR.

2.3.1.11. Thrombosis with thrombocytopaenia syndrome

No case report of thrombosis with thrombocytopenia syndrome was reported, however, one case report of deep vein thrombosis (DVT) and thrombocytopenia has been reported. It is presented below in Section "Thromboembolic AESIs (venous thromboembolism)".

Rapporteur assessment comment:

The MAH determined the primary risk window of thrombosis with thrombocytopenia syndrome as 1-14 days and the secondary risk window as 1-28 days. The PRAC Rapp does not agree with the proposed primary risk window. Most of the cases following vaccination with vector COVID-19 vaccines occurred within the first three weeks following vaccination. The PRAC Rapp therefore proposes to extend the primary risk window to 28 days as is also stated in the protocol V2.2. for Rapid safety assessment of

SARS-CoV-2 vaccines in EU Member States using electronic health care data sources. With respect to the primary risk window, the MAH is requested to revise or remove the secondary risk window. ***Next PSUR***

The MAH should continue to present data on TTS in the PSUR.

2.3.1.12. Thromboembolic AESIs (venous thromboembolism)

Six serious cases reported different types of thromboembolic AESIs, one reported pulmonary embolism, one reported DVT, three reported thrombosis, and one fatal case reported cerebral venous sinus thrombosis (CVST) and were assessed against BCCD for thrombosis/thromboembolism:

• Case [redacted] reported pulmonary embolism from an HCP via [redacted]. A 75-year-old [redacted] experienced pulmonary embolus (Diagnosed through Computerized Tomography [CT] pulmonary angiogram) five days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient had difficulty breathing and chest discomfort. Fibrin D dimer was not > 4000 (poorly documented but pathologic or imaging findings consistent with thromboembolism: diagnosed through CT pulmonary angiogram). At the time of reporting, the outcome was recovering (no information about corrective measurements was provided). Previous and current laboratory investigations including Fibrin D Dimer date (results which were reported as not > 4000 [Units not provided]), excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case report meets BCCD level 1, considering diagnostic confirmation and experienced symptoms, however there is a lack of information on the patient's medical history, concomitant medications, and primary vaccination with COVID-19 vaccines.

• Case [redacted] reported DVT received from other HCP via [redacted]. An 88-years-old [redacted] experienced DVT five days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The concomitant medications included allopurinol; aspirin; felodipine; folic acid; furosemide; glyceryl trinitrate; paracetamol; salbutamol; and beclomethasone dipropionate, formoterol fumarate, glycopyrronium bromide. At the time of reporting, the outcome was recovering. Further information regarding previous COVID-19 vaccinations, indication of reported concomitant medications including aspirin, medical history and risk factors, laboratory investigations and context for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case meets BCCD level 4 for thrombosis/thromboembolism.

• Thrombosis was reported in three cases:

- Case [redacted] involving an 86-year-old [redacted] who experienced thrombus two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Symptoms were reported to be acute onset pain, paralysis, and numbness. A CT scan confirmed acute thrombus in right axillary artery. The patient had ongoing macular degeneration, hypertension and previous DVT/pulmonary embolism which constitutes a pre-existing risk factor. The patient had ongoing macular degeneration, hypertension and previous DVT/pulmonary embolism which constitutes a pre-existing risk factor. Further information regarding previous COVID-19 vaccinations, concomitant medications and other risk factors, complementary examination results and context for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be excluded. This case was assessed as BCCD level 1 for thrombosis/thromboembolism.

- Case [redacted] was reported from a consumer via [redacted] and referred to a [redacted] of an unknown age who experienced dyspnea, abdominal pain, and blood clots two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The concomitant medications included clopidogrel. The corrective treatment, outcome, and relevant details such as medical history was unknown. Further information on patient's age, weight, and body mass index (BMI), past medical history, thrombosis risk factors, current medications and current condition excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for thrombosis/thromboembolism.

- Case [redacted] received from HCP via [redacted] reported in a 78-year-old [redacted] with past medical history of immunodeficiency and ongoing hypothyroidism, atrial fibrillation and cardiac failure who experienced a DVT and thrombocytopenia three days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient has been complaining of calf swelling since vaccination. The patient also felt sweaty and had dizziness with a fainting episode. The lowest patient's platelet count after vaccination was reported as "132" and no previous platelet counts were known. Anti- platelet factor 4 (PF4) antibodies identified was unknown. The patient was diagnosed with DVT. The patient's past medical history of immunodeficiency and current condition of could be a confounding factor. Further information on patient's weight and BMI, allergy history, thrombosis risk factors, immunodeficiency type, previous platelet counts, current laboratory findings, and concomitant medication excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for thrombosis/thromboembolism.

• One fatal case of CVST ([redacted]) is presented in Table 1 of fatal cases in Appendix 6.3. This case involves 78-year-old [redacted] who experienced cerebral venous sinus thrombosis two days after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient has previous medical history of COVID-19 approximately three months ago and TIA approximately two years ago and was on aspirin. The patient had ongoing hypertension. Further information regarding previous COVID-19 vaccinations, indication of reported concomitant medications including aspirin, medical history and risk factors, examination results and context for the reported event are needed to fully assess this

Based on the medical review of cumulative data, no safety concern has been identified.

In addition, no increased O/E ratio has been detected for venous thrombo-embolism.

For CVST, no significant O/E ratio increase has been detected using a reporting rate of 100%. However, a significant O/E ratio increase has been detected using a reporting rate of 50% (meaning that only 50% of the cases were reported). This analysis presents limitation as it is based on only one event which makes this analysis unconclusive. In addition, this case has been assessed as BCCD level 4 for thrombosis/thromboembolism. This AESI will continue to be closely monitored.

The results of O/E analyses:

●/E ratio and its 95% confidence interval for UK - DLP: 2023-05-31

RR 100%	UK											
Cerebral venous sinus thrombosis	Spain_BI FAP_PC	Doses	Primary Risk Window					Secondary Risk Window				
			Expected	Observed	OE	95% CI	95% CI	Expected	Observed	OE	95% CI	95% CI
	IR per 100 000 person years		RW: 28 days	RW: 28 days		Lower bound	Higher bound	RW: 14 days	RW: 14 days		Lower bound	Higher bound
0-17	0.22	7	0.0	0	0	-	3124682.79	0.0	0	0	-	6249365.59
18-29*	0.3	165	0.0	0	0	-	97212.35	0.0	0	0	-	194424.71
30-39	0.36	336	0.0	0	0	-	39781.84	0.0	0	0	-	79563.68
40-49	0.25	815	0.0	0	0	-	23617.23	0.0	0	0	-	47234.47
50-59	0.29	2 501	0.0	0	0	-	6634.60	0.0	0	0	-	13269.21
60-69	0.37	15 112	0.0	0	0	-	860.60	0.0	0	0	-	1721.21
70-79	0.16	841 717	0.1	1	9.69	0.25	53.97	0.05	1	19.37	0.49	107.93
80+	0.32	1 145 552	0.3	0	0	-	13.13	0.1	0	0	-	26.25
ALL AGES	-	2 006 205	0.4	1	2.57	0.07	14.31	0.2	1	5.14	0.13	28.62

RR 50%	UK											
Cerebral venous sinus thrombosis	Spain_BI FAP_PC	Doses	Primary Risk Window					Secondary Risk Window				
			Expected	Observed	OE	95% CI	95% CI	Expected	Observed	OE	95% CI	95% CI
	IR per 100 000 person years		RW: 28 days	RW: 28 days		Lower bound	Higher bound	RW: 14 days	RW: 14 days		Lower bound	Higher bound
0-17	0.22	7	0.0	0	0	-	3124682.79	0.0	0	0	-	6249365.59
18-29*	0.3	165	0.0	0	0	-	97212.35	0.0	0	0	-	194424.71
30-39	0.36	336	0.0	0	0	-	39781.84	0.0	0	0	-	79563.68
40-49	0.25	815	0.0	0	0	-	23617.23	0.0	0	0	-	47234.47
50-59	0.29	2 501	0.0	0	0	-	6634.60	0.0	0	0	-	13269.21
60-69	0.37	15 112	0.0	0	0	-	860.60	0.0	0	0	-	1721.21
70-79	0.16	841 717	0.1	2	19.37	2.35	69.98	0.1	2	38.74	4.69	139.96
80+	0.32	1 145 552	0.3	0	0	-	13.13	0.1	0	0	-	26.25
ALL AGES	-	2 006 205	0.4	2	5.14	0.62	18.55	0.2	2	10.27	1.24	37.11

* For EEA, incidence rate applied to [18-29] age group corresponds to incidence rate of [20-29] age group

Blue cell: O/E>1

Orange cell: O/E>1 and lower bound of 95% CI >1

RR: reporting Rate; RW: Risk Window

Rapporteur assessment comment:

1 case of pulmonary embolism, 1 case of DVT, 3 cases of thrombosis and 1 case of CVST were reported. In the case of pulmonary embolism, DVT and in most of the cases reporting thrombosis there is limited information precluding in-depth assessment. When the cases contain only limited information, the MAH should not simply conclude that the causal relationship cannot be established but should carefully follow-up the cases in order to obtain as much available information as possible especially when the AEs are serious or unlisted. O/E analysis for thrombosis and pulmonary embolism is below 1.

In addition to the cases of pulmonary embolism and thrombosis, 1 fatal case of CVST ([redacted]) was reported during the covered period. In this case, CVST occurred 2 days after vaccination with

VidPrevtyn Beta in a 78-year-old [redacted] who experienced COVID-19 3 months ago and TIA 2 years ago. In the medical history, therapy with aspirin and ongoing hypertension is described. The MAH is requested to follow-up the case in order to obtain as much available information as possible. The case with updated information should be discussed in detail in the next PSUR. The result of O/E analysis is below 1, however when the reporting rate of 50% is considered, a significant O/E ratio increase is observed. The PRAC Rapp agrees with the MAH´s statement that no conclusion can be made based on the only case with limited information. ***Next PSUR***

The MAH should continue to present thromboembolic AESI in the PSUR. ***Next PSUR***

2.3.1.13. Stroke (haemorrhagic stroke and ischaemic stroke)

Six serious cases of stroke (all reported as cerebrovascular accident) were reported.

• Case [redacted] was reported from a consumer via [redacted] and referred to an 80-year-old [redacted] with no reported medical history who experienced cerebrovascular accident one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted) and was hospitalized. Past medications included cetirizine and topiramate. Patient's past vaccinations were not reported. Patient was reported as recovering. Further information regarding concurrent condition at the time of vaccination, previous vaccination, concomitant medication and tolerance, allergic history, laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case report was assessed as BCCD level 4 for thrombosis/thromboembolism.

• Case [redacted] was reported from a consumer via [redacted] involving an 85-year-old [redacted] who experienced stroke one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient also experienced confusional state, dysarthria, prosopagnosia, headache, and diarrhea of unknown duration after the vaccination. Concomitant medications included amlodipine; doxazosin; enalapril; tozinameran vaccine and elasomeran vaccine. The patient has not had a similar reaction to any other vaccine or medicine, any recent surgery or other trauma (eg, an accident). Reportedly, the patient had no history of blood clotting, irregular heart rhythm, deep venous thrombosis, lung, pulmonary embolism, brain (stroke) or coronary arteries (heart attack/myocardial infarction), intermittent claudication, any inflammatory or autoimmune diseases, eg, systemic lupus erythematosus (SLE), not any family problems with clots in blood vessels. Relevant investigations included CT head Scan; Blood Test; electrocardiogram (ECG); central nervous system (CNS)/neurological tests; magnetic resonance imaging (MRI); Ultrasound (results not reported). At time of reporting, the outcome was unknown. Further information on allergy history, medical condition at the time of vaccine and patient's laboratory investigation results precluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine be assessed. The case report was assessed as BCCD level 1 for thrombosis/thromboembolism.

• Case [redacted] was reported from a consumer via [redacted] and referred to a 76-year-old [redacted] with medical history of hypertension, who experienced stroke 28 hours after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Concomitant medications included bisoprolol; ezetimibe both for secondary prevention; pravastatin for blood cholesterol increased; ramipril for hypertension and aspirin for ADR not otherwise specified (NOS). Patient experienced facial droop on left side, left-sided weakness, and classic stroke symptoms. The patient underwent clot bursting treatment for the event. At time of

reporting, the outcome was not recovered. Further information on allergy history, family history, past medication, laboratory investigation, previous laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. The case report was assessed as BCCD level 3 for thrombosis/thromboembolism.

• Case [redacted] was reported from a consumer via [redacted] and referred to an 87-year-old [redacted] with ongoing immunodeficiency, diabetes and chronic kidney disease, experienced stroke eight hours after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient's past medical history included anemia. Stroke was confirmed by scans. At time of reporting, the outcome was not recovered. The patient's medical history included anemia, immunodeficiency, diabetes, and chronic kidney disease. Further information on allergy history, family history, thrombosis risk factors and previous events, past or concomitant medication, stroke type (ischemic or hemorrhagic), current patient condition and previous laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. The case report was assessed as BCCD level 1 for thrombosis/thromboembolism.

• Case [redacted] was reported from HCP via [redacted] involving a 78-year-old [redacted] with medical history including "ongoing" transient ischemic attack (TIA), class III obesity, palpitations and hypertension, and the patient experienced stroke one day after vaccination with fifth dose of COVID-19 vaccine (recombinant, adjuvanted). Concomitant medications included atorvastatin for TIA; clopidogrel; diltiazem for palpitations; flucloxacillin for cellulitis; lansoprazole and ramipril for hypertension. As per reporter, this case report was related to possible blood clots or low platelet counts and not related to possible myocarditis or pericarditis. It was reported that platelet count was <150 - 109/L, D-dimer was > 4000 and anti-PF4 antibodies identified was unknown. The patient had not any previous reactions to medications, especially heparin or anticoagulants, history of, or current, malignancy. The patient had not confirmed or suspected autoimmune or inflammatory disease, including vasculitis. At time of reporting, the outcome was not recovered. Further information on etiology of palpitations, allergy history, family history, thrombosis risk factors and previous events, time elapsed since last TIA, current patient condition and previous laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. BCCD level 4 for thrombosis/thromboembolism.

• Case [redacted] was reported from a consumer involving an adult patient, of unknown age and gender experienced a stroke within minutes after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient's past medical history, medical treatment(s), vaccination(s) and family history were not provided. It was not reported if the patient received a corrective treatment for the event. Further information on patient's age, gender, past medical history, allergy history, current medications, condition at the time of reported event, laboratory investigation excluding alternative aetiologies for the reported event, are needed to fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed. BCCD level 4 for thrombosis/thromboembolism.

Based on medical review of cumulative data, no safety concern has been identified nor pattern in thrombotic and thrombo-embolic events. In addition, no increased O/E ratio has been detected for ischemic and haemorrhagic stroke.

Rapporteur assessment comment:

There is a discrepancy between the number of stroke cases listed in the body of PSUR and in the Appendix 6.4.2. While 6 cases of stroke without specification of type are described in the PSUR body, 7

*cases of ischaemic stroke (1 case reported after DLP) and 6 cases of haemorrhagic stroke are stated in the Appendix. The MAH is requested to clarify this discrepancy within the **RSI**. In addition, the MAH is requested to discuss ischaemic and haemorrhagic stroke separately in next PSURs. **Next PSUR***

*Out of 6 cases described in the PSUR, 1 case was reported from a healthcare professional and 5 cases were reported from patients. In the medically confirmed case [redacted], a 78-year-old [redacted] with medical history of TIA, obesity, palpitations, and hypertension experienced stroke one day after vaccination with VidPrevtyn Beta. Within the laboratory results, thrombocytopaenia and D-dimer above 4000 were listed. The result of anti-PF4 is not known. The details about the type of stroke and the results of CT or MR were not provided (BCC level 4). The MAH is requested to follow up the case in order to obtain information about the results of CT/MR and other relevant examinations and tests. The MAH is asked to discuss the new information about the case in the respective section in the next PSUR. **Next PSUR***

O/E ratio is not increased for ischaemic or haemorrhagic stroke.

The MAH should continue to present data on stroke in the PSUR.

2.3.1.14. Guillain- Barré syndrome

No case report of Guillain-Barré syndrome has been reported.

2.3.1.15. Immune thrombocytopaenia

No case report of immune thrombocytopenia has been reported.

Rapporteur assessment comment:

The MAH should continue to present data on GBS and immune thrombocytopaenia in the PSUR.

2.3.1.16. Microangiopathy and thrombotic microangiopathy

No case report of microangiopathy or thrombotic microangiopathy has been reported.

Rapporteur assessment comment:

*The MAH proposed the primary risk window for purposes of O/E analysis as 14 days. However, the risk window of microangiopathy is established as 28 days in the Protocol V2.2 for Rapid Safety Assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources listed in ENCEPP. The MAH is requested to revise the risk window in the next PSUR. **Next PSUR***

The MAH should continue to present data on microangiopathy and thrombotic microangiopathy in the PSUR.

2.3.1.17. All Immune-mediated/autoimmune AESIs

Three case reports of different immune-mediated/autoimmune AESIs were reported:

• One serious case report of myocarditis ([redacted]) that is also mentioned in Myocarditis/pericarditis section.

• One serious case report of gout ([redacted]) reported from an HCP via [redacted] referred to a 91-year-old [redacted] patient with no reported medical history who developed gout flare two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient's concomitant medications included indapamide for renal hypertension. The patient's past vaccinations were not reported. The outcome was reported as not recovered. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded.

• One non-serious case report of vasculitis ([redacted]) that is also mentioned below in Single organ vasculitis section.

Based on medical review of the case reports, no safety concern nor pattern on immune-mediated/autoimmune AESIs has been identified.

Rapporteur assessment comment:

The MAH provided 3 case reports describing immune-mediated or autoimmune AEs. The case of myocarditis is discussed above in the section 2.3.1.2.

The case of gout is described in this section, however available information is insufficient to make any conclusion. Most of described cases in the PSUR contain very limited information precluding any meaningful assessment. In the next PSUR, the MAH is requested to provide a description how case follow-ups are processed depending on seriousness and listedness of the AEs. ***Next PSUR***

In addition, the MAH is requested to follow-up the case [redacted] concerning gout and to discuss the updated case in the respective section of the next PSUR. ***Next PSUR***

The MAH should continue to present data on immune-mediated/autoimmune AESIs in the PSUR.

2.3.1.18. Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multi-inflammatory Syndrome, Acute pancreatitis, Kawasaki disease, Sub-acute thyroiditis

No case report of Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multi-inflammatory Syndrome, Acute pancreatitis, Kawasaki disease, Sub-acute thyroiditis has been reported.

Rapporteur assessment comment:

The risk window of acute pancreatitis, subacute thyroiditis and Kawasaki disease are not listed in the Appendix 6.4. of PSUR. The risk window of pancreatitis and Kawasaki disease are established as 28 days and the risk window of thyroiditis as 180 days in the Protocol V2.2 for Rapid Safety Assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources listed, ENCEPP. The MAH is requested to include these risk window in the next PSUR. ***Next PSUR***

The MAH determined the primary risk window of narcolepsy as 1-42 days and the secondary risk window as 90-183 days. The gap between primary and secondary risk window is not clarified. The MAH states

that the secondary risk window was determined based on the consensus definition from the AESI Working Group of Vaccine Europe, March 2021 but the case definition of narcolepsy made within the ACCESS Project does not include information on the risk window. However, the risk period of 1-180 days is stated in the protocol V2.2 for Rapid safety assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources. The MAH is requested to correct the secondary risk window of narcolepsy according to the above-mentioned protocol (V2.2). ***Next PSUR***

The MAH should continue to present data on Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multi-inflammatory Syndrome, Acute pancreatitis, Kawasaki disease and Sub-acute thyroiditis in the PSUR.

2.3.1.19. Single organ cutaneous vasculitis

One case report of single organ cutaneous vasculitis has been reported.

• One non-serious case [redacted] of vasculitis from an HCP via [redacted] involving an 86-year-old [redacted] with medical history of heparin-induced thrombocytopenia experienced vasculitis three days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Reportedly, the patient presented with purpuric rash over lower limbs (but platelet count was 110) which seemed to be possibly due to vasculitis or immune mediated. Patient was tested antineutrophil cytoplasmic antibody (ANCA) positive. Patient's past vaccinations were not reported. Information on corrective treatment not reported and outcome was reported as not recovered. Further information regarding patient's medical conditions at the time of vaccine, concurrent illness and previous vaccinations and tolerance are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. The case report was assessed as BCCD level 5 for Single Organ Cutaneous Vasculitis.

Based on the medical review of the case report, no safety concern was identified. In addition, no increased O/E ratio has been detected for single organ cutaneous vasculitis.

Rapporteur assessment comment:

The MAH received one HCP case ([redacted]) describing single organ cutaneous vasculitis during the covered period, however some important information was not provided. The MAH is therefore requested to follow-up the case in order to obtain the results of biopsy, additional laboratory tests, information about possible involvement of other organs, information about concomitant medications and/or other comorbidities. The MAH is asked to discuss the updated case in the respective section in the next PSUR.
Next PSUR

The MAH should continue to present data on organ cutaneous vasculitis in the PSUR.

2.3.1.20. Renal AESI (including glomerulonephritis

No case report of renal AESIs has been reported.

Rapporteur assessment comment:

The MAH determined the primary risk window of AKI and glomerulonephritis for purposes of O/E analysis as 1-14 days. The PRAC Rapp is of opinion that the proposed risk window is too short and proposes to extend the primary risk window to 180 days in line with the protocol V2.2. for Rapid safety assessment of

SARS-CoV-2 vaccines in EU Member States using electronic health care data sources, ENCEPP in the next PSUR. ***Next PSUR***

The MAH should continue to present data on renal AESI in the PSUR.

2.3.1.21. Eye disorders (including optic neuritis)

A total of 16 case report of eye disorders were identified including nine serious cases and seven non-serious cases (no fatal outcome was reported). Of these, nine cases (56%) were reported as serious. Among these cases, four had another more likely explication, one had confounding factors for eye disorders onset (drug history including amitriptyline, which can cause eye disorders) and four did not provide medical and drug history, thus being not assessable for confounding factors.

• Case [redacted] was reported from an HCP via [redacted] and referred to a 93-year-old [redacted] with an unspecified ongoing food allergy experienced back pain, eye movement disorder, respiratory arrest, and erythema a couple of minutes after receiving COVID-19 vaccine (recombinant, adjuvanted). This case is presented under the Section on Anaphylactic reactions.

• Case [redacted] reported from an HCP via [redacted] referred to a 90-year-old [redacted] with no reported medical history who developed retinal haemorrhage the same day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient's past vaccinations were not reported. The outcome was reported as not recovered. Based on the limited reported information regarding condition at the time of vaccination, concomitant disease or risk factor excluding other predisposing aaetiologies, the role of suspect cannot be assessed.

• Case [redacted] received from consumer via [redacted] and referred to an 81-years-old unknown gender patient experienced subconjunctival haemorrhage one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). At time of reporting, the outcome was recovering for the event. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded.

• Case [redacted] was reported by a consumer via [redacted] and involves 76-year-old [redacted] with no reported medical history was unable to see properly through left eye 15 minutes after receiving the vaccine. Patient's sight returned to normal within one hour of injection. Patient's past medications were not reported. No corrective treatment was reported, and the event outcome was recovered. Based on the limited information reported, the role of suspect cannot be assessed.

• Case [redacted] was received from consumer via [redacted] and referred to an 82-years-old [redacted] who experienced blurry vision, cold sweat, and sweating attack two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Three days after vaccination, the patient experienced lymphadenopathy. The first attack (blurry vision/loss of focus) lasted only about 10 secs and was followed by a cold sweat lasting five-10 minutes. Another attack (no vision impairment this time) of heavy sweating accompanied by slight nausea occurred two hours later and lasted for about 10-15 mins. The next day, lymph nodes were swollen and tender. The patient's past vaccination(s) included SARS-COV-2 vaccine on 09 April 2022 and Comirnaty on 21 December 2020. Concomitant medications included atorvastatin, ramipril, indapamide, and bisoprolol fumarate for hypertension. At time of reporting, the outcome was recovered for all the events excepted swollen lymph nodes (recovering). Patient's hypertension could be confounding factor for event occurrence. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded.

• Case [redacted] reported from consumer via [redacted] and referred to a 76-year-old [redacted] with a medical history of renal neoplasm (removed) who experienced dry cough three days after, and lacrimation increased four days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient had ongoing hypertension, anaemia, and sciatica on and off. Concomitant medications included amlodipine, losartan for hypertension; aspirin, paracetamol, phenylephrine hydrochloride for nasopharyngitis; ibuprofen for sciatica and folic acid supplements. Patient's past vaccinations were not reported. At time of reporting, the outcome was recovering. Further information on patient's allergy history, medical condition at the time of vaccination, previous vaccination and tolerance are needed to fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed.

• Case [redacted] was reported from a consumer via [redacted] and referred to an 82-year-old [redacted] with no reported medical history experienced dizziness, visual impairment, nausea, malaise, heart rate increased, wheezing same day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient's past medical treatment included potassium and antihypertensives. Patient's past vaccinations were not reported. Outcome was reported as unknown. Further information regarding patient's medical history, allergy history, medical condition at the time of vaccination, previous vaccinations and tolerance are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

• Case [redacted] reported from a consumer via [redacted] referred to a 77-year-old [redacted] with medical history of post-polio syndrome (poliomyelitis) developed dizziness, vertigo, blood pressure decreased, and vision blurred within an hour of vaccination with COVID-19 vaccine (recombinant, adjuvanted) vaccine. Concomitant medications included amitriptyline for myalgia; atorvastatin for TIA; clopidogrel and lansoprazole for gastroesophageal reflux disease. The patient's past vaccinations were not reported. Outcome was reported as not recovered for dizziness and unknown for rest of events. The patient's past four concomitant medication could be confounding factors. Further information on allergy history, patient's clinical condition at the time of vaccination, previous vaccinations and tolerance excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed.

• Case [redacted] reported from consumer via [redacted] referred to a 77-year-old [redacted] with no reported medical history experienced tinnitus, ocular hypertension, parosmia and cluster headache one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient's past vaccinations were not reported. At time of reporting, the outcome was recovering for cluster headache and not recovered rest of the events. Further information on patient's past medical history, concomitant medication, concurrent conditions excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the limited reported information, the role of the individual suspect vaccine cannot be assessed.

• Seven non-serious cases of eye disorders were reported (44% of total). Median age of patients was 81.5 years. Four patients were female, one was male, and gender was not reported for two patients (Male/Female ratio: 0.25). Median time to eye disorders onset was 1.5 days (min: one day, max: four days). For three patients, time to symptom onset was not known. At time of reporting, three patients had recovered from the event, two were recovering, and two had not recovered. In one case of ocular itching there was a major confounding factor (pollen allergy). In four cases, medical and drug history was not provided. Two cases had a more likely explanation. In four cases, eye disorders were the only condition reported.

Based on medical review of cumulative data, no safety concern nor specific pattern has been identified.

Rapporteur assessment comment:

16 cases concerning eye disorders were reported during the reporting period. 9 cases were serious, 7 non-serious, no case is fatal. 2 serious cases were reported by healthcare professionals. In the first case, eye movement disorder occurred during hypersensitive reaction. In the second case ([redacted]) with very limited information, the patient experienced retinal haemorrhage the same day as vaccination with VidPrevtyn Beta. The MAH is requested to follow-up the cases and discuss new information in the respective section of the next PSUR. ***Next PSUR****.*

Within the consumer cases, visual impairment together with dizziness or vertigo is described in 2 cases. Subconjunctival haemorrhage without further details is described in one case.

No safety finding is identified based on the reported cases.

The MAH should continue to present data on eye disorders in the PSUR.

2.3.1.22. Appendicitis

No case report of appendicitis has been reported.

Rapporteur assessment comment:

The MAH should continue to present data on appendicitis in the PSUR.

2.3.1.23. Rhabdomyolysis

No case report of rhabdomyolysis has been reported.

Rapporteur assessment comment:

The risk window for rhabdomyolysis is not listed in the Appendix 6.4. of the PSUR. The risk window of rhabdomyolysis is established as 28 days in the Protocol V2.2 for Rapid Safety Assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources listed, ENCEPP. The MAH is requested to complete the risk window in the next PSUR. ***Next PSUR***

The MAH should continue to present data on rhabdomyolysis in the PSUR.

2.3.1.24. Sudden death

Two cases reporting sudden death were reported on the period ([redacted], [redacted]) and are presented in Table 1 of fatal case reports in Appendix 6.3 of PSUR.

Both cases had insufficient information for a comprehensive evaluation and the role of individual suspect vaccine cannot be assessed.

Case ID/ Age/Sex/ Batch Number	Receipt date	Latency	Short narratives / Assessment
			case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] 86[redacted] W2B042M	02-May-2023	One day	This case involves an 86-year-old [redacted] who died suddenly the day after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient's medical history included breathlessness. Further information on allergies, concurrent condition, previous laboratory investigations, and autopsy results to exclude alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] Unk/Unk Not reported	07-May-2023	Unknown	This case involves patient of an unknown age and gender who died suddenly (unknown latency) after receiving COVID-19 vaccine (recombinant, adjuvanted). Further information on allergies and autopsy results, patient's age and gender, past medical history, concomitant medication, previous laboratory investigations to exclude alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.

Rapporteur assessment comment:

A total of 13 fatal cases were reported during the covered period (see below the section 2.3.4.). The MAH assessed 2 of them as sudden death. Both cases include only scarce information precluding any meaningful assessment. The cases with the fatal outcome are the most serious cases, which should be carefully monitored and assessed. Therefore, the MAH is strongly requested to make an effort to obtain as much information as possible and to discuss the fatal cases in view of the new information including the assessment of the causal relationship with VidPrevtyn in the next PSUR. ***Next PSUR***

The MAH should continue to present data on sudden death in the PSUR.

2.3.2. Additional request from the EMA Committee for Medicinal Products for Human Use

2.3.2.1. Heavy menstrual bleeding

No case report of heavy menstrual bleeding has been reported.

Rapporteur assessment comment:

The MAH should continue to present data on heavy menstrual bleeding in the PSUR.

2.3.2.2. Swelling face/angioedema

In addition to Anaphylactic reactions specific analysis, MedDRA search strategy was conducted for SMQ: "Angioedema" (Narrow) and retrieved 17 cases including seven serious cases and 10 non-serious cases of swelling face/angioedema, none met BCCD level 1 or 2 for anaphylaxis. The serious cases are discussed below followed by a brief overview of the non-serious cases is presented:

• Case [redacted] was reported from a HCP via [redacted] involving a 79-year-old [redacted] with ongoing asthma and multiple allergies who developed swelling face and rash erythematous one hour after receiving COVID-19 vaccine (recombinant, adjuvanted). Patient's past medical history included anaphylactic reaction with Haemaccel. Patient's past vaccinations were not reported. The patient took cetirizine on[redacted] own. The patient was hospitalized and recovered on the same day. Patient's ongoing asthma and multiple allergies with cats, dust, wool could be confounding factor for the events. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for anaphylaxis.

• Case [redacted] reported from an HCP via [redacted] involving a 90-year-old [redacted] who experienced lower lip angioedema two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient had urticaria rash to inside elbow. At time of reporting, the outcome was not recovered for the event. Insufficient information was provided for assessment. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded. This case was assessed as BCCD level 5 for anaphylaxis.

• Case [redacted] reported from [redacted]. An 83-year-old patient of unknown gender experienced red neck, urticaria, rash (from neck down to breasts and on the back), ache and back pain one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient also experienced headache, fatigue, and asthenia six days after vaccination. At time of reporting, the patient was recovering from all the events excepted tiredness, feeling of total lack of energy, headache, ache (not recovered). Further information on allergy history, previous laboratory investigations; patient's medical history excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.

• Case [redacted] reported from consumer via [redacted] A 76-year-old[redacted] with past medical history of myocardial infarction and hepatic steatosis, experienced allergy, hives two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Rash was like hives with large red lumps over most of body. On an unknown date, the patient developed lip swelling. Concomitant medications included generics bisoprolol for coronary heart disease. At time of reporting, the outcome was not resolved for the event allergy, and was unknown for the event lip swelling and hives. Further information on allergies, previous laboratory investigations to exclude alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.

• Case [redacted] reported from consumer via [redacted] A patient of an unknown age and gender experienced hives two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Concomitant medications included simvastatin for blood cholesterol increased; and nitrofurantoin and co-amoxiclav for urinary tract infection. At time of reporting, the outcome was not recovered. The patient's concomitant medications could be confounding factors. Further information on allergies, past medical history, patient's age, and gender to exclude alternative aetiologies for the reported event are needed to

fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.

• Case [redacted] was reported from a consumer via [redacted] A 78-year-old [redacted] experienced severe cutaneous AR, pruritus, urticaria and rash five days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Concomitant medications included amlodipine, atenolol, and losartan for hypertension; warfarin for atrial fibrillation; lansoprazole for Barrett's oesophagus. Five days after the COVID booster injection, the patient experienced pruritus of entire upper arm which intensified rapidly over the next week to severe urticaria affecting both arms, backs of hands, left thigh, both feet and backs of upper left arm. Patient sought advice from local pharmacist on second day and obtained an antihistamine (Chlorpheniramine) which the patient has taken six times daily since then. Rash and itching persisted even after nine days. At time of reporting, the outcome was not recovered / not resolved. The patient's past three previous COVID vaccines and past medical history included immune thrombocytopenia. Further information on allergies, current condition precluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.

• Case [redacted] reported from a consumer via [redacted] and referred to an unknown age [redacted] patient who developed pruritus, pharyngeal swelling, vaccination site bruising, vaccination site warmth and lymphadenopathy unknown duration after the vaccination. This case is already presented under Section 15.1.1.1 Anaphylactic reactions.

In addition, 10 non-serious cases (59% of total) were retrieved reporting facial swelling and angioedema during the period of this report. The median age of patients was 80 years (seven elderly/three adults). There were six males and four females reported in these cases (Male/Female ratio: 1.50). Median time to onset (TTO) of events was two days (min: the same day, max: four days). For four patients, time to symptom onset was not known. At time of reporting, the outcome was reported as not recovered/not resolved in five patients, recovering/resolving in three patients, recovered/resolved in one patient and unknown in remaining one case. In two cases there were confounding factors (such as co-suspect medications/ thyroid disorder) whereas remaining eight cases had insufficient information regarding the relevant case details such as onset latency, medical history, concomitant medications for a comprehensive evaluation. All these cases were assessed as BCCD level 5 for anaphylaxis.

Based medical review of cumulative data, a signal on Allergic including anaphylactic reactions has been opened on 17 May 2023 and has been validated on 14 June 2023.

Rapporteur assessment comment:

During the covered period, 17 cases of angioedema were reported. It is not clear why the MAH assessed the cases of angioedema according to the case definition for anaphylaxis. Angioedema is only one symptom of anaphylaxis and it cannot be expected that the cases of angioedema will automatically fulfil the criteria for anaphylaxis. 2 serious cases were reported by healthcare professionals, 4 serious cases were reported by patients and 1 case was received from the MHRA. Angioedema is described in 4 serious cases, 3 serious cases describe urticaria without face swelling.

In August 2023 the MAH submitted a variation of the marketing authorisation related to hypersensitivity reactions, where angioedema is also covered.

The MAH should continue to present data on angioedema in the PSUR.

2.3.2.3. Dizziness

Based on the MedDRA search strategy outlined in Appendix 6.4.1, 40 case reports of dizziness were reported cumulatively on the period: Of these, 16 cases (40%) were reported as serious.

Among these cases, one case ([redacted]) had another more likely explanation, nine had confounding factors for dizziness onset (drug history including anti-hypertensive, methotrexate, or endocrine treatment, which can cause dizziness; medical history including post-polio syndrome) and six did not provide medical and drug history, thus being not assessable for confounding factors. None of these cases reported a fatal outcome. Of the serious cases, two cases ([redacted], [redacted]) are already presented under Eye disorders (See Section 15.1.1.22 of the PBRER) and one case ([redacted]) is presented under Anaphylactic reactions (See Section 15.1.1.1 of the PBRER) The remaining 13 serious cases are discussed below with a brief overview of the non-serious cases:

Rapporteur assessment comment:

In the case [redacted], a patient with a medical history of potassium and antihypertensives and with no medical history of dizziness experienced dizziness and visual impairment, nausea, malaise, heart rate increased, wheezing on the day of vaccination. The outcome is not known. Although antihypertensives are described in the medical history, the patient did not experience dizziness until vaccination and considering other possible symptoms of reactogenicity, the PRAC Rapp concludes this case as probably related to VidPrevtyn Beta.

In the case [redacted], a patient experienced dizziness, vertigo, hypotension and blurred vision within one hour after the vaccination. Vagal/anxiety-related reaction, which is already listed in section 4.4 of the SmPC, cannot be excluded in this case.

• Case [redacted] involving a 75-year-old [redacted] who experienced dizziness on the same day patient received COVID-19 vaccine (recombinant, adjuvanted). On the following day, the patient experienced shaking, flu-like symptoms, unsteadiness, syncope, and weakness. The patient recovered on the next day. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be assessed. Further information regarding concurrent condition during vaccination, previous vaccination, concomitant medication and tolerance, allergic history, laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case.

Rapporteur assessment comment:

In this case a patient experienced dizziness on the day of vaccination, shaking, flu-like symptoms, unsteadiness, syncope and weakness occurred the next day and the patient recovered two days after vaccination. With respect to close time relationship, other possible symptoms of reactogenicity and transient character of the reactions, the PRAC Rapp concludes the causal relationship probably related to VidPrevtyn Beta.

• Case [redacted] involving a 91-year-old [redacted] who experienced shortness of breath, light headedness, hoarse voice, and unsteady gait on the same day the patient received COVID-19 vaccine

(recombinant, adjuvanted). Treatment history included lercanidipine, which could be a confounding factor. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be assessed.

Rapporteur assessment comment:

A patient experienced dyspnoea, light headedness, unsteady gait and hoarse voice on the day of vaccination. Hypersensitive reaction cannot be excluded without additional information on course, outcome and treatment of the reactions.

• Case [redacted] involving an 86-year-old [redacted] who experienced abdominal pain, vomiting, painful arm, dizziness, and diarrhoea one day after receiving COVID-19 vaccine (recombinant, adjuvanted). Medical history included rheumatoid arthritis treated with methotrexate, which could be a confounding factor. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be assessed.

Rapporteur assessment comment:

In this case, a patient experienced dizziness, abdominal pain, vomiting, diarrhoea and painful arm one day after vaccination with VidPrevtyn Beta. Rheumatoid arthritis and use of methotrexate are described in the medical history. The Rapp does not agree with the MAH's conclusion, that the case is confounded by the chronic condition and long-term medication. The use of concomitant medication cannot be automatically interpreted as a confounding factor. If a patient with long-term medication did not suffer with dizziness in the past and the reaction occurred shortly after vaccination, the influence of long-term medication is not very likely. With respect to close time relationship and other possible symptoms of reactogenicity the Rapp concludes this case as probably related to VidPrevtyn Beta.

• Case [redacted] involving an 84-year-old patient (gender unknown) who experienced heart fluttering, light-headedness, shortness of breath, wheezing, headache, injection site pain and tiredness on the same day the patient received COVID-19 vaccine (recombinant, adjuvanted). Additional information regarding condition at the time of vaccination, concomitant disease or risk factor excluding other predisposing aetiologies would be needed for complete assessment of the case. Based on the reported information, the role of the company suspect product cannot be assessed.

Rapporteur assessment comment:

A patient experienced dizziness together with heart fluttering, shortness of breath, wheezing, headache, tiredness and injection site pain on the day of vaccination. Without additional information on the course and treatment it is not possible to conclude whether dizziness together with dyspnoea and wheezing are not the symptoms of hypersensitivity.

• Case [redacted] involving an 84-year-old patient (gender unknown) who experienced neck pain, fainting, low blood pressure, headache, nausea and felt generally ill on the same day the patient received COVID-19 vaccine (recombinant, adjuvanted). The patient was hospitalized for these events. Medical history included myocardial infarction. Treatment history included eplerenone, lisinopril and citalopram, which could be confounding factors. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be assessed.

Rapporteur assessment comment:

The case [redacted] contains only limited information, no information about examinations, laboratory test, diagnosis and treatment during hospitalisation were provided. The MAH is requested to carefully follow-up the serious cases to obtain as much information as possible for the possibility of a meaningful assessment. The updated cases should be discussed in the next PSUR in view of the new information.
Next PSUR

• Case [redacted] involving an 84-year-old [redacted] who experienced vomiting, dizziness, disorientation, cold sweats, stomach tenderness, pain in arm, nausea and fever the same day patient received COVID-19 vaccine (recombinant, adjuvanted). Medical history included cardiac stenting. Treatment history included bisoprolol and losartan, which could be confounding factors. Further information on allergy history, patient's medical history, family history, past medication, previous laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

Rapporteur assessment comment:

In this case, a patient experienced dizziness together with vomiting, disorientation, cold sweats, stomach tenderness, nausea, fever and pain in arm on the day of vaccination with VidPrevtyn Beta. The MAH concluded that the case is confounded by the medications described in the medical history. As already discussed above, the MAH should carefully consider the possible influence of long-term medication on a new adverse event not described in the past, which occurred shortly after vaccination together with other symptoms. Considering the close time relationship and other possible symptoms of reactogenicity the Rapp concludes this case as probably related to VidPrevtyn Beta

• Case [redacted] involving a 91-year-old [redacted] who experienced night sweats, dyspnoea, dizziness, and fatigue one day after receiving COVID-19 vaccine (recombinant, adjuvanted). Treatment history included bimatoprost and timolol eye drops, as well as amlodipine and Bendroflumethiazide. All these medications could be confounding factors for the safety topic of interest. Further information on allergy history, past medical history excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the report, the role of the individual suspect vaccine cannot be assessed.

Rapporteur assessment comment:

In this case, a patient experienced dizziness together with dyspnoea, night sweats and fatigue one day after vaccination with VidPrevtyn Beta. The MAH concluded that the case is confounded by the medications described in the medical history. As already discussed above, the MAH should carefully consider the possible influence of long-term medication on a new adverse event not described in the past, which occurred shortly after vaccination together with other symptoms. Considering the close time relationship and other possible symptoms of reactogenicity, the Rapp concludes this case as probably related to VidPrevtyn Beta.

• Case [redacted] involving a [redacted] of an unknown age who experienced dizziness, unsteadiness, and short-term memory loss two days after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient was hospitalized for these events. Further information on past medical history, neurological

workup, and concomitant medication excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the limited reported information, the role of the individual suspect vaccine cannot be assessed.

Rapporteur assessment comment:

This case concerns a patient who experienced dizziness, unsteadiness and memory loss two days after vaccination and was hospitalized. No information about the performed examinations, laboratory results, diagnosis or treatment was provided. The MAH is requested to carefully follow-up the serious case [redacted] to obtain as much information as possible for the possibility of a meaningful assessment. The updated case should be discussed in the next PSUR in view of the new information. ***Next PSUR***

• Case [redacted] involving a 78-year-old [redacted] who experienced dizziness and sickness two days after receiving COVID-19 vaccine (recombinant, adjuvanted). According to reporter, these events were leading to a disability. Medical history includes thyroid cancer treated by thyroxin, which could be a confounding factor. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be assessed.

Rapporteur assessment comment:

A patient experienced dizziness and sickness two days after vaccination with VidPrevtyn Beta. The MAH concluded that the use of thyroxin for treatment of thyroid cancer was a confounding factor. Thyroxin is used as suppressive therapy of thyroid cancer and changed to the substitution therapy when remission is achieved. It is not clear if the suppressive therapy is ongoing at the time of vaccination. The Rapp concludes this case as possible related with limited information.

• Case [redacted] involving a 78-year-old [redacted] who experienced dizziness, shortness of breath, and tiredness one day after receiving COVID-19 vaccine (recombinant, adjuvanted). On the next day, the patient developed muscle pain. On the following day the patient developed neck pain. According to reporter, these events were leading to a disability. Further information on allergy history, patient's medical history, family history, past medication, laboratory investigation, previous laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

Rapporteur assessment comment:

In this case a patient experienced dizziness with dyspnoea and tiredness one day after vaccination. Considering the close time relationship and other possible symptoms of reactogenicity, the Rapp concludes this case as probably related to VidPrevtyn Beta.

• Case [redacted] involving an adult [redacted] (age unknown) who experienced dizziness and syncope on the same day patient received COVID-19 vaccine (recombinant, adjuvanted). According to report, symptom appeared around three hours after the injection. After the syncope, it was reported that dizziness perdured "for the next few hours". Further information regarding concomitant medication and tolerance, laboratory investigations excluding alternative aetiologies for the reported event are needed to

fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

Rapporteur assessment comment:

In this case a patient experienced dizziness with dyspnoea and tiredness one day after vaccination. Considering the close time relationship and other possible symptoms of reactogenicity, the Rapp concludes this case as probably related to VidPrevtyn Beta.

• Case [redacted] involving an adult [redacted] (age unknown) who experienced syncope, dizziness, nausea and vomiting two days after receiving COVID-19 vaccine (recombinant, adjuvanted). Patient was reported to be recovered from these events two days after their onset. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded. Case will be reevaluated post further update on the patient's underlying disease conditions, past medical and drug history, concurrent illnesses, and concomitant medications.

Rapporteur assessment comment:

In this case a patient experienced dizziness together with syncope, nausea and vomiting two days after vaccination. Considering the close time relationship and other possible symptoms of reactogenicity, the Rapp concludes this case as probably related to VidPrevtyn Beta.

• Case [redacted] involving a 78-year-old [redacted] who experienced unspecified arthralgia and arm pain on the same day patient received COVID-19 vaccine (recombinant, adjuvanted). On the following day, patient developed a serious dizziness. On an unknown date, nausea, fatigue, and pyrexia appeared. Medical history included arthritis, which is a major confounding factor for reported arthralgia. Treatment history includes amlodipine, which could be a confounding factor for reported dizziness. At the time of reporting (four days after vaccine injection), patient was recovering from nausea, fatigue, and arm pain, and had already recovered (unknown date) from dizziness, pyrexia and arthralgia. Additional information regarding condition at the time of vaccination, concomitant disease or risk factor excluding other predisposing aetiologies would be needed for complete assessment of the case. Based upon the reported information, the role of suspect cannot be assessed.

Rapporteur assessment comment:

In this case a patient experienced arthralgia and arm pain on the day of vaccination, dizziness occurred the next day. In addition, the patient experienced nausea, fatigue and pyrexia. Considering the close time relationship and other possible symptoms of reactogenicity, the Rapp concludes this case as probably related to VidPrevtyn Beta.

• In addition, 24 non-serious cases of dizziness were reported (60% of total). Median age of patients was 78 years, of which 15 patients were female, four were male and gender was not reported for five patients (Male/Female ratio: 0.27). Median time to dizziness onset was the same day (max: three days). For three

patients, time to symptom onset was not known. At time of reporting, seven patients had recovered from the event, seven were recovering, six had not recovered and for four patients the outcome was unknown. When reported, time to recovery ranged between the same day and one day after dizziness onset. In eight cases, there were confounding factors (such as anti-hypertensive or endocrine treatment which can induce dizziness). In 10 cases, medical and drug history was not provided. Two cases had another more likely explanation (vasovagal syndrome and its aftereffects). Four cases were free from confounding factors. In eight cases, dizziness was the only symptom reported.

Based on the medical review of reported case reports of dizziness, no pattern or safety concern has been identified.

Rapporteur assessment comment:

24 non-serious cases of dizziness were reported. Time to onset was 0 – 3 days which is consistent with TTO of dizziness described in the serious cases and with TTO of reactogenicity symptoms generally.

Rapporteur assessment conclusion:

40 cases concerning dizziness were reported during the covered period and also cumulatively. The MAH provided the individual review of each serious case only, but dizziness is usually non-serious, subjective, temporary, self-limited, short-term reaction and most cases being reported as non-serious can be expected. In next reviews, the MAH should take into account the character of the reactions and the non-serious cases should be described in detail when appropriate. ***Next PSUR***

The MAH concluded that many cases reporting dizziness contain limited information for conclusion on the causal relationship, but it is not fully clear why the results of various examinations and tests, family, vaccination and allergic history should be necessary for the assessment of the short-term, self-limited reaction which is usually subjective and mostly non-serious. Medical practice for the specific conditions should be considered during the assessment.

The MAH applied a hyper-conservative approach in the assessment, the cases with concomitant medication are assessed as confounded irrespective of the possible influence of the concomitant medication on the occurrence of dizziness. This approach is not acceptable. The use of concomitant medication cannot be automatically interpreted as a confounding factor. If a patient with long-term medication did not experience dizziness in the past and the reaction occurs shortly after the vaccination, the influence of long-term medication is not very likely.

In all described cases, dizziness occurred in the first days after vaccination with VidPrevtyn Beta. In one case reporting dizziness, a vagal/anxiety-related reaction occurred. In several cases, hypersensitivity reaction cannot be excluded. The Rapp concluded 9 serious cases as probably related to VidPrevtyn Beta especially based on the close time relationship and simultaneous occurrence of other possible symptoms of reactogenicity.

The PRAC Rapporteur considers a causal relationship between VidPrevtyn Beta and dizziness is at least a reasonable possibility. Dizziness should be added to the product information. The MAH is requested to propose a frequency of this new adverse reaction based on the available data.

2.3.2.4. Paraesthesia

No case report of paraesthesia has been reported.

Rapporteur assessment comment: *The MAH should continue to present data on paraesthesia in the PSUR.*

2.3.3. Specific requirement from the MHRA

2.3.3.1. Other peripheral and polyneuropathies

No case report of other peripheral and polyneuropathies has been reported.

2.3.3.2. Multiple sclerosis and other demyelinating disorders

No case report of multiple sclerosis and other demyelinating disorders has been reported.

2.3.3.3. Optic neuritis

No case report of optic neuritis was reported.

Rapporteur assessment comment: *The MAH is requested to discuss neuropathies/polyneuropathies, demyelinating disorders incl. MS and optic neuritis under the section of neurological AESI in the subsequent PSUR.* ***Next PSUR***

2.3.3.4. Myocardial infarction

One case of myocardial infarction ([redacted]) has been reported, it is presented above under coronary artery disease section.

Rapporteur assessment comment: *Please, see the section 2.3.1.10. Coronary artery disease of the AR*

2.3.3.5. Encephalitis

No case report of encephalitis has been reported.

Rapporteur assessment comment: *It is not clear why encephalitis which falls under the AESI meningoencephalitis listed in the RMP version 1.0 is not discussed in the section 2.3.1. Requests based on the core RMP guidance. The MAH is asked to discuss AESI meningoencephalitis in the respective section in the next PSURs.* ***Next PSUR***

2.3.3.6. Myasthenia gravis

No case report of myasthenia gravis has been reported.

2.3.3.7. Fibromyalgia

No case report of fibromyalgia has been reported.

Rapporteur assessment comment:

The MAH is requested to discuss myasthenia gravis under the section immune mediated AESI and fibromyalgia under the section musculoskeletal AESI together with rhabdomyolysis in the subsequent PSUR. ***Next PSUR***

2.3.3.8. Immune thrombocytopenic purpura/autoimmune thrombocytopenia

No case report of Immune thrombocytopenic purpura/autoimmune thrombocytopenia has been reported.

Rapporteur assessment comment:

The terms immune thrombocytopenic purpura and autoimmune thrombocytopaenia fall under the term immune thrombocytopaenia and should be discussed in the section of immune thrombocytopaenia in the next PSUR. ***Next PSUR.***

The MAH determined the primary risk window of thrombotic thrombocytopenic purpura as 1-14 days and the secondary risk window as 1-28 days. The windows proposed by the MAH seems to be too short for immune mediated reactions. The PRAC Rapp proposes to harmonise the risk window with the risk window determined for immune thrombocytopaenia. ***Next PSUR***

The MAH should continue to present data on Immune thrombocytopenic purpura and immune thrombocytopenia in the PSUR.

2.3.3.9. Post orthostatic tachycardia syndrome

No case of Post orthostatic tachycardia syndrome has been reported.

2.3.3.10. Seizures (including general convulsions and all other seizure presentations)

Based on the MedDRA search strategy, total of five cases reported seizures. All these cases were reported as serious with no fatal outcome being reported. Four of these cases were reported in the elderly population and the age group was unknown in remaining case. All these cases were assessed as per the BCCD for seizures as presented below:

• Case [redacted] reported from an HCP via [redacted] and referred to an 89-year-old [redacted] with no history of seizures who experienced seizures two days after receiving COVID-19 vaccine (recombinant, adjuvanted) vaccine and was hospitalized. Patient also experienced loss of consciousness of unknown duration after the vaccination. Patient's head CT was reported as normal. Patient had ongoing unspecified [redacted] and past vaccination included two COVID-19 mRNA vaccine BioNTech. The concomitant medications included carbomer for dry eye. The patient was treated with levetiracetam for generalized

tonic-clonic seizure. The outcome was reported as not recovered for seizures and unknown for loss of consciousness. The patient's concurrent condition of dementia might be an expression of a common underlying confusion factor. Further information regarding patient's tolerance of previous vaccinations and other laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 2 for generalized convulsions.

• Case [redacted] reported from HCP via [redacted] and involving a 71-year-old [redacted] with ongoing immunodeficiency and Parkinson's disease who experienced respiratory arrest and seizures 10 minutes after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Adrenaline was administered for query of anaphylaxis, patient was intubated and transferred to emergency and was discharged after 48 hours. Lorazepam and levetiracetam were given as corrective treatment for seizure. Patient's past vaccination(s) included COVID-19 Vaccine from AstraZeneca, Comirnaty and from Moderna. Further information on allergy history and previous laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD Level 4 for generalized convulsions.

• Case [redacted] reported from an HCP via [redacted] and involving a patient of unknown age and gender who experienced seizure the day of vaccination with COVID-19 vaccine (recombinant, adjuvanted). Further episode of hands twitching, and deterioration of consciousness were reported later. No history of chest pain, shortness of breath was reported. The patient was started on levetiracetam 250 mg and recovered. Further information on past medical history, concomitant medication excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for generalized convulsions.

• Case [redacted] reported from consumer via [redacted] and involving an 81-year-old [redacted] who experienced unconscious and fits (non-epileptic) the day of vaccination with COVID-19 vaccine (recombinant, adjuvanted). It was not reported if the patient received a corrective treatment. The outcome was reported as recovered. Further information on allergy history, past medical history, concomitant medication, current condition excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for generalized convulsions.

• Case [redacted] reported from consumer via [redacted] and involving a 79-year-old [redacted] with no medical history who experienced seizure one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted) and who was admitted to hospital for five days. Reportedly, patient lost consciousness completely, was unresponsive for around 10 mins, came round but took two-three hrs. All tests were clear for stroke/TIA/heart attack, bloods. Other laboratory investigations included blood test, CT, and ECG; results were not reported. At the time of reporting, the outcome was recovering for the event. The patient had no medical history. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded. This case was assessed as BCCD level 4 for generalized convulsions.

Based on medical review of the case reports, no safety concern has been identified. In addition, no increased O/E ratio has been detected for seizures.

Rapporteur assessment comment:

5 cases of general convulsions were reported during the covered period. 3 cases were reported by healthcare professionals, 2 cases were reported by consumers. All cases contain limited information about results of ECG, the result of CT is described only in 1 case. Not all cases describe whether loss of consciousness occurred. The MAH is requested to follow-up the cases in order to get as much information as possible for a meaningful assessment.

The MAH is requested to further monitor general convulsions/seizures in the subsequent PSUR where the new information received during the follow-ups should be also described. ***Next PSUR***

2.3.4. Fatal cases

A total of thirteen case reports with fatal outcome have been received during the period (including two cases that reported sudden death).

All cases are reported in elderly patients, some of them reported medical history that could give alternative explanation for the fatal outcome. Fatal outcome is mostly reported shortly after the vaccination, same day to one day in six case reports, two to six days in four case reports, 10-20 days in two patients and it was unknown in remaining one case. All case reports provided insufficient information on the patients' medical history, concurrent conditions, previous laboratory investigations, and no autopsy results excluding alternative aetiologies for the reported event to fully assess the cases. No new safety concern was identified from the medical review of fatal cases.

Case ID/ Age/Sex/ Batch Number	Receipt date	Latency	Short narratives / Assessment
[redacted] 92/F Not reported	13-Apr-2023	One day	This case involves a 92-year-old female who died in sleep in the night one day after receiving a booster dose of COVID-19 vaccine (recombinant, adjuvanted). The patient had a past medical history of cardiac failure and was previously vaccinated with five unspecified COVID vaccines. Further information on concurrent conditions, allergies, previous laboratory investigations and autopsy results, excluding alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed
[redacted] 28/[redacted]	18-Apr-2023	Same day	This case involved a 28-year-old male with ongoing dementia who experienced vomiting shortly after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient then developed an aspiration pneumonia and died in hospital. The patient was fine on the morning of the vaccination day. The patient's concomitant medication included amlodipine, lisinopril, omeprazole and folic acid. The patient's past medical history, medical treatment(s), vaccination(s) and family history were not provided. Based on the minimal information provided, and potentially incorrect information available (dementia + concomitant medications suggesting altered cardiac condition in a 28-year-old patient), the case is unassessable. Of note, further information is awaited including confirmation of the age of the patient who was reported to have severe dementia and several underlying conditions that could correspond to an elderly age group.
[redacted] 78[redacted]	02-May-2023	Two days	This case involves 78-year-old female who experienced cerebral venous sinus thrombosis two days after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient has previous medical history of COVID-19 approximately three months ago and TIA approximately two years ago and was on aspirin. The patient had ongoing hypertension. Further information regarding previous COVID-19 vaccinations, indication of reported concomitant medications including aspirin, medical history and risk factors, examination results and context for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] 86/M [redacted]	02-May-2023	One day	This case involves an 86-year-old male who died suddenly the day after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient's medical history included breathlessness. Further information on allergies, concurrent condition, previous laboratory investigations, and autopsy results to exclude alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.

[redacted] 74/M [redacted]	02-May-2023	One day	This case involves a 74-year-old male who died due to unknown reason (death unexplained) the day after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient's past medical history included kyphoscoliosis, hypospadias, prostatism, gastroesophageal reflux disease, vertigo, COPD and hypertension and the patient had four previous COVID vaccines. Further information on allergies, concurrent condition, previous laboratory investigations, coroner referral and autopsy results to exclude alternative aetiologies for the reported event are needed to fully assess this case. As per reporter, this case report was not related to possible blood clots or low platelet counts or possible myocarditis or pericarditis. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] 75/M [redacted]	02-May-2023	Four days	This case involves a 75-year-old male who was found dead four days after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient's medical history included essential hypertension, breathlessness, and Chronic obstructive lung disease. Further information on allergies, concurrent condition, previous laboratory investigations, and autopsy results to exclude alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] Unk/Unk Not reported	07-May-2023	Unknown	This case involves patient of an unknown age and gender who died suddenly (unknown latency) after receiving COVID-19 vaccine (recombinant, adjuvanted). Further information on allergies and autopsy results, patient's age and gender, past medical history, concomitant medication, previous laboratory investigations to exclude alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] 84/F [redacted]	07-May-2023	Six days	This case involves a 94-year-old female who died six days after receiving COVID-19 vaccine (recombinant, adjuvanted). Further information on allergies, concurrent condition, medical history, previous laboratory investigations, and autopsy results to exclude alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] 93/M [redacted]	07-May-2023	Three days	This case involves a 93-year-old male who died three days after receiving COVID-19 vaccine (recombinant, adjuvanted). Further information on allergies, autopsy results, past medical history, and concomitant medications to exclude alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] 90/F [redacted]	07-May-2023	One day	This case involves a 90-year-old female who died next day after receiving COVID-19 vaccine (recombinant, adjuvanted). Further information on allergies, past medical history, concurrent condition, autopsy results to exclude alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] 98/M [redacted]	07-May-2023	10 days	This case involves a 98-year-old male who died 10 days after receiving COVID-19 vaccine (recombinant, adjuvanted). Further information on allergies, concurrent condition, medical history, previous laboratory investigations, and autopsy results to exclude alternative aetiologies for the reported event are needed to fully assess this

			case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] 90/F [redacted]	07-May-2023	20 days	This case involves a 90-year-old female who died 20 days after receiving COVID-19 vaccine (recombinant, adjuvanted). Further information on allergies, concurrent condition, medical history, previous laboratory investigations, and autopsy results to exclude alternative aetiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed.
[redacted] Unk/Unk Not reported	09-May-2023	Same day	This case involves an adult patient, of unknown age and gender, who died a few hours after receiving COVID-19 vaccine (recombinant, adjuvanted). Further information on patient's age, gender, past medical history, allergy history, current medications, condition at the time of reported event, laboratory investigations, and autopsy results to exclude alternative aetiologies for the reported event, are needed to fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed.

In addition, no increased O/E ratio has been detected for fatalities (primary or sensitivity analyses) (excluding the case reported in a 28-year-old male).

Rapporteur assessment comment:

13 fatal cases were reported during the covered period and also cumulatively. All cases contain very limited information without including results of the laboratory tests, other examinations or the results of autopsy precluding any assessment.

One fatal case ([redacted]) concerns a 28-year-old-male with dementia who experienced vomiting and aspiration pneumonia. The MAH stated that further information is awaited. The MAH is requested to discuss the case in view of the new information in the next PSUR. ***Next PSUR***

Another fatal case concerns a 78-year-old-female who experienced cerebral sinus venous thrombosis 2 days after vaccination with VidPrevtyn Beta. The case was already discussed above in the section 2.3.1.12. Thromboembolic AESI and follow-up was requested.

Fatal cases are the most serious cases, which should be carefully monitored and assessed. However, based on limited information, an in-depth assessment of the missing details is not possible. Therefore, the MAH is strongly requested to make an effort to obtain as much information as possible and to discuss the cases in view of the new information including the assessment of the causal relationship with VidPrevtyn Beta in the next PSUR. In addition, the MAH is requested to provide a description how case follow-ups are processed depending on seriousness and listedness of the AEs. ***Next PSUR***

The MAH should continue to present data on fatal cases in the PSUR.

2.3.5. Vaccination failure

Based on the MedDRA search criteria as outlined in Appendix 6.4.1, a total eight case reports of COVID-19 infection were reported, of which two were reported as serious case reports and are detailed below ([redacted] and [redacted]). No fatal outcomes or severe cases were being reported.

• One serious case [redacted] reported from a consumer via [redacted] and involving a 77-year-old [redacted] with medical history of atrial fibrillation, hypertension, and hypercholesterolemia, who experienced SARS-coronavirus-1 (CoV-1) infection (SARS) 14 days after vaccination with COVID-19 vaccine (recombinant, adjuvanted) and SARS-CoV-2 infection (COVID-19: confirmed by test) 15 days after vaccination. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as serious with the criteria of Medically significant, but the intensity of severity was not reported. This case was assessed as BCCD level 5 for VAED and is detailed under Section 15.1.1.8 as Respiratory AESI.

• One serious case [redacted] received from consumer via [redacted] and involving an 86-year-old patient (unknown gender) with a medical history included atrial fibrillation with pacemaker fitted for heart, experienced COVID-19, coughing, flu, flu like symptoms and mucus discharge six days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). At the time of reporting, the outcome was recovering for all the events. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded. This case was assessed as serious with the criteria of medically significant with disability, but the intensity of severity was not reported for the events. This case was assessed as BCCD level 5 VAED.

• Remaining six non-serious cases ([redacted], [redacted], [redacted], [redacted], [redacted], [redacted]) were all consumer-reported and were assessed as BCCD level 5 for VAED. The TTO ranged from few hours after the vaccination to few days in most cases except for two cases which reported respectively a TTO of four weeks ([redacted]) and of more than three months ([redacted]). The available information in all these cases was insufficient for a conclusive evaluation and the role of individual suspect vaccine could not be ascertained.

Based on medical review of cumulative data, no safety concern was identified.

Rapporteur assessment comment:

8 case of SARS-CoV-2 infection were reported during the reporting period. All cases were reported from patients and contain limited information. 2 cases are serious and 6 cases are non-serious. Based on the limited information provided in the serious cases, VAED/VAERD cannot be identified.

In case [redacted], a 77-year-old [redacted] patient with atrial fibrillation, hypertension, and hypercholesterolemia experienced SARS-CoV-2 infection 14 days after vaccination with VidPrevtyn Beta. The infection was confirmed by test. The MAH stated that the role of the vaccine cannot be assessed based on the available information. The Rapp does not agree with this conclusion. Although some information is missing, e.g., information about previous vaccination, the available data is sufficient to assess the causal relationship. Similarly, the causal relationship is concluded as non-assessable in all non-serious cases. The MAH is requested to provide a detailed description how the causal assessment between VidPrevtyn Beta and vaccination failure is performed in the next PSUR. ***Next PSUR***

The MAH should continue to present data on vaccination failure in the PSUR.

2.4. Characterisation of risks

2.4.1. New information on important identified risks

There are no important identified risks for COVID-19 vaccine (recombinant, adjuvanted). Therefore, this section is not applicable.

2.4.2. New information on important potential risks

The MAH has determined that there was no new relevant safety information that would have an impact on the understanding and characterization of the previously recognized potential risks. However, details regarding the new relevant safety information are included below.

Myocarditis/Pericarditis

Source of new information: Cases retrieved from the reference interval from GPV Safety database

• Background relevant to the evaluation: For more details on this risk, see also Section 16.4.

• Method(s) of evaluation including data sources, search criteria, and analytical approaches: The GPV Safety database was searched for the following MedDRA PTs: "Autoimmune myocarditis", "Eosinophilic myocarditis", "Giant cell myocarditis", "Hypersensitivity myocarditis", "Immune-mediated myocarditis", "Lupus myocarditis", "Myocarditis, "Myocarditis post infection", "Radiation myocarditis". In addition, O/E analyses are conducted based on the methodology and recommendations described by Mahaux et al.

• Results: From the review of the GPV safety database, one case of myocarditis was retrieved for COVID-19 vaccine (recombinant, adjuvanted) during the reference period. In addition, no increased O/E ratio has been detected for myocarditis/pericarditis (Refer to Appendix 6.4.2 and Section 16.4).

• Discussion: One serious case report of myocarditis was reported from consumer via [redacted] in an elderly patient of unknown gender two days after vaccination. An 81-year-old and unknown gender patient experienced positional dizziness and myocarditis two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). At time of reporting, the outcome was not recovered. Further information on patient underlying disease condition, past medical and drug history, concomitant medications, description of the reported symptoms, complementary investigations and results excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for myocarditis.

• Conclusion: Based on medical review of cumulative data supported by O/E analysis, no safety concern has been identified.

Rapporteur assessment comment:

Please, see the assessment of the single case report of myocarditis in the section 2.3.1.2. of the AR.

Vaccines-Associated Enhanced Disease including Vaccine-Associated Enhanced Respiratory Disease

There were no cases that reported VAED/VAERD (Refer to Section 15.1.5 for Vaccination Failure and Section 15.1.1.3 for COVID-19 AESIs).

2.4.3. New information on other identified risks not categorized as important

There are no identified risks not categorized as important for COVID-19 vaccine (recombinant, adjuvanted), therefore this section is not applicable.

2.4.4. New information on other potential risks not categorized as important

Utilizing the surveillance activities, the MAH has not identified any new safety information during the reporting interval that would have an impact on the understanding and characterization of the previously recognized potential risk(s) not categorized as important.

2.4.5. Update on missing information

Utilizing the surveillance activities, the MAH has not identified any new safety information during the reporting interval that would have an impact on the understanding and characterization of missing information.

Use in pregnancy and while breast-feeding

No case reports of use in pregnancy were reported.

Two systematic review and meta-analysis were published in relation to pregnancy. One concerning pregnancy outcome following COVID-19 vaccination with BNT162b2, Moderna, ChAdOx1 and Janssen vaccines (8) and the second in relation to pregnancy outcome and risk of pregnancy related complications in COVID-19 vaccinated pregnant population that found no increased risks in pregnant women or neonates of vaccinated women compared to non-vaccinated, and no significant effects on maternal-foetal complication.

Rapporteur assessment comment: *The systematic reviews are discussed in section 1.3.5.5. Literature of the AR.*

Use in immunocompromised subjects

One literature article presented the use of a protein-based COVID-19 vaccine (SpikoGen) in patients undergoing kidney transplant receiving immunosuppressive therapy. The observed safety profile in this patient population was similar to the previously known safety profile of the vaccine and no SAEs reported.

Use in frail subjects with unstable health conditions and co-morbidities (e.g., Chronic Obstructive Pulmonary Disease, diabetes, chronic neurological disease, cardiovascular disorders)

No significant information about the use with unstable health conditions and co-morbidities was identified.

Rapporteur assessment comment: *The article is discussed in section 1.3.5.5. Literature of the AR.*

Use in subjects with autoimmune or inflammatory disorders

No significant information about the use with autoimmune or inflammatory disorders was identified.

Interactions with other vaccines

No information about the use with other vaccines was identified.

Long-term safety

No new information is available from post-marketing sources since the vaccine has been only approximately five months on the market.

Rapporteur assessment comment: *The safety concerns remain unchanged.*

3. Benefit evaluation

COVID-19 vaccine (recombinant, adjuvanted) is approved as a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults who have previously received a messenger ribonucleic acid (mRNA) or adenoviral vector COVID-19 vaccine. The mechanism of action consists of the induction of immune responses against the antigens contained in the vaccine. The S glycoprotein of SARS-CoV-2 associated with AS03 adjuvant stimulates neutralizing and other functional S-specific antibodies, as well as cellular immune responses directed against the S antigen, which may contribute to protection against COVID-19 (47).

Epidemiology:

Epidemiological data collected since the beginning of the pandemic have shown that individuals of any age can acquire infection of SARS-CoV-2, however, there is an uneven distribution of infections per defined age group. According to data published by the WHO, people aged 30 to 39 years have the highest amount of confirmed and probable cases, followed by 20 to 29, 40 to 49 and 50 to 59 years age groups respectively. This age-based distribution, however, does not correlate across gender-based distribution, with infections occurring at similar rates between males and females.

Globally, till 09 May 2023, there have been 766 029 927 confirmed cases of COVID-19, including 6 928 795 deaths, reported to WHO. Although all regions have reported substantive numbers of cases, the greatest cumulative numbers of confirmed cases to date have been in Europe (>276 million cases), the Western Pacific (>203 million cases) and the Americas (>178 million cases).

Key risk factors for severe COVID-19 disease include but not limited to CVD, diabetes, chronic respiratory disease, COPD, hypertension, malignancies, obesity, chronic kidney disease, cerebrovascular disease and stroke, with higher risk of severity and mortality ranging 1.14 to 7.1 times higher in these risk groups. Older age (particularly ≥65 years) is a recognized risk factor for more severe COVID-19 disease and death, with populations aged 65 to 74 years at five times higher risk of hospitalization and 90 times higher risk of death than population aged 18 to 29 years old in the US.

New and emerging variants are playing an important role in local and global epidemiology.

Omicron has established itself as the dominant SARS-CoV-2 lineage globally. In early 2022, a large number of Omicron-descendent sub-lineages emerged (BA.1, BA.2, BA.3, BA.4, BA.5), with ECDC categorizing these sub-lineages separately to better distinguish their relative impacts to the epidemiological situation. Amongst these sub-lineages, BA.2, BA.4 and BA.5 consistently circulated in the

EU/EEA until late 2022. The current epidemiological situation is hallmarked by a highly diverse landscape of co-circulating BA.2 and BA.5 descendent variants, which have different properties to their parental lineages and require individual assessment.

Efficacy data/Immunogenicity data:

Efficacy of CoV2 preS dTM-AS03 (B.1.351 strain) vaccine has been inferred by immuno-bridging of immune responses to an authorized COVID-19 vaccine, for which VE has been established. The clinical immunogenicity of CoV2 preS dTM-AS03 (B.1.351 strain) vaccine given as a booster injection is being evaluated in two clinical studies: VAT00013 (Study 1) in COVID-19 mRNA vaccine-primed participants and VAT00002 Cohort 2, Beta arm (Study 2) that included participants primed with various types of COVID-19 vaccines.

Immunogenicity results from Study VAT00013

This is a randomized, single-blinded multicenter investigator-initiated clinical study conducted in France, which evaluated the immune response induced by a booster dose of either CoV2 preS dTM-AS03 (B.1.351 strain) vaccine, or Pfizer COVID-19 mRNA vaccine or Sanofi investigational booster vaccine (protein-based adjuvanted COVID-19 vaccine, D614, 5 µg) in individuals previously vaccinated with two doses of Pfizer COVID-19 mRNA vaccine. The per-protocol analysis population included 217 participants 18 years of age and older primed with two doses of COVID-19 mRNA vaccine three to seven months prior to receiving CoV2 preS dTM-AS03 (B.1.351 strain) vaccine (N = 67), COVID-19 mRNA vaccine (N = 76) and Sanofi investigational booster D614 vaccine (N = 74). The mean age was 40.6 years (range 18 to 73 years). The mean duration between the second dose of the primary series and the booster dose was 174 days and was comparable across groups.

Among this per-protocol population, samples from prior to vaccination and 28 days after booster of 114 participants (54 from CoV2 preS dTM-AS03 [B.1.351 strain] vaccine and 60 from Pfizer COVID-19 mRNA vaccine and 48 from Sanofi investigational booster D614 vaccine) were tested by Pseudovirus Neutralization Assay. The Geometric Mean Titers (GMT) of neutralizing antibodies 28 days after CoV2 preS dTM-AS03 (B.1.351 strain) vaccine or Pfizer COVID-19 mRNA vaccine booster in COVID-19 mRNA vaccine-primed participants were compared.

Superiority of GMT against Omicron BA.1 was demonstrated for CoV2 preS dTM-AS03 (B.1.351 strain) vaccine group in comparison with Pfizer COVID-19 mRNA vaccine group. Non-inferiority of seroresponse rate against Omicron BA.1 and D614G strains for CoV2 preS dTM-AS03 (B.1.351 strain) vaccine compared to Pfizer COVID-19 mRNA vaccine was demonstrated with seroresponse rate defined as a four-fold or greater rise in serum neutralization titer 28 days post-booster dose relative to pre-booster dose.

Across all variants tested, the levels of neutralizing Ab titers 28 days post-booster dose observed in CoV2 preS dTM-AS03 (B.1.351 strain) vaccine group were higher than in Pfizer COVID-19 mRNA vaccine group, with the GMT ratio between 1.43 and 2.53.

Immunogenicity results from Study VAT00002 (Cohort 2, Beta arm)

CoV2 preS dTM-AS03 (B.1.351 strain) vaccine given as a booster is being evaluated in an ongoing multicenter phase 3 clinical study in participants 18 years of age and older in Australia, France, Honduras, Spain, UK, and United States. Per-protocol analysis population included 615 participants who received CoV2 preS dTM-AS03 (B.1.351 strain) vaccine 4 to 10 months after receiving primary vaccination with 2 doses of Pfizer COVID-19 mRNA vaccine (nucleoside modified) (n = 325) or Moderna COVID-19 mRNA Vaccine (nucleoside modified) (n = 93), AstraZeneca COVID-19 Vaccine (ChAdOx1-S [recombinant]) (n =

94), Sanofi investigational primary vaccine (protein-based adjuvanted COVID-19 vaccine, D614, 5 to 15 µg of antigen dose) (n = 72), or with one dose of Janssen COVID-19 vaccine (Ad26.COV2-S [recombinant]) (n = 31).

In per-protocol analysis population receiving CoV2 preS dTM-AS03 (B.1.351 strain) vaccine booster, the mean age of participants was 46.0 years (range 18 to 93 years); 435 (70.7%) were 18 to 55 years of age 180 (29.3%) were 56 years of age and older, 78 (12.7%) were 65 years of age and older. Among them, 47.0% were male, 53.0% were female, 67.6% were White, 11.7% were Black or African American, 3.4% American Indian or Alaska Native, and 2.9% were Asian.

Immunogenicity was assessed by measuring neutralizing Ab titers (ID50) against a pseudo virus expressing the SARS-CoV-2 S protein from a USA_WA1/2020 isolate with the D614G mutation and B.1.351 variant using a SARS-CoV-2 Pseudo virus Neutralization Assay.

A booster response to CoV2 preS dTM-AS03 (B.1.351 strain) vaccine was demonstrated regardless of the vaccine used for primary vaccination with the Geometric Mean Titers Ratio (GMTR [GMTR], fold increase) 14 days post-booster relative to pre-booster against B.1.351 strain ranging from 38.5 to 180, and from 14.5 to 148 for D614G strain.

No new relevant efficacy and/or effectiveness findings in approved indications were identified during the reporting interval.

Based on the review of the data received for Vaccine failure/VAED, a total of eight cases (two serious and six non-serious) that reported COVID-19 after vaccination. All were consumer reported cases with a BCCD level 5 assessment. These cases did not have sufficient data for a comprehensive evaluation; However, based on the limited information available, no cases reported VAED/VAERD and no cases reported lack of efficacy. Based on the medical review of cumulative safety data, no information on changes in the therapeutic environment could be identified that could impact efficacy and/or effectiveness or lead to vaccine failure.

No new relevant efficacy findings in approved indications were identified during the reporting interval, and the efficacy profile of COVID-19 vaccine (recombinant, adjuvanted), is unchanged.

The data available from the studies performed for this vaccine remain the reference information on the robustness of the immune response elicited by the vaccine. No new immunogenicity data that would put these conclusions in question have been made available during the reporting period.

Rapporteur assessment comment:

There are no new data on efficacy that alters previous assessments.

4. Benefit-risk balance

VidPrevtyn Beta is indicated as a booster for active immunisation to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine.

No new significant information that would impact the benefit-risk balance was identified during the assessment of the data in this PSUR.

The update of the product information is recommended to include dizziness as a new adverse reaction to the section 4.8 of the SmPC and PIL.

Based on the PRAC Rapporteur review of the available safety and efficacy/effectiveness data for VidPrevtyn Beta and with the recommended update of the PI, the benefit-risk balance of VidPrevtyn Beta remains unchanged.

5. Rapporteur Request for supplementary information

1. The MAH is requested to propose a frequency of the new ADR Dizziness based on the available data.
2. The MAH is requested to provide information, why the exposures in Scotland, Wales and North Ireland were not included in the PSUR.
3. The MAH is requested to clarify discrepancy between number of stroke cases listed in the body of PSUR and in the Appendix 6.4.2.

6. MAH responses to Request for supplementary information

1. The MAH is requested to propose a frequency of the new ADR Dizziness based on the available data.

Response:

Dizziness is an unspecific medical term which encompasses multiple different conditions. Generally, it can be differentiated into vertigo (affection of the vestibular system), disequilibrium (caused by Parkinson's disease or peripheral neuropathies), presyncope (with cardiovascular aetiology) or psychogenic light-headedness.

Vertigo is the most common aetiology of dizziness, accounting for nearly half of cases referred to general practitioners, and it can be acute, recurrent or chronic. Acute vertigo may result from a vertebrobasilar stroke/transient ischaemic attack (TIA) or from a vestibular neuritis (VN). Recurrent vertigo can be caused by benign paroxysmal positional vertigo (BPPV) or by migraine (thus being called vestibular migraine, VM). Chronic vertigo includes rare conditions such Menière's disease (MD) and persistent postural- perceptual dizziness (PPPD). Among vertigos, BPPV is the most common, followed by VM and VN. Interestingly, the male:female ratio among VM patients lays between 1:1.5 and 1:5, probably because of the greater prevalence of migraine among women. In a cross-sectional retrospective study, including 1535 patients who referred for dizziness to a tertiary care hospital, 20% of them was diagnosed an acute syndrome, 35% of them an episodic syndrome, 5% a chronic syndrome, and in remaining 40% of cases the initial workup failed to make a clear diagnosis. According to follow-up data, 18% of initial diagnoses are not correct, and 45% of patients had no clear diagnosis at the end of the follow-up. This observation is in agreement with the estimation that 20% of patients referring for dizziness to general practitioners do not receive a clear diagnosis. In a longitudinal prospective study including 1666 patients, stroke/TIA was diagnosed in 3.2% of patients

presenting with dizziness, vertigo, or imbalance. Presence of isolated dizziness was negatively correlated with stroke/TIA diagnosis ($p<0.01$), only 0.7% of such patients having been diagnosed a stroke/TIA.

Other studies investigated the interplay between psychogenic factors and dizziness. In a cross-sectional study, including 544 patients, those who scored worse in anxiety and depression psychometric questionnaires had also greater scores in dizziness symptoms questionnaires. It has been showed that such association can work in both ways, being anxiety or depression a risk factor for a specific dizziness onset as well as a consequence of recurrent or chronic dizziness of organic origin. Interestingly, a case-control study including 92 BPPV patients and 141 healthy controls suggested that women may be more than men at risk of developing anxiety and phobic anxiety secondary to dizziness experience. Presyncope is the prodrome of syncope, in which the patient can display autonomic activation, light- headedness, or palpitations, basing on syncope aetiology, before to lose consciousness. The European Society of Cardiology (ESC) resumed the complex physiopathology of syncope (Figure 1). Elderly patients are particularly vulnerable to orthostatic hypotension, because of the addition of primary age- related autonomic nervous system failure (ANF) and polymedication. In facts, anti-hypertensives, antidepressants, antiparkinsonian, myorelaxants and opioids (which are commonly prescribed drugs in the elderly) can induce various degrees of secondary ANF.

Clinical Studies (Interventional)

Dizziness was collected as an unsolicited adverse event (AE) during clinical development of COVID-19 vaccine (VAT00002 Cohort 2 Clinical Study involving 705 participants 18 years of age and older who received the vaccine (Monovalent (B.1.351) booster) 4 to 10 months after receiving primary vaccination and VAT00002 Cohort 2/VAT00008 Stage 2 Clinical study involving an additional 7093 participants 18 years of age and older having received primary or booster vaccine formulation containing the same Beta antigen (bivalent (B.1.351 + D614) formulation).

In VAT00002 Cohort 2, two (2) participants reported non-serious adverse reactions involving the Preferred Term (PT) dizziness. In one (1) case, dizziness occurred the same day of vaccination and participant recovered 2 days after; in the other case, dizziness occurred one day after vaccination and the participant recovered on the same day. In both cases, dizziness was associated with other AEs which could be confounding factors in the occurrence of dizziness. No related AEs of dizziness were reported in the vaccine group in VAT00008 Stage 2.

From the COVID-19 vaccine (recombinant, adjuvanted) Development International Birth Date (28 August 2020) up to the first Marketing Authorization (10 November 2022), analysis of unsolicited AE from VAT00002 Cohort 2 and VAT00008 Stage 2 clinical studies did not conclude to select dizziness as part of the expected AEs to be mentioned in the RSI.

As of 30 June 2023, around 5000 participants received a booster dose of COVID-19 vaccine (recombinant, adjuvanted) in the booster extension phase of VAT00008. As of the cut-off, no AEs of dizziness have been reported in the booster extension.

No (0) serious adverse events (SAEs) including dizziness PT have been reported in any clinical trial.

In conclusion, during clinical development stage of COVID-19 vaccine (recombinant, adjuvanted), the frequency and characteristics of reports of dizziness were not in favor of a possible relationship between administration of COVID-19 vaccine (recombinant, adjuvanted) and the occurrence of dizziness.

Cumulative cases reports analysis

Methodology

A search from 10 November 2022 to 30 June 2023 was performed in the Sanofi Global PV database (encompassing post-marketing cases and serious cases and pregnancy exposures from clinical studies) completed by analysis of non-serious cases reporting dizziness during clinical studies. This search was performed to identify all solicited and unsolicited cases, both Health Care Professional (HCP) and non- HCP (consumer) of safety signal(s) reported after the use of VidPrevtyn Beta as a suspect drug including diagnosis and symptoms using Medical Dictionary for Regulatory Activities (MedDRA) version 26.0, coded with the following PT: Dizziness (MedDRA Code 10013573).

Results

From Sanofi Global PV Database, the search retrieved a total of 50 cases from post-marketing sources. In addition, the 2 non-serious cases which were retrieved from clinical studies, were further analyzed and included in this analysis. Stratification by source and seriousness is displayed in table below.

Source type	Serious	Non-serious	Total
Clinical sponsored	0	2	2
Consumer	3	5	8
Health authority	0	0	0
Health authority/Consumer	14	18	32
Health authority/Healthcare professional	4	5	9
Healthcare professional	0	1	1
Literature	0	0	0
Total	21	31	52

All spontaneous cases were reported from UK; the majority (32/50)were reported non medically confirmed as reported from consumer via Health Authority (MHRA).

Overview of cases

Two (2) cases ([redacted] and [redacted], both of which were serious) were excluded from the following analysis, since the reported dizziness rather evokes a cardiogenic pre-syncope in patients with cardiac manifestations.

Fifty (50) remaining cases with a compatible chronology (31 non-serious and 19 serious) have been further stratified on presence of co-reported events, presence of confounding factors, and seriousness, as follows:

- Dizziness reported with other events (82%; n=41, 21 non-serious and 18 serious)
  - without identified relevant confounding factor(s) (n=2, all non-serious)

- with identified relevant confounding factor(s) (n=15, 5 non-serious and 10 serious))
- with insufficient information on confounding factors (n=24, 16 non-serious and 8 serious)

- Dizziness being the only reported event (18%; n=9, 8 non-serious and 1 serious)
  - without identified relevant confounding factor(s) (n=1, non-serious)
  - with identified relevant confounding factor(s) (n=4, 3 non-serious and 1 serious)
  - with insufficient information on confounding factors (n=4, all non-serious) None (0) of the reported cases had fatal outcome

None (0) of the reported cases had fatal outcome.

Pattern Analysis

Among the 50 cases with compatible chronology, 43 cases (86%) were reported in elderly patients, which is expected as per the indication of the vaccine in elderly population. The majority of patients were female (27/50, 54%). The most common time to dizziness onset was on the same day (22/50, 44%), 86% of cases having occurred within 2 days from the vaccination (43/50, 86%). At the time of reporting, 13 patients (26%) had already recovered and 12 other patients (24%) were recovering. Among the patients who already recovered, 58% recovered within one day after dizziness onset (7/11). The most frequent confounding factor was the treatment with anti-hypertensive drugs (14/50, 28%), which again is expected as per the indication of the vaccine in elderly population.

Table 2 - Pattern Analysis (Case Level) of all cases with compatible chronology (n = 50)

Parameters		All cases (n=50)		With co-reported PTs (n=37)		Isolated dizziness (n=9)	
		n	%	n	%	n	%
Age	Adult	5	10%	5	12%	0	0%
	Elderly	43	86%	34	83%	9	100%
	Unknown	2	4%	2	5%	0	0%
Gender	Female	27	54%	21	51%	6	67%
	Male	11	22%	9	22%	2	22%
	Unknown	12	24%	11	27%	1	11%
Time to Onset (TTO)	Same day	22	44%	19	46%	3	33%
	1 day	13	26%	11	27%	2	22%
	2 days	8	16%	7	17%	1	11%
	3 days	1	2%	0	0%	1	11%
	19 days	0	0%	0	0%	0	0%
	Unknown	6	12%	4	10%	2	22%
Outcome	Recovering	12	24%	11	27%	1	11%
	Recovered	13	26%	9	22%	4	44%
	Sequelae	0	0%	0	0%	0	0%
	Not recovered	16	32%	12	29%	4	44%
	Fatal	0	0%	0	0%	0	0%
	Unknown	9	18%	9	22%	0	0%
Time to Recovery (TTR)	Same day	3	25%	3	7%	0	0%
	1 day	4	33%	1	2%	3	75%
	2 days	2	17%	2	5%	0	0%
	Unknown	3	25%	2	5%	1	25%
	Not yet recovered (at the time of reporting)	38		33		5	
Patients with at least one confounder,		19	38%	15	37%	4	44%
	Relevant medical history	1	2%	1	2%	0	0%
	Concomitant products known to induce the reaction, of which:	18	36%	14	34%	4	44%
	Anti-hypertensive drug (CV)	14	28%	11	27%	3	33%
	Drugs active on the Central Nervous System (CNS)	3	6%	3	7%	0	0%
	Thyroxine (T4)	3	6%	2	5%	1	11%
	Hormone replacement therapy (HRT)	1	2%	1	2%	0	0%
	Methotrexate (MTX)	1	2%	1	2%	0	0

The most common PTs reported together with dizziness were (Supplementary Table 1):

- nausea (14/50, 28%)
- pain (13/50, 26%)
- fatigue (11/50, 22%)
- malaise (11/50, 22%)
- dyspnoea (10/50, 20%)

Supplementary table 1

Supplementary Table 1 - other preferred terms (PTs) reported with Dizziness

PT	n	% on cases (n=50)	% on reported PT total (n=216)
DIZZINESS	50	100.0	23.1
NAUSEA	14	28.0	6.5
PAIN	13	26.0	6.0
FATIGUE	11	22.0	5.1
MALAISE	11	22.0	5.1
DYSPNOEA	10	20.0	4.6
ABDOMINAL PAIN	5	10.0	2.3
HEADACHE	5	10.0	2.3
BALANCE DISORDER	4	8.0	1.9
VOMITING	4	8.0	1.9
PAIN IN EXTREMITY	4	8.0	1.9
MYALGIA	4	8.0	1.9
ARTHRALGIA	4	8.0	1.9
SYNCOPE	3	6.0	1.4
ASTHENIA	3	6.0	1.4
ABDOMINAL PAIN UPPER	3	6.0	1.4
VERTIGO	3	6.0	1.4
DIARRHOEA	3	6.0	1.4
PYREXIA	3	6.0	1.4
ILLNESS	3	6.0	1.4
HYPOTENSION	2	4.0	0.9
CHEST PAIN	2	4.0	0.9
NECK PAIN	2	4.0	0.9
VACCINATION SITE PAIN	2	4.0	0.9
VISION BLURRED	2	4.0	0.9
LETHARGY	2	4.0	0.9
DECREASED APPETITE	2	4.0	0.9
WHEEZING	2	4.0	0.9
DISORIENTATION	1	2.0	0.5
TREMOR	1	2.0	0.5
INFLUENZA LIKE ILLNESS	1	2.0	0.5
NIGHT SWEATS	1	2.0	0.5
GAIT DISTURBANCE	1	2.0	0.5

DYSPHONIA	1	2.0	0.5
CARDIAC FLUTTER	1	2.0	0.5
INJECTION SITE PAIN	1	2.0	0.5
ERYTHEMA	1	2.0	0.5
MILIARIA	1	2.0	0.5
COLD SWEAT	1	2.0	0.5
AGEUSIA	1	2.0	0.5
AMNESIA	1	2.0	0.5
BLOOD PRESSURE DECREASED	1	2.0	0.5
FEELING HOT	1	2.0	0.5
LOSS OF CONSCIOUSNESS	1	2.0	0.5
CHEST DISCOMFORT	1	2.0	0.5
DYSSTASIA	1	2.0	0.5
RASH MACULAR	1	2.0	0.5
PRURITUS	1	2.0	0.5
MUSCLE SWELLING	1	2.0	0.5
RETCHING	1	2.0	0.5
PALPITATIONS	1	2.0	0.5
RHEUMATOID ARTHRITIS	1	2.0	0.5
FALL	1	2.0	0.5
CHILLS	1	2.0	0.5
VACCINATION SITE WARMTH	1	2.0	0.5
CONSTIPATION	1	2.0	0.5
ABDOMINAL DISTENSION	1	2.0	0.5
DRY MOUTH	1	2.0	0.5
DRY SKIN	1	2.0	0.5
EXTERNAL EAR PAIN	1	2.0	0.5
INSOMNIA	1	2.0	0.5
TASTE DISORDER	1	2.0	0.5
HEART RATE INCREASED	2	2.0	0.9
FEELING ABNORMAL	1	2.0	0.5
ABDOMINAL DISCOMFORT	1	2.0	0.5
VISUAL IMPAIRMENT	1	2.0	0.5
BLOOD PRESSURE FLUCTUATION	1	2.0	0.5

The most common High Level Terms (HLTs) of co-reported conditions were Asthenic conditions (22/50, 44%), Nausea and vomiting symptoms (15/50, 30%) and Breathing abnormalities (10/50, 20%) (Supplementary Table 2).

Reported dizziness was analyzed to be either as a symptom of a larger diagnosis, or could the the consequence of one of co-reported events mentioned above (n=41), all listed except dysponea, with dyspnoea being rather another expression of pain and autonomous nervous hyperactivation (refer to section "Interpretation of observed pattern").

The analysis of isolated dizziness cases (n=9) reveals that all cases were reported in elderly patients, and most of them were females (6/9, 67%). The most common time to dizziness onset was on the same day (3/9, 33%), 67% of cases having occurred within 2 days from the vaccination (6/9, 67%). At the time of reporting, 4 patients (44%) had already recovered and 1 other patient (11%) was recovering. Among the

patients who already recovered, 75% recovered within one day after dizziness onset (3/4). The most frequent confounding factor was the treatment with anti-hyperthensive drugs (3/9, 33%).

In one non-serious case of isolated dizziness (case [redacted]), patient was free of confounding factors. Reportedly, he/she felt dizzy 5 minutes after the vaccination, and he/she recovered the day after: such clinical presentation is highly compatible with a psychogenic reaction.

Detail of cases without confounding factors

Three (3) non-serious cases with compatible chronology and without identified relevant confounding factor(s) were reported:

Case [redacted] detailed above.

Case [redacted] reported by a consumer and involving a 77-year-old [redacted] who experienced dizziness, balance disorder and hypotension one day after receiving VidPrevtyn Beta. Patient had a medical history of breast cancer and an unspecified immunodeficiency. At the time of reporting, the recovery status was unknown. Based upon the reported information, the causal relationship between hypotension and dizziness could not be excluded.

Case [redacted] reported by a HCP via the health authority and involving a 78-year-old [redacted] who experienced dizziness 2 days following the administration of VidPrevtyn Beta. The patient also experienced fatigue and nausea an unspecified time after the vaccination. According to the reporter, there were neither signs of BPPV nor of OHT. The patient was not tested for COVID-19 since having the vaccine. [redacted] concomitant medications included lansoprazole, mirabegron and Plantago ovata. At the time of reporting, the patient was recovering. Based upon the reported information, differential diagnosis of dizziness was not completed, and thus the role of the vaccine could not be excluded nor retained.

LITTERATURE

Dizziness is a common medical condition which affects between 15% and 35% of general population at least once during lifetime. Yearly incidence of dizziness has been estimated at 3.1% (95% CI 2.6 – 3.8) in general population, with an higher incidence among women (4.1%, 95% CI 3.2 – 5.0). Incidence among elderly people is several time higher, having been estimated between 10% and 31%. It has been estimated that dizziness accounts for 2.5% to 4% of emergency department (ED) consultations each year in the United States with a 37% increase from 1995 to 2004. Such rate is consistent with the 3.5% estimation made for an Italian ED, and rise up to 5% when we consider dizziness cases on total of primary care clinic visits each year in the United States.

A recent meta-analysis estimated that incidence of dizziness among COVID-19 patients is 12.2% (95% CI 7% – 20%); nonetheless, such estimation is based on 9 studies with a low strength of evidence and with an high heterogeneity, so it should be cautiously interpretated. The proposed mechanisms linking SARS-CoV-2 infection and dizziness onset are neuroinflammation or silent hypoxia of the inner ear. Among the COVID-19 vaccines currently available in Europe, dizziness is reported as an Uncommon adverse event in the Summary of Product Characteristics (SmPC) of Comirnaty, Spikevax, Vaxzevria, Bimervax and Jcovden (but not in Nuvaxovid's). Of note, dizziness is also included in the paragraph "anxiety-related reactions" of the Comirnaty SmPC, Section 4.4 "Special warnings and precautions for use".

DISCUSSION

Based on the post-marketing data retrieved, dizziness reporting rate was 2.36/100 000 people vaccinated (very rare event), which is below the baseline yearly incidence rate reported in literature (3.1%)

Furthermore, the analysis of all retrieved dizziness cases showed a preponderance of non-serious cases, occurring in elderly women the same day of vaccination, with a rapid (1 day) and benign resolution.

INTERPRETATION OF OBSERVED PATTERN

The Global Advisory Committee for Vaccine Safety included dizziness in the wide manifestations spectrum of immunization stress-related responses (ISRR),which ranges from tachycardia and headache to syncope, hyperventilation syndrome and dissociative or conversion disorders. ISRR rises from autonomic nervous system overactivations, which can be strengthened in presence of psychological vulnerabilities or in particular social contexts. The female-to-male ratio in retrieved cases, together with the short time to onset, rather drive the interpretation of reported dizziness toward a condition driven by psychogenic factors, in agreement with the findings of Staab et al. et Ferrari et al. In particular, it can be confidently assumed that the vaccination campaign is a stressful context, especially for elder people, and that this factor can add to pre-existent depression or anxiety disorders, ending up in psychosomatic manifestations like the reported dizziness. Furthermore, the stressful vaccination campaign could have triggered a BPPV recrudescence, in agreement with findings of Monzani et al. and with the fact that BPPV is an underdiagnosed condition of which many patients are still unaware of.

The most frequently reported PTs in the retrieved cases were nausea, fatigue, malaise, pain and dyspnoea. Whereas the three first symptoms are immediately relatable to an autonomous nervous activation, and thus to an ISRR, the last two deserves a further comment. In a large retrospective cohort study based on 266,000 electronic patients records, Clark et al. found that pain and dyspnoea are closely related. In their logistic regression, patients with pain complaints were still more at risk to complain for dyspnoea, even after adjusting for pulmonary diseases known to induce dyspnoea itself. This finding could account for a shared visceral receptorial downstream pathway, which make patients feel to breathe worse when they are in pain. Such element can be immediately translated to our data, allowing us to conclude that reported dyspnoea does not depend on anaphylactoid reactions or other pulmonary aetiologies, but is rather another expression of pain and autonomous nervous hyperactivation.

EXCLUDED DIFFERENTIAL DIAGNOSES

The substantial lack of co-reported neurologic conditions such as sensory-motor deficits or speech disorders, as well as the reassuring follow-up data, excludes the link between reported dizziness cases and possible vertebrobasilar strokes or TIA. This interpretation is fully in agreement with the findings of Kerber et al., who remind that patients referring for dizziness rarely have a cerebrovascular accident. In several of reported cases, asthenia and headache have been reported together with dizziness. While these subjective symptoms are widely recognized as reactogenicity manifestations, because of their known inflammatory pathogenesis, [21] no systemic inflammation pathways are known yet to be linked with dizziness. Thus, in the present analysis we did not consider dizziness as a possible manifestation of vaccine-induced systemic reactogenicity. In other reported cases, nausea and dyspnoea have been reported together with dizziness. Such conditions may be the consequence of a systemic type I immune hypersensitivity reaction.

CONFOUNDING FACTORS

More than one third of patients who reported dizziness were also treated with anti-hypertensives, anti-depressants, hormones or immunosuppressants. These molecules, according to their pharmacodynamics, may represent a potential confounding factor in the present analysis, even in patients which are taking them on the long course. Here we discuss two potential mechanisms of confounding.

Firstly, long courses of anti-hypertensive drugs are known to induce ANF, as explained in the ESC guidelines for diagnosis and management of syncope. This is usually not a concern, as long as treatment is tailored and patient stays compliant. Nonetheless, ANF is an acquired risk factor which may contribute to the dysregulated neurovegetative activation which occurs in ISRR.

Secondly, it should be reminded that medication errors are quite a common issue with that kind of drugs. Since dizziness is a highly subjective condition, and pharmacokinetics may vary widely across individuals, it could not be excluded that even a "simple" double dose of anti-hypertensive, anti-depressant or thyroxine could have induced a temporary dizziness (which is indeed listed as a potential AE in the vast majority of SmPC of such drug classes). Data provided in reported cases was not sufficient to confidently exclude such event.

CONCLUSION

Based on medical review of cases of dizziness reported after the use of COVID-19 vaccine (recombinant, adjuvanted), the cumulative evidence is considered not evocative of a causal association between dizziness as an isolated event and COVID-19 vaccine (recombinant, adjuvanted).The collected evidence is in favour of an association between dizziness and the vaccination act itself (with no regard to the injected product) as part as procedure-related psychogenic reactions. Nonetheless, since "anxiety-related reactions" are already mentioned in section 4.4 paragraph three of the SmPC's characteristics, no further update is deemed necessary.

Dizziness safety topic remains under close monitoring and further assessments will be performed as needed

The following table of the cases supporting the causal relationship between VidPrevtyn Beta and dizziness was created by the PRAC Rapporteur based on the data provided by the MAH.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Case number	Seriousness	Case outcome	Age/Gender	Events	Time to onset	Time to recovery	Confounding factors
[redacted]	Yes	Recovered	75 [redacted]	Dizziness, Tremor, Influenza-like illness, Balance disorder, Syncope, Asthenia	0	2	Insufficient information on confounding factors
	Yes	Recovering	86	Abdominal pain, Vomiting, Dizziness, Pain in extremity, Diarrhoea	1		Methotrexate
	Yes	Recovering	74	Dizziness, Dyspnoea, Erythema, Miliaria, Asthenia	1		Drugs – cardiovascular and CNS
	No	Recovered	88	Dizziness	1	1	Drugs - cardiovascular
	No	Not recovered	83	Dizziness, Vertigo	2		Insufficient information on confounding factors
	No	Recovering	87	Dizziness, Myalgia	0		Drugs - cardiovascular

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

[redacted]	No	Recovering	78/[redacted]	Dizziness	3		Insufficient information on confounding factors
	No	Recovering	77/	Dizziness, Nausea, Diarrhoea, Fatigue	2		Drug – T4
	Yes	Unknown	84/	Vomiting, Dizziness, Disorientation, Cold sweat, Abdominal pain upper, Pain in extremity, Nausea, Pyrexia	0		Drug-cardiovascular
	No	Recovering	[redacted]	Dizziness, Dyspnoea, Abdominal pain upper, Vomiting, Nausea	1		Insufficient information on confounding factors
	Yes	Not Recovered	91/	Night sweats, Dyspnoea, Dizziness, Fatigue, Nausea	1		Drug - cardiovascular
	No	Recovered	87	Dizziness, Malaise	1	0	Drug - HRT
	Yes	Not Recovered	78/	Dizziness, Illness	2		Drug- T4
	No	Not Recovered	77	Dizziness, Ageusia, Fatigue, Arthralgia, Malaise	2		Insufficient information on confounding factors
	Yes	Not Recovered	78/	Dizziness, Dyspnoea, Neck pain, Fatigue, Myalgia	1		Insufficient information on confounding factors

[redacted]	No	Recovering	78[redacted]	Dizziness, Fatigue, Nausea	2		No identified relevant confounding factors
	Yes	Recovered	[redacted]	Loss of consciousness, Dizziness, Vomiting, Nausea	2	2	Insufficient information on confounding factors
	Yes	Recovered	78[redacted]	Pain in extremity, Dizziness, Nausea, Fatigue, Pyrexia, Arthralgia	1		Drug - cardiovascular
	No	Unknown	[redacted]	Muscle swelling, Dizziness, Vaccination site pain, Headache	1		Insufficient information on confounding factors
	No	Not Recovered	79	Dizziness, Balance disorder, Asthenia, Lethargy, Decreased appetite, Constipation	1		Insufficient information on confounding factors
	No	Recovered	23[redacted]	Dizziness, Vision blurred, Taste disorder, Lethargy, Nausea, Fatigue	1	0	Insufficient information on confounding factors

Rapporteur assessment comment:

During the developmental program 2 participants experienced the non-serious AE of dizziness. In the 1st case, a 23-year-old [redacted] experienced dizziness, vision blurred, taste disorder, lethargy, nausea and fatigue with TTO 1 day, which subsided the same day. The delayed onset acts against the immunisation-stress related reaction (ISRR). In the 2nd case, a 66-year-old [redacted] experienced several events including dizziness, fatigue, abdominal pain, dry mouth, dry skin, insomnia, external ear pain on the day of vaccination without exact time specification. The events subsided after 2 days. No further details were provided. No case of dizziness was reported during the booster extension phase of VAT00008.

The MAH provided an updated review of dizziness from the post-marketing period until 30 June 2023. 50 cases of dizziness were reported cumulatively. 32/50 cases are not medically confirmed. This can be expected considering the number of non-serious cases (31/50) and subjective character of the reaction. 43/50 (86%) cases were reported in elderly, which is in line with the exposure data of the vaccine. Dizziness was reported slightly more often in women, in 27/50 (54%) cases. No data about exposure by sex was provided in the PSUR. However, as the vast majority of doses was administered in the age groups of 70-79 years and 80+ years, it might be assumed that elderly women were vaccinated more often than men. The MAH´s comment that the higher proportion of women suggests a psychogenic nature of the reaction is not endorsed. At the time of reporting, patients recovered or were recovering in 25/50 (50%) cases.

Dizziness occurred the same day in 22/50 (44%) cases, TTO 1 -2 days was reported in 21/50 (42%) cases, TTO 3 days was reported in 1/50 (2%) cases and TTO was unknown in 6/50 (12%) cases.

The most common co-reported PTs were nausea (14/50), pain (13/50), fatigue (11/50), malaise (11/50) and dyspnoea (10/50). Only dizziness was reported in 9 cases. The MAH concluded that dizziness was a symptom of a larger diagnosis or the consequence of co-reported events and the data indicates an association between dizziness and the vaccination act itself. This is not endorsed. The PRAC Rapp agrees that the most often co-reported reactions can occur as symptoms of the immunisation-stress related reaction already included in the product information of the vaccine, but these events except dyspnoea are also the expected reactogenicity reactions listed for VidPrevtyn Beta. In addition, dizziness is a listed ADR for other COVID-19 vaccines including recombinant, adjuvanted vaccine Bimervax.

The PRAC Rapp created a table of 21 cases (please see above this comment), where delayed TTO acts against the ISRR or where dizziness occurred with other symptoms of reactogenicity, and these cases suggest a causal relationship between VidPrevtyn Beta and dizziness.

Considering that a total of 2949 participants received the monovalent beta B.1.351 booster vaccine during all clinical studies 1 -3 Phase and 5000 participants received a booster dose of the vaccine in the booster extension phase of VAT00008**, the PRAC Rapp proposes to include dizziness in the product information with a frequency "rare".**

2. The MAH is requested to provide information, why the exposures in Scotland, Wales and North Ireland were not included in the PSUR.

Response:

Scotland, Wales and North Ireland exposures are not included in the PSUR as not available from Department for Business, Energy & Industrial Strategy from the UK Government which is the source to track doses administered in the United Kingdom. Only doses administered in England are available.

Rapporteur assessment comment:

The information is acknowledged.

3. The MAH is requested to clarify discrepancy between number of stroke cases listed in the body of PSUR and in the Appendix 6.4.2.

Response:

Six case reports of stroke are listed in the body of PSUR (refer to 15.1.1.14 Stroke (haemorrhagic stroke and ischemic stroke)) and seven case reports of stroke are listed in Appendix 6.4.2. This is explained by the note highlighting the differences between PSUR DLP (09 May 2023) and Observed/Expected analysis DLP (31 May 2023):

* Case [redacted] has been received after 9 May 2023 and included in this analysis which corresponds to the second summary safety report (DLP: 31 May 2023). A 77-year-old [redacted] patient, with past medical history including stroke (12 years ago) and arterial disorder NOS, experienced TIA (transient ischemic attack), was unable to say any word (speech disorder), only [redacted] could make noises and unable to think (thinking abnormal) 2 days after vaccination with VidPrevtyn Beta. At the time of the event, the patient had ongoing slurred speech. No information on diagnostic tests was provided. Concomitant medications included acetylsalicylic acid (aspirin); bisoprolol; lansoprazole; finasteride; citalopram; losartan; atorvastatin; cod-liver oil; vitamins and clopidogrel. Twelve years ago, the patient had a stroke and recovered from it. [redacted] had no problem since then. According to the patient, when [redacted] had the first stroke 12 years ago, I felt (inaudible) down and felt empty. [redacted] is feeling better now. It was not reported if the patient received a corrective treatment for the events. Comment: Previous occurrence of stroke and unspecified arterial disorder are major confounders, as well as the patient's elderly age. Stroke was not confirmed by diagnostic tests. No information on previous primary vaccination with COVID-19 vaccines.

Rapporteur assessment comment:

The MAH clarified that the discrepancy in the number of stroke cases was a result of the difference in dates between the PSUR DLP and O/E analysis DLP. One additional case was provided, which is already described in the Appendix of PSUR as a case of ischaemic stroke reported after DLP. However, the difference in number of stroke cases between the PSUR body and the Appendix 6.4.2 is higher. 6 cases of stroke (haemorrhagic or ischaemic) are described in the body of the PSUR and 13 cases (7 cases of

ischaemic stroke and 6 cases of haemorrhagic stroke) are described in the Appendix.

In the next PSUR, the MAH is requested to provide a review of the 6 stroke cases which were not assessed in the current PSUR. **Next PSUR**

7. Comments from Member States

Member states' comments:

Preliminary AR was fully endorsed by MS1, MS2 and MS3

Sanofi recherche et développement
1 avenue Pierre Brossolette
91385 Chilly-Mazarin Cedex. FRANCE

PERIODIC BENEFIT RISK EVALUATION REPORT

RECOMBINANT PREFUSION SPIKE DELTATM PROTEIN (SARS-COV-2 STRAIN) VACCINE

Covered period: 10-Nov-2022 to 09-May-2023

International Birth Date (IBD): 10-Nov-2022

Report reference: VV-PV-0514136
Name: Owen Haney, Pharm D (on behalf of
Anne-Laure Chabanon, Pharm D, Ph D)
Function: Global Safety Officer
By delegation from the Sanofi QPPV
Signature: Signature on file

Date: 13-Jul-2023

Total number of pages: 95 (+Appendices)

EXECUTIVE SUMMARY

This Periodic Benefit Risk Evaluation Report for Recombinant Prefusion Spike DeltaTM Protein (severe acute respiratory syndrome-coronavirus-2 Strain) Vaccine, hereafter referred to as "COVID-19 vaccine (recombinant, adjuvanted)", was prepared in accordance with the content and format proposed by the International Conference on Harmonisation guideline (ICH E2C [R2] step 5): Periodic Benefit Risk Evaluation Report and Guideline on Good Pharmacovigilance Practices Module VII - Periodic Safety Update Report (revision #1).

It summarizes the cumulative safety information for the marketing authorization holder products containing COVID-19 vaccine (recombinant, adjuvanted), received by the Sanofi's Global Pharmacovigilance department from worldwide sources, from 10 November 2022 through 09 May 2023.

COVID-19 vaccine (recombinant, adjuvanted) belongs to the pharmacotherapeutic group "Vaccine", "Other Viral Vaccine"; Anatomical Therapeutic Chemical code: J07BX03.

COVID-19 vaccine (recombinant, adjuvanted) is a recombinant protein vaccine derived from the severe acute respiratory syndrome coronavirus-2 prefusion Spike delta TM (B.1.351 strain). COVID-19 vaccine (recombinant, adjuvanted) is an adjuvanted vaccine composed of the soluble trimeric severe acute respiratory syndrome coronavirus-2 recombinant spike protein (B.1.351 strain) stabilized in its prefusion conformation and deleted of its transmembrane and intracellular domains. The combination of antigen and adjuvant enhances the magnitude of immune response, which may contribute to protection against Coronavirus Disease-2019.

COVID-19 vaccine (recombinant, adjuvanted) is available as solution and emulsion for emulsion for injection. The volume after mixing one vial of antigen solution (2.5 mL) with one vial of adjuvant emulsion (2.5 mL) allows for delivery of 10 doses of vaccine (0.5 mL per dose). One dose (0.5 mL) of COVID-19 vaccine (recombinant, adjuvanted) contains five micrograms of recombinant severe acute respiratory syndrome coronavirus-2 spike protein (B.1.351 strain) formulated with adjuvant system 03 adjuvant for booster vaccination and is administered intramuscularly.

COVID-19 vaccine (recombinant, adjuvanted) is approved as a booster dose for active immunization to prevent Coronavirus Disease-2019 caused by severe acute respiratory syndrome coronavirus-2 in adults who have previously received a messenger ribonucleic acid or adenoviral vector Coronavirus Disease-2019 vaccine.

Approved posology:

Individuals 18 years of age and older

COVID-19 vaccine (recombinant, adjuvanted) is administered intramuscularly as a single dose of 0.5 mL at least four months after a previous Coronavirus Disease-2019 vaccine. COVID-19 vaccine (recombinant, adjuvanted) may be given once as a booster to adults that have received prior vaccination series with either messenger ribonucleic acid or adenoviral vector Coronavirus Disease-2019 vaccines.

Elderly

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Pediatric population

COVID-19 vaccine (recombinant, adjuvanted) is not indicated in pediatric population.

A global safety data exchange agreement is in place between Sanofi Pasteur and GlaxoSmithKline Biologicals SA for multiple territories. This Periodic Benefit Risk Evaluation Report includes all individual case safety reports received by GlaxoSmithKline Biologicals SA and transmitted to Sanofi Pasteur.

The first marketing authorization for COVID-19 vaccine (recombinant, adjuvanted) was obtained in the European Union on 10 November 2022.

COVID-19 vaccine (recombinant, adjuvanted) is approved in 32 countries worldwide.

During the period covered by this report, a marketing authorization for COVID-19 vaccine (recombinant, adjuvanted) was granted in Great Britain on 20 December 2022.

Cumulatively, there were 17 132 participants exposed to COVID-19 vaccine (recombinant, adjuvanted) in marketing authorization holder sponsored interventional clinical trials.

Exposure data based on administered doses when available have been retrieved from publicly available data sources such as national or international Coronavirus Disease-2019 vaccination trackers. For European Union/European Economic Area countries, administered doses are retrieved from the European Centre for Disease Prevention and Control Vaccine Tracker[1]. European Union/European Economic Area countries can upload data at any time, but as a minimum they are requested to report twice a week (on Tuesdays for the previous week and Thursdays for the current week). Considering this reporting timeframe and the time European Centre for Disease Prevention and Control needs to process

[1] Available from: https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab

the data, some discrepancies may be observed between the figures published by European Centre for Disease Prevention and Control and the ones presented in official national reports or websites. It is worthy to note that all data are subject to retrospective corrections. In addition, for some countries, number of doses administered by age-group is not available, for others vaccine breakdown by vaccine brand name is not available. No stratification by gender is available.

Cumulatively, the total number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered is approximately 6920 up to 20 April 2023 in European Union.

Cumulatively, the total number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered is approximately 1 630 039 up to 07 May 2023 in England.

Cumulatively, the total number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered is approximately 1 636 959 up to 07 May 2023.

The European Union summary of product characteristics for COVID-19 vaccine (recombinant, adjuvanted), version 1.0 dated 10 November 2022 was the reference safety information valid at the beginning of the Periodic Benefit Risk Evaluation Report period.

No safety related changes were made in the reference safety information during the period covered by this report.

No actions were taken for safety reasons during the period covered by this report.

Since the data lock point for this Periodic Benefit Risk Evaluation Report, the marketing authorization holder has identified the following new information regarding potentially important safety and efficacy and/or effectiveness: one signal on allergic including anaphylactic reactions has been opened on 17 May 2023 and validated on 14 June 2023. On 26 June 2023, signal of allergic including anaphylactic reactions was confirmed as an identified risk. The weighted cumulative evidence was considered sufficient to support a causal association between COVID-19 vaccine (recombinant, adjuvanted) and allergic including anaphylactic reactions that should be reflected in the reference safety information.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis during the reporting interval, the benefit-risk balance of COVID-19 vaccine (recombinant, adjuvanted) in the approved indication remains positive in the currently approved conditions of use.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS

Ab:	Antibody
ADE:	Antibody Dependent Enhancement
ADR:	Adverse Drug Reaction
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
ANCA:	Antineutrophil Cytoplasmic Antibody
APHP:	Assistance Publique Hôpitaux Paris
AR:	Adverse Reaction
AS03:	Adjuvant System 03
BCCD:	Brighton Collaboration Case Definition
BMI:	Body Mass Index
CDC:	Centers for Disease Control and Prevention
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CNS:	Central Nervous System
COPD:	Chronic Obstructive Pulmonary Disease
CoV-1:	Coronavirus-1
CoV-2:	Coronavirus-2
CoV-2 preS dTM:	CoV-2 Prefusion Spike Delta TM
COVID:	Coronavirus Disease
COVID-19:	Coronavirus Disease-2019
CT:	Computerized Tomography
CTAP:	Coronavirus Treatment Acceleration Program
CVD:	Cardiovascular Disorders
C-VIPER:	Coronavirus Disease-2019 Vaccines International Pregnancy Exposure Registry
CVST:	Cerebral Venous Sinus Thrombosis
DART:	Developmental and Reproductive Toxicity
DIBD:	Development International Birth Date
DLP:	Data Lock Point
DRC:	Democratic Republic of the Congo
DRCI:	Direction de la Recherche Clinique et de l'Innovation
DVT:	Deep Vein Thrombosis
EC:	European Commission
ECDC:	European Centre for Disease Prevention and Control
ECG:	Electrocardiogram
ECMO:	Extracorporeal Membrane Oxygenation
EEA:	European Economic Area
EMA:	European Medicines Agency

ESC:	Externally Sponsored Collaborative
ESDR:	Early Safety Data Review
EU:	European Union
EUL:	Emergency Use Listing
Fc:	Fragment Crystallizable
FDA:	Food and Drug Administration
GMT:	Geometric Mean Titer
GMTR:	Geometric Mean Titer Ratio
GPV:	Global Pharmacovigilance
GSK:	GlaxoSmithKline
GVP:	Good Pharmacovigilance Practices
HCP:	Healthcare Professional
HIV:	Human Immunodeficiency Virus
IBD:	International Birth Date
ICH:	International Conference on Harmonisation
ICSR:	Individual Case Safety Report
ICU:	Intensive Care Unit
IMV:	Invasive Mechanical Ventilation
IND:	Investigational New Drug
IRR:	Incidence Rate Ratio
LMP:	Last Menstrual Period
MA:	Marketing Authorization
MAAE:	Medically Attended Adverse Event
mAb:	Monoclonal Antibody
MAH:	Marketing Authorization Holder
MedDRA:	Medical Dictionary for Regulatory Activities
MHRA:	Medicines and Healthcare products Regulatory Agency
MINOCA:	Myocardial Infarction with Nonobstructive Coronary Arteries
MRI:	Magnetic Resonance Imaging
mRNA:	Messenger Ribonucleic Acid
NHP:	Non-Human Primates
NIAID:	National Institute of Allergy and Infectious Diseases
NOS:	Not Otherwise Specified
O/E:	Observed Versus Expected
PASS:	Post-Authorization Safety Studies
PBRER:	Periodic Benefit Risk Evaluation Report
PC:	Product Complaint
PF4:	Platelet Factor 4
PK:	Pharmacokinetic
PRAC:	Pharmacovigilance Risk Assessment Committee
PT:	Preferred Term
PV:	Pharmacovigilance

RA:	Regulatory Authority
RMM:	Risk Minimization Measures
RMP:	Risk Management Plan
ROR:	Reporting Odds Ratio
RSI:	Reference Safety Information
S:	Spike
SAE:	Serious Adverse Event
SAR:	Serious Adverse Reaction
SARS:	Severe Acute Respiratory Syndrome
SDEA:	Safety Data Exchange Agreement
SLE:	Systemic Lupus Erythematosus
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Queries
suPAR:	Soluble Urokinase Plasminogen Activator Receptor
TIA:	Transient Ischemic Attack
TTO:	Time to Onset
UAE:	United Arab Emirates
UK:	United Kingdom
UN:	United Nation
UNK MFR:	Unknown Manufacturer
VAED:	Vaccine Associated Enhanced Disease
VAERD:	Vaccine Associated Enhanced Respiratory Disease
VE:	Vaccine Efficacy
VOC:	Variant of Concern
WHO:	World Health Organization

1 INTRODUCTION

This Periodic Benefit Risk Evaluation Report (PBRER) for Recombinant Prefusion Spike DeltaTM Protein (severe acute respiratory syndrome [SARS]-coronavirus-2 [CoV-2] Strain) Vaccine, hereafter referred to as "Coronavirus Disease-2019 (COVID-19) vaccine (recombinant, adjuvanted)", was prepared in accordance with the content and format proposed by the International Conference on Harmonisation (ICH) guideline (ICH E2C [R2] step 5): PBRER and Guideline on Good Pharmacovigilance Practices (GVP) Module VII - Periodic Safety Update Report (revision #1).

It summarizes the cumulative safety information for the marketing authorization holder (MAH) products containing COVID-19 vaccine (recombinant, adjuvanted), received by the MAH's Global Pharmacovigilance (GPV) department from worldwide sources, from 10 November 2022 through 09 May 2023.

The International Birth Date (IBD) of COVID-19 vaccine (recombinant, adjuvanted) is 10 November 2022.

COVID-19 vaccine (recombinant, adjuvanted) belongs to the pharmacotherapeutic group "Vaccine", "Other Viral Vaccine"; Anatomical Therapeutic Chemical code: J07BX03.

COVID-19 vaccine (recombinant, adjuvanted) is a recombinant protein vaccine derived from the SARS CoV-2 prefusion Spike (S) delta TM (CoV-2 preS dTM) (B.1.351 strain). COVID-19 vaccine (recombinant, adjuvanted) is an adjuvanted vaccine composed of the soluble trimeric SARS-CoV-2 recombinant S protein (B.1.351 strain) stabilized in its prefusion conformation and deleted of its transmembrane and intracellular domains. The combination of antigen and adjuvant enhances the magnitude of immune response, which may contribute to protection against COVID-19.

COVID-19 vaccine (recombinant, adjuvanted) is available as solution and emulsion for emulsion for injection. The volume after mixing one vial of antigen solution (2.5 mL) with one vial of adjuvant emulsion (2.5 mL) allows for delivery of 10 doses of vaccine (0.5 mL per dose). One dose (0.5 mL) of COVID-19 vaccine (recombinant, adjuvanted) contains five micrograms of recombinant SARS-CoV-2 S protein (B.1.351 strain) formulated with adjuvant system 03 (AS03) adjuvant for booster vaccination and is administered intramuscularly.

COVID-19 vaccine (recombinant, adjuvanted) is approved as a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults who have previously received a messenger ribonucleic acid (mRNA) or adenoviral vector COVID-19 vaccine.

Approved posology:

Individuals 18 years of age and older

COVID-19 vaccine (recombinant, adjuvanted) is administered intramuscularly as a single dose of 0.5 mL at least four months after a previous COVID-19 vaccine. COVID-19 vaccine (recombinant, adjuvanted) may be given once as a booster to adults that have received prior vaccination series with either mRNA or adenoviral vector COVID-19 vaccines.

Elderly

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Pediatric population

COVID-19 vaccine (recombinant, adjuvanted) is not indicated in pediatric population.

A global safety data exchange agreement (SDEA) is in place between Sanofi Pasteur and GlaxoSmithKline (GSK) Biologicals SA for multiple territories. This PBRER includes all individual case safety report (ICSRs) received by GSK Biologicals SA and transmitted to Sanofi Pasteur.

During the reporting interval this is the only PBRER prepared by the MAH for this product including periodic reports prepared by the contractual partner.

2 WORLDWIDE MARKETING APPROVAL STATUS

The first marketing authorization (MA) for COVID-19 vaccine (recombinant, adjuvanted) was obtained in the European Union (EU) on 10 November 2022.

The detailed cumulative worldwide marketing approval status is provided in Appendix 5.1.

COVID-19 vaccine (recombinant, adjuvanted) is approved in 32 countries worldwide.

During the period covered by this report, a MA for COVID-19 vaccine (recombinant, adjuvanted) was granted in Great Britain on 20 December 2022.

COVID-19 vaccine (recombinant, adjuvanted) is approved as a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine.

COVID-19 vaccine (recombinant, adjuvanted) is available as solution and emulsion for emulsion for injection. The volume after mixing one vial of antigen solution (2.5 mL) with one vial of adjuvant emulsion (2.5 mL) allows for delivery of 10 doses of vaccine (0.5 mL per dose). One dose (0.5 mL) of

COVID-19 vaccine (recombinant, adjuvanted) contains five micrograms of recombinant SARS-CoV-2 S protein (B.1.351 strain) formulated with AS03 adjuvant for booster vaccination.

Approved posology:

Individuals 18 years of age and older

COVID-19 vaccine (recombinant, adjuvanted) is administered intramuscularly as a single dose of 0.5 mL at least four months after a previous COVID-19 vaccine. COVID-19 vaccine (recombinant, adjuvanted) may be given once as a booster to adults that have received prior vaccination series with either mRNA or adenoviral vector COVID-19 vaccines.

Elderly

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Pediatric population

COVID-19 vaccine (recombinant, adjuvanted) is not indicated in pediatric population.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

No actions were taken during the reporting interval for safety reasons related to either investigational uses or marketing experience by the MAH, sponsors of clinical trial(s), Regulatory Authorities (RAs), data monitoring committees, or ethics committees that had:

- A significant influence on the risk-benefit profile of the approved medicinal product; and/or
- An impact on the conduct of a specific clinical trial(s) or on the overall clinical development program.

4 CHANGES TO REFERENCE SAFETY INFORMATION

The EU summary of product characteristics (SmPC) for COVID-19 vaccine (recombinant, adjuvanted), version 1.0 dated 10 November 2022 was the reference safety information (RSI) valid at the beginning of the PBRER period.

No safety related changes were made in the RSI during the period covered by this report.

The current RSI at the data lock point (DLP) is the EU SmPC version 1.0, dated 10 November 2022 attached in Appendix 1.

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 CUMULATIVE SUBJECT EXPOSURE IN CLINICAL TRIALS

This section presents estimates of cumulative numbers of participants, from ongoing or completed MAH-sponsored clinical trials where COVID-19 vaccine (recombinant, adjuvanted) was the investigational product under study or development, exposed to the investigational product, placebo, and/or active comparator(s) since the development international birth date (DIBD).

The cumulative exposure to COVID-19 vaccine (recombinant, adjuvanted), in interventional clinical trials sponsored by the MAH is estimated to be 17 132 participants. Actual exposure data from completed or open-label clinical trials (Note: none of the three ongoing clinical studies have been completed as of the DLP) and enrollment estimates according to randomization schemes for ongoing and blinded trials are presented in Table 1. Cumulative exposure to COVID-19 vaccine (recombinant, adjuvanted), is displayed as SARS-CoV-2 preS dTM monovalent and bivalent. Comparing the cumulative participant exposure numbers to previous reports is not appropriate as participants progress from dose 1 to dose 2.

Table 1 - Estimated cumulative participant exposure to SARS-CoV-2 recombinant protein monovalent and bivalent vaccines in all Phases 1 to 3 clinical studies

Treatment	Number of Participants
One injection	
SARS-CoV-2 preS dTM Monovalent D614	2148
SARS-CoV-2 preS dTM Monovalent B.1.351	2949
SARS-CoV-2 preS dTM Bivalent D614+B.1.351	676
Placebo	1061
Two injections	
SARS-CoV-2 preS dTM Monovalent D614	7636
SARS-CoV-2 preS dTM Bivalent D614+B.1.351	6057
Placebo/Placebo	10 783
Total:	
SARS-CoV-2 preS dTM Monovalent and Bivalent	**17 132**
Placebo	**11 844**

Data as of 09-May-2023 from ongoing studies: VAT00001, VAT00002, and VAT00008.
VAT00002 and VAT00008 participants may choose to receive 1 booster injection after a primary series vaccination.
VAT00008 placebo participants may choose to receive a primary series vaccination (if unvaccinated) or 1 booster injection (if vaccinated) after meeting specific criteria.
Participants who received more than one treatment are counted in each of the treatments, as received injections.

Treatment	Number of Participants

Study: OVERALL Program: t001.sas Dataset=ADSL Output: DEVOPS/SP0253/OVERALL/PBRER_2023/REPORT/OUTPUT/TABLE1_x.rtf (06JUN2023 16:45)

As of 09 May 2023 (DLP), a total of 2949 participants received the monovalent beta B.1.351 booster vaccine.

The cumulative exposure of COVID-19 vaccine (recombinant, adjuvanted) by demographic characteristics of age range, gender, and race/ethnicity is listed in Appendix 5.2.1.

5.2 CUMULATIVE AND INTERVAL PATIENT EXPOSURE FROM MARKETING EXPERIENCE

5.2.1 Post-approval (non-clinical trial) exposure

As this is the first PBRER, the interval and cumulative patient exposure are the same and are presented below. Therefore, Appendix 5.2.2 and Appendix 5.2.3 are not applicable.

Exposure data based on administered doses when available have been retrieved from publicly available data sources such as national or international COVID-19 vaccination trackers. For EU/ European Economic Area (EEA) countries, administered doses are retrieved from the European Centre for Disease Prevention and Control (ECDC) Vaccine Tracker[2]. European Union/European Economic Area countries can upload data at any time, but as a minimum they are requested to report twice a week (on Tuesdays for the previous week and Thursdays for the current week). Considering this reporting timeframe and the time ECDC needs to process the data, some discrepancies may be observed between the figures published by ECDC and the ones presented in official national reports or websites. It is worthy to note that all data are subject to retrospective corrections. In addition, for some countries, number of doses administered by age-group is not available, for others vaccine breakdown by vaccine brand name is not available. No stratification by gender is available.

The number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered per European country and age group as of 20 April 2023 are presented in Table 2.

Table 2 - Number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in European Union by country and age group through 20 April 2023

Country	Europe								Total
	Unknown	0-17	18-24	25-49	50-59	60-69	70-79	80+	
AUSTRIA	0	0	12	93	49	50	37	21	262

[2] Available from: https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab

Country	Europe								Total
	Unknown	0-17	18-24	25-49	50-59	60-69	70-79	80+	
FRANCE	6456	0	0	0	0	0	0	0	6456
ITALY	0	0	0	46	16	42	18	10	132
PORTUGAL	0	0	1	21	14	17	14	3	70
Total	6456	0	13	160	79	109	69	34	6920

For the United Kingdom (UK), COVID-19 vaccine (recombinant, adjuvanted) administered doses are received directly from the Department for Business, Energy, and Industrial Strategy from the UK government. Of note, COVID-19 vaccine (recombinant, adjuvanted) doses administered in Scotland, Wales and North Ireland are not included. The number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in England per age group as of 07 May 2023 are presented in Table 3.

Table 3 - Number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in England per age group as of 07 May 2023

Country	UK									Total
	Unknown	0-17	18-29	30-39	40-49	50-59	60-69	70-79	80+	
	9	5	128	264	636	1971	13 046	653 305	960 675	1 630 039

UK: United Kingdom.

The total number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered is approximately 1 636 959 up to 07 May 2023.

5.2.2 Post-approval use in special populations

The MAH does not have access to exposure regarding use in special populations from the IBD of COVID-19 vaccine (recombinant, adjuvanted) through the DLP of the PBRER except for elderly population as more than 99.8% of the exposure in England is in elderly population which represents 1 627 026 doses administered (60 years and older (Department for Business, Energy, and Industrial Strategy from the UK government).

Use in the pregnancy and breast-feeding is being studied in non-interventional studies with study ID VAT00012 and VAT00007 (not yet initiated). No exposure in these studies. Use in the pregnancy and breast-feeding is missing information. Please refer to Section 16 for further information.

- Of note, feasibility of VAT00006 Clinical Study (A Phase 3, Randomized, Modified Double-Blind, Crossover Study to Assess the Safety and Immunogenicity of a SARS-CoV-2 Adjuvanted Recombinant Protein Variant Booster Vaccine in Healthy Pregnant Women Aged 18 to 35 Years) has been re-assessed. It has been considered that VAT00006 is no longer an option,

and it has been cancelled. The rationale of this decision has been included in an Answers to Questions document submitted to European Medicines Agency (EMA) through a procedure (EMEA/H/C/005754/MEA/001). According to the review timetable, the Committee for Medicinal Products for Human Use (CHMP) outcome is expected on 20 July 2023.

Use in the immuno-compromised subjects is being studied in externally sponsored collaborative (ESC) studies with study ID VAT00027, VAT00028 and in non-interventional study ID VAT00007 (not yet initiated). Cumulative exposure in these studies is 32 participants. Use in the immuno-compromised subjects is missing information. Please refer to Section 16 for further information.

Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders [CVD]) is being studied in non-interventional studies with study ID VAT00007 (not yet initiated). No exposure in this study. Use in frail subjects with unstable health conditions and co-morbidities (eg, COPD, diabetes, chronic neurological disease, CVD) is missing information. Please refer to Section 16 for further information.

Use in subjects with autoimmune or inflammatory disorders is being studied in non-interventional studies with study ID VAT00007 (not yet initiated). No exposure in this study. Use in subjects with autoimmune or inflammatory disorders is missing information. Please refer to Section 16 for further information.

Use in elderly:

In the UK, country where most doses were administered, the local recommendation is targeting the population aged 75-year-old and above. Thus, most of the postmarketing cases are reported in the older population (See Section 5.2.1) with approximately 86% of cases reported in 70-year-old and above. Safety data presented in this PBRER can be considered as reflecting the safety data in this age group.

5.2.3 Other post-approval use

No patterns of use with COVID-19 vaccine (recombinant, adjuvanted) beyond that recommended in the reference product information, including overdose, drug abuse and misuse considered relevant for the interpretation of safety data were identified.

6 DATA IN SUMMARY TABULATIONS

The MAH routinely screens multiple data sources to identify new safety information on COVID-19 vaccine (recombinant, adjuvanted) in addition to the review of the summary tabulations appended to this PBRER. Data sources routinely screened to identify relevant new safety information are listed in Section 15, Overview of Signals: new, ongoing, or closed.

6.1 REFERENCE INFORMATION

The Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 was used for the coding of adverse events (AEs) and adverse drug reactions (ADRs) and for analyses based on Standardized MedDRA Queries (SMQ).

6.2 CUMULATIVE SUMMARY TABULATIONS OF SERIOUS ADVERSE EVENTS FROM CLINICAL TRIALS

Appendix 2.1 provides the cumulative tabulation of serious adverse events (SAEs) reported from MAH-sponsored, interventional clinical trials where the COVID-19 vaccine (recombinant, adjuvanted) was the product under investigation.

The cumulative SAE tabulation is presented by treatment arm for completed or unblinded trials and blinded for ongoing blinded trials.

A total of 902 cumulative SAEs were reported from MAH-sponsored clinical trials.

6.3 CUMULATIVE AND INTERVAL SUMMARY TABULATIONS FROM POSTMARKETING DATA SOURCES

The tabulation in Appendix 2.2 includes:

- Serious and non-serious adverse drug reactions from spontaneous ICSRs, including reports from healthcare professional (HCPs), consumers, scientific literature, and RAs;
- Serious adverse reactions (SARs) from non-interventional studies and
- Solicited reports of SARs.[3]

As described in ICH Guideline E2D, for marketed medicinal products, spontaneously reported AEs imply suspicion of causality by the reporter and are therefore considered to be adverse reactions (ARs) for regulatory reporting purposes.

A total of 1227 cumulative ARs have been reported, all of which were reported during the present reporting period for COVID-19 vaccine (recombinant, adjuvanted) (see Appendix 2.2.1).

A total of 19 cumulative ARs have been reported, all of which were reported during the present reporting period for an unknown manufacturer (UNK MFR) (see Appendix 2.2.2).

[3] Does not include data from MAH-sponsored interventional trials included in Appendix 2.1

7 SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL

During the reporting interval of this PBRER, no clinical trials have been completed. As of 09 May 2023 (DLP), a total of three clinical trials (VAT00001, VAT00002, VAT00008) are ongoing.

There were no MAH-sponsored interventional trials ongoing or completed during the reporting period with the primary aim of identifying, characterizing, or quantifying a safety hazard or confirming the safety profile of COVID-19 vaccine (recombinant, adjuvanted). Therefore, Appendix 4.1 is not applicable.

7.1 COMPLETED CLINICAL TRIALS

7.1.1 Efficacy findings

Not applicable since no clinical trials were completed during the reporting interval.

7.1.2 Safety findings

Not applicable since no clinical trials were completed during the reporting interval.

7.2 ONGOING CLINICAL TRIALS

VAT00001: A parallel group, Phase I/II, first in human, placebo controlled, dose ranging, multi-center study with a Sentinel Safety Cohort and Early Safety Data Review (ESDR) to assess immunogenicity and safety of SARS-CoV-2 recombinant protein vaccine formulations (two antigen formulations [high or low dose] with either AF03 or AS03 as adjuvants, or no adjuvant for the high antigen dose formulation) and injection schedule (one or two injections) in healthy adults 18 years of age and older (1), (2).

All vaccination in the study occurred prior to the review period. The safety follow-up period of the study has been completed. No safety issue was identified during the long-term safety follow-up. The clinical study report is currently under development.

VAT00002: A Phase II randomized, modified double-blind, multicenter, dose finding study has been conducted in adults 18 years of age and older to evaluate the safety, reactogenicity, and immunogenicity of two injections of five µg, 10 µg, or 15 µg of the CoV2 preS dTM (D614) vaccine, adjuvanted with AS03. Interim data from this Phase II study was used to decide on progression to Phase III and to select an antigen dose formulation for further clinical development evaluating the vaccines when used as a late booster (3).

Supplemental cohorts were tested as part of VAT00002 Phase II/III study to address various prime boost options (the Monovalent B.1.351 [Beta variant] formulation was used in the Supplemental Phase III Cohort 2) (4).

- Supplemental Phase III Cohort 1 to evaluate the safety and immunogenicity of a booster dose of the parental strain (Monovalent D614) vaccine among adults previously vaccinated with a primary series of mRNA (Pfizer/BioNTech or Moderna) or adenovirus-vectored vaccines (Janssen or AstraZeneca).
- Supplemental Phase III Cohort 2 to evaluate the safety and immunogenicity of a booster dose of a variant vaccine (Monovalent B.1.351 [Beta variant] or Bivalent [D614/B.1.351]) in adults previously primed with mRNA or adenovirus-vectored vaccines.
- In addition, available and willing individuals previously primed with the adjuvanted recombinant protein vaccine (different formulations) as part of the Phase II Original Cohort were enrolled into the Supplemental Phase III Cohort 2 and randomized to a booster dose of the parental strain booster vaccine or Monovalent variant booster vaccine.
- Selection of the five µg dose was based on the immunogenicity results in non-naive participants of the original cohort of VAT00002.
- All vaccination for the Original Phase II cohort (primary series) occurred prior to the review period. The safety follow-up of the Original Cohort was completed prior to the review period. No related SAEs and no AESI reported in the original cohort. No safety issue was identified for the Original Cohort following completion of the safety follow-up.
- Vaccination for the Supplemental Cohorts in the Phase III portion of the VAT00002 study occurred prior to the review period. Overall, no safety concerns were identified, nor any specific risk group identified for whom safety was of concern. Among participants receiving booster vaccine, there was a favorable safety profile. The safety profile was consistent across booster formulations. No safety issues were identified in subgroups (defined by age or the presence of a high-risk medical condition). These safety data were supportive of the use of the vaccine as a booster, regardless of priming vaccine. The safety data were consistent with and further supports the safety profile established with the primary series formulation seen in the VAT00002 Phase II Original Cohort and other studies.

VAT00008: This is a phase III randomized, modified double-blind, placebo-controlled, multi-stage, multi-center, multi-country study being conducted to assess the efficacy, safety, and immunogenicity of two CoV2 preS dTM-AS03 vaccines (Monovalent [original variant first identified in Wuhan; D614] and Bivalent: D614/B.1.351) in adults 18 years of age and older with two stages as a primary series and open-label extension to assess immunogenicity, safety, efficacy of a Monovalent (B.1.351) booster dose of SARS-CoV-2 adjuvanted recombinant protein vaccine.

- For stage 1, 10 µg antigen Monovalent D614 adjuvanted vaccine is evaluated against placebo. This antigen dose level selection mitigates the risk of having lower antibody (Ab) titers against

variants that would be circulating at the time of the efficacy study with potential to result in lower observed vaccine efficacy (VE) for the Monovalent D614 vaccine.

- For stage 2, five µg (D614 component) + five µg (B.1.351 component) antigen dose (Bivalent [D614/B.1.351] adjuvanted vaccine) is evaluated against placebo. It is reasonable to expect that similar homologous responses would be elicited by the B.1.351 component of the bivalent vaccine. Thus, by design, the inclusion of the B.1.351 antigen with the D614 antigen in the bivalent vaccine mitigates the risk of lower Ab responses against circulating variants anticipated with the Monovalent D614 vaccine.
- A booster extension: all participants enrolled in Stages 1 and 2 are offered a Monovalent (B.1.351) booster dose if they are eligible and if they consent to receive it. A safety follow-up of 12 months after booster administration is implemented (unsolicited AE, medically attended adverse event [MAAE], SAE, and adverse event of special interest [AESI]) (5).

No safety concern was raised from the VAT00008 study for the monovalent or bivalent vaccine formulations.

There was no new clinically important information arising from studies ongoing during the reporting interval.

7.3 LONG-TERM FOLLOW-UP

No significant safety findings have been identified during the reporting interval in the long-term follow-up in studies VAT00002 and VAT00008.

7.4 OTHER THERAPEUTIC USE OF MEDICINAL PRODUCT

Not applicable; no expanded access programs, compassionate use programs, particular patient use, single patient Investigational New Drugs (INDs) or treatment INDs were ongoing or completed during the reporting interval.

7.5 NEW SAFETY DATA RELATED TO FIXED COMBINATION THERAPIES

Not applicable since the development program does not include a fixed combination product or a multi-drug regimen.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

During the reporting interval, one non-interventional study was ongoing.

VAT00012: This is an international, non-interventional, postmarketing cohort study designed to collect prospective safety data among women vaccinated with a COVID-19 vaccine during pregnancy or within 30 days prior to the first day of the last menstrual period (LMP).

The study population includes two cohorts of pregnant women 18 years of age and older matched by country and gestational age (±two weeks):

- Cohort 1: pregnant women exposed from 30 days prior to the first day of the LMP to end of pregnancy to at least one dose of a COVID-19 vaccine. These participants are enrolled as part of the Coronavirus Disease-2019 Vaccines International Pregnancy Exposure Registry (C-VIPER).
- Cohort 2: pregnant women unexposed to a COVID-19 vaccine during pregnancy. These participants are enrolled through the Pregistry International Pregnancy Exposure Registry with the same methods as those in Cohort 1. Women vaccinated before 30 days prior to the first day of the LMP are eligible for inclusion.

The total duration of the study is five years. Obstetric, neonatal, and infant outcomes will be assessed on an ongoing basis as data become available. Data on pregnancy, neonatal and infant outcomes will be included in the interim reports.

There were no safety or efficacy findings relevant to the benefit-risk assessment identified from the non-interventional study during the reporting interval.

A listing of all MAH-sponsored non-interventional studies completed or ongoing during the reporting period, and with the primary aim of identifying, characterizing, quantifying a safety hazard, confirming the safety profile of COVID-19 vaccine (recombinant, adjuvanted), or measuring the effectiveness of risk management measures is presented in Appendix 4.2.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 OTHER CLINICAL TRIALS

During the reporting interval, one investigator-initiated study (VAT00013 sponsored by [Assistance Publique Hôpitaux Paris] [APHP] - [Direction de la Recherche Clinique et de l'Innovation] [DRCI]) and three ESC studies (VAT00026, VAT00027 and VAT00028 sponsored by National Institute of Allergy and Infectious Diseases [NIAID]) are ongoing.

VAT00013: An investigator-sponsored, randomized, single-blinded multicenter clinical trial to assess the immunogenicity and safety following a booster dose of the COVID-19 mRNA vaccine original formulation (Pfizer/BioNTech) and two adjuvanted sub-unit vaccines (Monovalent D614 or Monovalent B.1.351) administered in adults who received two doses of Pfizer/BioNTech mRNA original formulation vaccine as a primary vaccination (ClinicalTrials.gov Identifier: NCT05124171).

VAT00026: This phase 2 clinical trial will evaluate the safety and immunogenicity of an additional dose of prototype and variant (alone or in combination) vaccine candidates in previously vaccinated participants with or without prior SARS CoV-2 infection. The participants should have had a primary series of a Food and Drug Administration (FDA) approved vaccine plus a booster to be eligible for participation in this trial (ClinicalTrials.gov Identifier: NCT05289037).

VAT00027: This study is an open label, non-randomized pilot study to evaluate the safety and immunogenicity of a dose of the Sanofi-GSK Monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine in kidney transplant recipients with a persistently low SARS-CoV-2 Ab titer (ClinicalTrials.gov Identifier: NCT05518487).

VAT00028: This is a randomized, multi-site, adaptive, open-label clinical trial comparing the immune response to different additional doses of COVID-19 vaccine in participants with autoimmune disease requiring immunosuppressive medications (ClinicalTrials.gov Identifier: NCT05000216).

There were no safety or efficacy findings relevant to the benefit-risk assessment in other clinical trials or study sources during the reporting period.

9.2 MEDICATION ERRORS

Medication Error coding in the Sanofi GPV database follows MedDRA introductory guide and MedDRA Term Selection - Points to Consider.

Events are coded in the GPV database utilizing the medication error preferred terms (PTs) as reported and assessed against the locally approved product information.

The MAH routinely screens multiple data sources to identify new safety information on medication errors. Data sources routinely screened to identify relevant new safety information are listed in Section 15.

Refer to Appendix 6.2.1 and Appendix 6.2.2 for the numbers of PTs in the broad MedDRA SMQ "*Medication errors*" reported with serious or non-serious adverse reactions from post-authorization sources for COVID-19 vaccine (recombinant, adjuvanted) and UNK MFR, respectively. Appendix 6.2.1 and Appendix 6.2.2 complies with the expectations defined in Table A2-1 in the good practice guide on recording, coding, reporting, and assessment of medication errors for COVID-19 vaccine (recombinant, adjuvanted) and UNK MFR, respectively. As, there are no "*Medication errors*" reported with serious or non-serious adverse reactions from post-authorization sources for UNK MFR; therefore, Appendix 6.2.2 is not applicable.

During the reporting period, the most frequently reported PTs within the Medication error SMQ with COVID-19 vaccine (recombinant, adjuvanted) are presented in Table 4.

It is to be noted that some cases involved more than one type of medication error. Therefore, the total number of medication errors included in the Table 4 is higher than the reported number of cases.

Table 4 - Most frequently reported medication errors reported during the interval

Medication Error description	PT for Medication Error	Count of events of Medication Error
• Three reporters think a reaction occurred as a result of a mistake made in the administration of the vaccine. One of them reported "May have been too much administered". • A consumer who was on anticoagulant medication when the patient received the vaccine - realized that it is not advised to have this vaccine when taking medication to prevent blood clots. • A nurse suggested the burning pain was caused by the blunt needle. • Another reporter stated, "vaccination administered halfway up deltoid muscle, patient described hitting the bone with the needle".	*Medication error*	6
Patients mistakenly received COVID-19 vaccine (recombinant, adjuvanted) vaccine as their first or second primary dose.	*Product use in unapproved indication*	5
COVID-19 vaccine (recombinant, adjuvanted) was administered less than four months after the previous dose.	*Inappropriate schedule of product administration*	4
• During the reconstitution of the product, the sampling was difficult, the syringe emptied directly during the pressure[a]. • According to a consumer, injection was made in unhygienic situation ("injected directly from a syringe in a clear plastic box containing many already made-up mixtures of supposed injection").	*Product preparation error*	2
• In one case[a], during the reconstitution of the product, the sampling was difficult, the syringe emptied directly during the pressure. Product was administered but incorrect dose administered. A product technical complaint has been initiated. • No more details in the other case reported with "Incorrect dose administered by product.	*Incorrect dose administered/Incorrect dose administered by product*	2

a Same case reported with Incorrect dose administered and Product preparation error.
PT: Preferred Term.

Out of the 18 cases of medication errors reported during the review period, nine (four serious and five non-serious) were reported with AEs (50 %) and nine cases with no reported AEs (50 %). The nine cases associated with AEs are described in Table 5 below:

Table 5 - Interval medication error cases reporting adverse events

Case ID Seriousness	Medication Error PT	PT(s) of reported AE(s)	Comment
[redacted]/Serious	*Medication error*	Myalgia	Serious medically significant case reported by a consumer: A 77-year-old patient experienced myalgia on the day of vaccination. The patient consulted a general physician and was advised to rest for three days and take paracetamol. The consumer thinks the reaction occurred as a result of a mistake made in the administration of the vaccine. At time of reporting, the patient was recovering.
[redacted]/Serious	*Medication error*	Erythema	Serious medically significant case reported by other health professional: An 82-year-old patient experienced localized erythema on an unknown time after vaccination. Initially the area was extensive on mid-level of deltoid muscle, described as six-seven cm round with significant depth and painful swelling with tenderness. It lasted for three days then became increasingly erythematous and acutely painful. A medication error was reported: "vaccination administered halfway up deltoid muscle, client described hitting the bone with the needle." At the time of reporting, the patient was recovering.
[redacted]/Serious	*Medication error*	• Abdominal Pain upper, • Malaise, • Diarrhea, • Fatigue	Serious medically significant case reported by a consumer: A 45-year-old patient experienced malaise, diarrhea, abdominal pain upper, and fatigue four days after booster administration. Concomitant medications included pregabalin; folic acid; mirtazapine; propranolol; oxybutynin and Vitamin D all for

Case ID Seriousness	Medication Error PT	PT(s) of reported AE(s)	Comment
			anxiety. According to reporter, reactions occurred as a result of a mistake made in the administration of the vaccine: "May have been too much administered."
[redacted]/Serious	*Inappropriate schedule of product administration*	Asthenia	Serious case leading to disability reported by other health professional: An 83-year-old patient with ongoing Multiple System Atrophy (a progressive neurodegenerative disorder which has caused weakness) received two doses of vaccine within time span of six days. The patient experienced weakness worsened one day after the second injection: the patient was unable to sit up in bed, unable to walk unaided and unable to manipulate cutlery to eat. The patient also suffered extreme fatigue, fever 37.7°C, painful injection site and anorexia. A low-grade fever has continued resulting in weakness and fatigue. At time of reporting, the patient was not recovered.
[redacted]/Non-serious	*Medication error*	Adverse drug reaction (Injection site redness and tenderness)	Non-serious case reported by a consumer who reported redness and tenderness surrounding injection site one day after vaccination. The consumer thinks the reaction occurred as a result of a mistake made in the administration of the vaccine. Case outcome is unknown.
[redacted]/Non-Serious	*Product Use in Unapproved Indication*	• Rash, • Diarrhea,	Non-serious case reported by a consumer who hasn't been vaccinated against COVID-19 before and experienced rash in groin and diarrhea respectively 23 and 25 days after vaccination. The patient didn't experience any immediate vaccination.
[redacted]/Non-Serious	*Medication error*	• Pain In Extremity, • Chills, • Pyrexia,	Non-serious case reported by a consumer. who experienced pain in extremity, chills, pyrexia, nausea,

Case ID Seriousness	Medication Error PT	PT(s) of reported AE(s)	Comment
		• Nausea, • Asthenia, • Vaccination Site Bruising, • Lymphadenopathy	asthenia, vaccination site bruising and lymphadenopathy the day of vaccination. As per reporter, this reaction occurred as a result of a mistake made in the administration of the vaccine: It was administered rapidly without due care and attention. This was the first time a COVID injection had been administered one inch below the top of the patient's shoulder. The nurse suggested the burning pain was caused by the blunt needle.
[redacted]/Non-Serious	*Product Preparation Error*	• Pain in extremity • Diarrhea • Malaise	Non-serious case reported by a consumer who reported painful arm, diarrhea, and feeling unwell and unknown time after vaccination. As per reporter, injection was made in unhygienic situation ("injected directly from a syringe in a clear plastic box containing many already made-up mixtures of supposed injection", "injection needle exposed to the air as box was uncovered in a shop).
[redacted]/Non-Serious	*Medication error*	Diarrhea	Non-serious case reported by a consumer who experienced diarrhea an unknown time after vaccination. As per reporter, this reaction occurred as a result of a mistake made in the administration of the vaccine: the patient was under anticoagulation medication when the patient received the vaccine and realized that it is not advised to have this vaccine when taking medication to prevent blood clots.

PT: Preferred Term; AE: Adverse Event; COVID-19: Coronavirus Disease-2019; COVID: Coronavirus Disease.

There were no relevant safety findings on patterns of medication errors and potential medication errors identified which would require specific risk minimization measures (RMM) at this time. The information on patterns of medication errors and potential medication errors does not change the overall benefit-risk evaluation of COVID-19 vaccine (recombinant, adjuvanted). No published significant safety findings regarding medication errors have been available during the reporting interval.

10 NON-CLINICAL DATA

No significant findings have been identified during the reporting interval.

11 LITERATURE

This section summarizes new and significant safety findings from literature relevant to COVID-19 vaccine (recombinant, adjuvanted) that the MAH became aware of during the reporting interval.

In accordance with the GVP, the MAH is screening literature articles to search for any new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts when relevant to the medicinal product. If relevant and applicable, information on other active substances of the same class should be considered.

Commencement of literature screening has been determined by the last date of package submission of the MA application(s) for COVID-19 vaccine (recombinant, adjuvanted) (March 2022) and a broad strategy has been applied with search criteria including any COVID-19 vaccine product, irrespective of manufacturer or vaccine technology, and a report of AE(s) without restriction by seriousness or severity as stated in EU Risk Management Plan (RMP) version 1.0 DLP 08 November 2022. In the Responses to Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur Rolling review RMP final assessment report received on 01 October 2021 and in EU RMP version 1.0 DLP 08 November 2022, the following is stated: “as knowledge of the SARS-CoV-2 virus, COVID-19 and vaccines evolves, it is expected that the above strategies will likewise change evolve”. Indeed, the MAH would propose to implement a focused strategy with search criteria on protein and/or nano particle and/or adjuvanted COVID-19 vaccine product now that safety profiles of other COVID-19 vaccine platforms are considered stabilized with millions of doses distributed and taken into account that they are closely monitored by their respective MAHs.

Records identified are reviewed for periodic report inclusion using the criteria below:

- Publications describing non-case safety topics for Sanofi products
- Publications describing medication error, misuse, abuse, or overdose (acute or chronic)
- Publications describing lack of efficacy
- Publications describing off-label use with safety impact
- Publications describing unlisted interactions or new data on listed interactions
- Publications reporting pregnancy or drug exposure via parent events (regardless of outcome, even if a normal outcome)
- Publications describing medically important safety information in a special population (not in the target population) that is not described in the product information.

- Publications related to AESIs for vaccines implying an increased risk following vaccination or demonstrating no association between the AESIs and the vaccine
- Publications including non-clinical data related to safety, such as in-vitro studies and animal studies
- Publications including clinical data related to safety, such as pharmacokinetic (PK) studies

During the reporting period, four publications identified from the scientific (including non-clinical) and medical literature, contained relevant safety findings summarized hereafter.

Adverse events of special interest - Myocarditis and pericarditis

Macias Saint-Gerons D, Ibarz MT, Castro JL, Fores-Martos J, Tabares-Seisdedos R. Myopericarditis Associated with the Novavax COVID-19 Vaccine (NVX-CoV2373): A Retrospective Analysis of Individual Case Safety Reports from VigiBase. Drugs Real World Outcomes. 2023 Jun;10(2):263-70. (6)

The authors presented a retrospective analysis of myopericarditis, an AESI, associated with a protein sub-unit vaccine, NOVAVAX® (NVX-CoV2373), reported to the World Health Organization (WHO) global safety database and compared to the rates reported with other COVID-19 vaccines. From 31 703 998 ICSRs, there were 61 812 ICSRs of myopericarditis and 61 were reported for NOVAVAX vaccine. Out of 61 included cases, 45 reported pericarditis, 11 myocarditis, four myopericarditis and one both terms (myocarditis and pericarditis). Most of the cases were reported from Australia (82%). The median age of individuals was 35.5 years old, and most were males (38; 62.3%). Twenty-four (24) reports (39.3%) were considered serious, none of them were fatal. The median induction period for myopericarditis from vaccination (after the most recent immunization) estimated from 40 ICSRs, was three days. Increased disproportionality for myopericarditis was found for NVX-CoV2373 (Reporting Odds Ratio [ROR] 14.47, 95% confidence interval [CI] 11.22–18.67) and mRNA vaccines: BNT162b2 (ROR 17.15, 95% CI 16.88-17.42) and mRNA-1273 (ROR 6.92, 95% CI 6.77-7.08). Higher values were found in males. Disproportionality for the NVX-CoV2373 vaccine was found in the age groups 18-44 and 45-65 years in both sexes, but with higher values in males. Chest pain was the most common co-reported event 43 (70.5%). The adenoviral vector-based vaccine Ad26.COV2.S showed slightly increased disproportionality (ROR 1.83, 95% CI 1.70-1.98), whereas no increased disproportionality was found for ChAdOx1 adenoviral vector-based vaccine. The authors concluded that new NVX-CoV2373 vaccine shows an increased disproportionality for myopericarditis similar to mRNA vaccines (6).

MAH Comment: Based on the study conducted by the authors suggesting an increased disproportionality with the protein sub-unit vaccines. However, a greater risk of hospitalization and death has been observed in association with COVID-19 infection than with the vaccination. This study also had several limitations. The data source for the study was retrieved from spontaneous reports database from which no definitive causal associations can be drawn. Relevant information such as viral

testing for myocarditis was lacking from the reports. In addition, the exact mechanism of action for vaccine-induced myopericarditis remains to be elucidated. More evidence from controlled studies is necessary. Myocarditis/ Pericarditis is already an important potential risk for COVID-19 vaccine (recombinant, adjuvanted). Please also refer Section 16.3 and Section 16.4 for details.

Special population - Patients with kidney transplant receiving immunosuppressive therapy

Nafar M, Mostafaloo N, Firouzan A, Poorrezagholi F, Samadian F, Dalili N, et al. Immunogenicity and Safety of SpikoGen, an Adjuvanted Recombinant SARS-CoV-2 Spike Protein, as a Heterologous Third Booster Dose in Kidney Transplant Patients: A Single-arm Clinical Trial. Clinical Therapeutics. 2022 Dec 1;44(12):1566-76. (7)

The authors assessed the immunogenicity and safety of the SpikoGen® vaccine as a third booster dose in special patient population (43 patients undergoing kidney transplant receiving immunosuppressive therapy) at a referral center for kidney transplantation in Iran. The patients had received their primary vaccination based on an inactivated whole virus platform (Sinopharm) one to three months earlier. SpikoGen is a subunit recombinant S protein vaccine combined with Advax-CpG55.2 TM adjuvant, a microcrystalline polysaccharide particle engineered from delta inulin. The most common local and systemic reported solicited AEs were injection site pain in 19 patients (44.19%) and fatigue in 10 (23.26%), which were largely mild and transient. No SAEs were reported (7).

MAH Comment: In this article, the authors performed a single-arm, open-label, prospective clinical trial including 43 patients with SpikoGen (adjuvanted recombinant S protein trimer vaccine). The authors observed that a single booster dose of the vaccine given one to three months after primary vaccination with two doses of Sinopharm vaccine induced positive humoral and cellular immune responses in immunosuppressed patients undergoing renal transplant, thereby achieving S Ab levels predictive of protection. While positive responses are observed, the number of transplant patients was relatively low and there was no control group. In addition, this was a single-center study. Further information would be needed from larger, multicenter studies to extend these results. Use in immunocompromised subjects is a missing information for COVID-19 vaccine (recombinant, adjuvanted). Please refer Section 16.3 and Section 16.4 for details.

Special population - Pregnant women

Cole C, Tsakiroglou M, Waitt C. Communication is crucial: Lessons from COVID-19 vaccination and pregnancy. Br J Clin Pharmacol. 2023 Feb;89(2):582-93. (8)

The authors presented findings from the systematic review and meta-analysis concerning pregnancy outcomes following COVID-19 vaccination with BNT162b2, Moderna, ChAdOx1 and Janssen vaccines from multiple studies. No difference in maternal outcomes, neonatal outcomes or AEs and no increased risks in pregnant women or neonates were found in vaccinated women compared to non-vaccinated. (8)

MAH Comment: Based on the systematic review of safety outcomes associated with COVID-19 vaccines, this article summarizes key aspects and outcomes due to COVID-19 vaccination during pregnancy. For a vast majority of the studies, the reported side-effects in pregnant women were similar to the general population and no significant impact on the adverse maternal or fetal outcomes were observed with the vaccines. The various studies and recommendations further affirm that COVID-19 vaccines reduce the risk of hospitalizations and deaths in pregnant women as in the nonpregnant population. The authors highlight the importance of advice and reassurance on the safety of COVID-19 vaccinations in pregnant population for effective benefit-risk communication. Use in pregnant women and while breastfeeding is a missing information for MAH COVID-19 vaccine (recombinant, adjuvanted). Please refer Section 16.3 and Section 16.4 for details.

Tormen M, Taliento C, Salvioli S, Piccolotti I, Scutiero G, Cappadona R, et al. Effectiveness and safety of COVID-19 vaccine in pregnant women: A systematic review with meta-analysis. BJOG. 2023 Mar;130(4):348-57. (9)

The authors presented a systematic review and meta-analysis of pregnancy outcomes and risk of pregnancy related complications in COVID-19 vaccinated pregnant population with Pfizer, AstraZeneca, and Jansen vaccines (no protein-based vaccine included in the analysis) and a comparison to unvaccinated population. Administration of a COVID-19 vaccine during pregnancy resulted in a statistically significant reduction in SARS-CoV-2 infection and COVID-19-related hospitalizations, but the certainty of evidence was very low. The effect appeared to be greater for both infection and hospitalizations when considering only fully vaccinated women, although the level of certainty was still very low. Conversely, the difference in Intensive Care Unit (ICU) admissions related to COVID-19 did not reach statistical significance, likely due to the small number of total cases of both vaccinated and unvaccinated women. Nine (9) studies evaluated fetal complications occurring during pregnancy in vaccinated versus unvaccinated women. No significant differences were observed for the following outcomes: pregnancy loss, fetal abnormalities, small for gestational age, intrauterine growth restriction, preterm birth, stillbirth, meconium-stained amniotic fluid, neonatal ICU admission and hypoxic-ischemic encephalopathy between vaccinated and unvaccinated women.

MAH comment: It was concluded that COVID-19 vaccination administered during pregnancy seems to reduce SARS-CoV-2 infection and COVID-19-related hospitalization, with no significant effects on maternal-fetal complications (9). However, the certainty of evidence was low as the data was identified from observational studies. Use in pregnant women and while breastfeeding is a missing information for MAH COVID-19 vaccine (recombinant, adjuvanted). Please refer Section 16.3 and Section 16.4 for details.

No articles on patients vaccinated with protein-based vaccines or COVID-19 vaccine (recombinant, adjuvanted) in pregnant women were identified.

12 OTHER PERIODIC REPORTS

During the reporting interval this is the only PBRER prepared by the MAH for this product including periodic reports prepared by the contractual partner.

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

No new controlled clinical trials indicating a lack of efficacy of COVID-19 vaccine (recombinant, adjuvanted), in the authorized indications, relevant for the benefit-risk evaluation were identified during the reporting interval.

14 LATE-BREAKING INFORMATION

Since the DLP for this PBRER, the MAH has identified the following new information regarding potentially important safety and efficacy and/or effectiveness:

One signal on allergic including anaphylactic reactions has been opened on 17 May 2023, validated on 14 June 2023. On 26 June 2023, signal of allergic including anaphylactic reactions was confirmed as an identified risk. The weighted cumulative evidence was considered sufficient to support a causal association between COVID-19 vaccine (recombinant, adjuvanted) and allergic including anaphylactic reactions that should be reflected in the RSI.

Regarding anaphylactic reactions, highest levels of certainty for the diagnosis of anaphylaxis (levels 1 and 2 of the Brighton Collaboration Case Definition (BCCD) [10]) were not reached for any case; however anaphylactic reactions could be expected after any vaccination. In addition, the pattern observed of allergic reactions reported after the use of COVID-19 vaccine (recombinant, adjuvanted) (rash, urticaria, rash erythematous, pruritus, swelling face) supports the fact that the signal detected is judged to be of sufficient likelihood to justify verificatory action and moves to full evaluation and further characterize allergic including anaphylactic reactions. Further details regarding this signal will be discussed in the next PBRER interval.

15 OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

There are no signals that were ongoing at the DLP or closed during the reporting interval. Therefore, Appendix 3 is not applicable.

The sources routinely screened to identifying relevant new safety information include:

- Global pharmacovigilance (PV) database, to identify signals from ICSRs and clusters of cases as well as from aggregate reports

- Scientific literature to identify signals from case reports or case series, published studies, meta-analyses
- Data mining in Eudravigilance database (when the product is included in the *Eudravigilance data mining pilot)*
- Product complaints (PCs) database
- Regulatory Authority websites

The following sources of routine safety surveillance are also taken into consideration, as applicable:

- Safety queries and requests from RAs
- Clinical trials and other studies in human (individual study data and integrated study data), Independent Data Monitoring Committee reports
- Non-clinical safety information (ie, toxicology, safety pharmacology, PK data, in-vitro studies)
- Pharmacoepidemiology studies, registries or other observational studies, analysis of pre-existing data
- Manufacturing site quality systems review
- Competitive intelligence
- Signals identified by partners
- Queries and requests from Ethics Committees, Institutional Review Boards
- Media (eg, press, television, internet including social media)

Depending on the source screened for signal detection and product-specific criteria, the following signal detection methods are used to identify new drug-event combinations, or an increased reporting of an event or a group of events, requiring further evaluation:

- Qualitative: Manual medical review of ICSRs recorded in the GPV database, and review of aggregate data to detect any new relevant AEs or a change in nature, and/or increased severity of a known ADR, with a particular focus on increased trends in reporting, newly reported events, and medication errors, non-case literature review.
- Semi-quantitative: Manual review of aggregate data from internal databases (eg, PV or PC database) such as event counts and frequency or proportion thresholds, sorting, and cross-tabulations, based on thresholds, evaluation algorithms and medical judgment.

15.1 TOPICS REQUESTED BY A REGULATORY AUTHORITY TO BE MONITORED IN THE PBRER

The following safety topics were monitored during the reporting period upon request by a RA:

15.1.1 EMA request based on the Core-RMP guidance, Responses to Rapporteurs Final List of Questions on Risk Management Plan dated 23 June 2022 (Reference submission: EMEA/H/C/005754/0000), dated 15 August 2022 (Reference submission: EMEA/H/C/005754/0000)

15.1.1.1 Anaphylactic reactions

Based on the MedDRA search criteria SMQ Anaphylactic reaction Algorithmic, a total of five serious case reports of potential anaphylactic reactions were retrieved on the period; none met level 1 or 2 BCCD level for anaphylaxis.

- Case [redacted] reported from an HCP via [redacted] and involving a 93-year-old [redacted] with an unspecified ongoing food allergy experienced back pain, eye movement disorder, respiratory arrest, and erythema a couple of minutes after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient was laid down and recovered 10 mins later with feet elevation. Based on the limited reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 3 for anaphylaxis (10).
- Case [redacted] was reported from an HCP via [redacted] A [redacted] with no reported medical history experienced acute anaphylaxis, two min after receiving COVID-19 vaccine (recombinant, adjuvanted). The patient was given adrenaline two times (half an hour apart) and was transferred to a hospital. The patient recovered. The concomitant medications included apixaban; macrogol 3350, potassium chloride, sodium bicarbonate, sodium chloride; furosemide; gabapentin; Hypromellose; omeprazole; paracetamol and cholecalciferol. Further information regarding detailed symptoms, concurrent condition during vaccination, medical history, tolerance of previous vaccinations, and investigations excluding alternative etiologies for the reported event are needed to fully assess this case. This case was assessed as BCCD level 4 for anaphylaxis.
- Case [redacted] was reported from a consumer via [redacted] A 74-year-old [redacted] with no reported medical history developed dizziness, dyspnea, erythema, miliaria, and asthenia one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient's past vaccination was COVID-19 vaccine Moderna, and past medications included atorvastatin, clopidogrel for cerebrovascular accident and paracetamol for headache. Concomitant medications included lisinopril for blood pressure; pantoprazole for gastroesophageal reflux disease; and venlafaxine for depression. Patient was reported as recovering. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for anaphylaxis.

- Case [redacted] was reported by a consumer via [redacted] and involves a 77-year-old [redacted] with medical history of bronchitis improved after diet, gastritis and ongoing glaucoma who experienced coughing, influenza, headache, flushing and productive cough two days after receiving the vaccine. The patient also experienced fatigue unknown duration after the vaccination. The patient was treated with paracetamol for headache. The patient recovered from coughing and had not recovered from influenza, productive cough, fatigue, flushing and headache. The patient's past medical history of bronchitis could be a confounding factor. Based on the reported information, the role of suspect cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.
- Case [redacted] was reported from a consumer via [redacted] An unknown age [redacted] with no reported medical history developed diarrhea on the day of vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient also developed pruritus, pharyngeal swelling, vaccination site bruising, vaccination site warmth and lymphadenopathy unknown duration after the vaccination. The patient's past vaccinations were not reported. Outcome was reported as not recovered for vaccination site bruising, vaccination site warmth, diarrhea and unknown for pruritus, lymphadenopathy, and pharyngeal swelling. Based on the minimal information reported, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for anaphylaxis.

In addition to Anaphylactic reactions specific analysis, 17 cases including seven serious and 10 non-serious cases reported swelling face/angioedema based on the MedDRA search strategy for SMQ: "*Angioedema*" (Narrow); none met BCCD level 1 or 2 for anaphylaxis. Please refer to Section 15.1.2.2.

Based on medical review of cumulative data, a signal on Allergic including anaphylactic reactions has been opened on 17 May 2023 and has been validated on 14 June 2023. Please also refer Section 14 of the PBRER.

15.1.1.2 Myocarditis/Pericarditis

Myocarditis/pericarditis is considered an important potential risk. Please refer to Section 16.3.1.1 for further details.

15.1.1.3 COVID-19 AESIs

Based on the MedDRA search strategy outlined in Appendix 6.4.1, a total eight case reports of COVID-19 infection were reported. Case reports of COVID-19 are presented in Section 15.1.5 of the PBRER for Vaccination Failure and Section 16.3.1.2 for Vaccine Associated Enhanced Disease (VAED)/Vaccine Associated Enhanced Respiratory Disease (VAERD).

Based on medical review of cumulative data, no safety concern has been identified.

15.1.1.4 Dermatological AESIs (including Chilblains, Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis)

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no cases reporting these reactions have been identified.

15.1.1.5 Facial paralysis (Bell's palsy)

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no cases reporting these reactions have been identified. No case report of facial paralysis (Bell's Palsy) has been reported.

15.1.1.6 Hepatic AESIs

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of hepatic AESI has been reported.

15.1.1.7 Pregnancy related AESIs

There was no reported use in pregnancy. Use in pregnancy is also a missing information for COVID-19 vaccine (recombinant, adjuvanted) (see also Section 16.4 of the PBRER).

15.1.1.8 Respiratory AESIs

Based on the MedDRA search strategy outlined in Appendix 6.4.1 focused on acute respiratory distress syndrome, three serious case reports of respiratory AESIs were identified: one case of respiratory arrest ([redacted]) also reported hypersensitivity manifestations and is presented under Anaphylactic reactions (see Section 15.1.1.1), one case ([redacted]) reported seizures along with respiratory arrest and it is presented below under "Seizures" Section 15.1.3.10) and remaining one case of severe acute respiratory distress syndrome ([redacted]) is presented here.

- Case [redacted] reported by a consumer via [redacted] referred to a 77-year-old [redacted] with medical history of atrial fibrillation, hypertension, and hypercholesterolemia, who experienced SARS-CoV-1 infection (SARS) 14 days after vaccination with COVID-19 vaccine (recombinant, adjuvanted) and SARS-CoV-2 infection (confirmed by test but no test result was provided) 15 days after vaccination. The concomitant medications included apixaban for atrial fibrillation; atorvastatin for blood cholesterol increased; bisoprolol for heart rate increased; and ramipril for hypertension. Symptoms were extreme coughing, sneezing, runny nose, shortness of breath and difficulty breathing for which the patient was given antibiotics to prevent chest infection. The outcome was reported as not recovered from SARS and recovering from COVID-19. Further information regarding SARS-CoV-2 vaccination history, other risk factors, complementary examination results and time of first symptoms appearance for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect

vaccine cannot be assessed, and a potential vaccination failure cannot be retained. This case was assessed as BCCD level 5 for VAED (11). See also below Vaccination Failure in Section 15.1.5 and VAED/VAERD in Section 16.3.1.2.

Based on medical review of cumulative data, no safety issue on respiratory AESIs has been identified. In addition, no increased observed versus expected (O/E) ratio has been detected for respiratory AESIs (Refer to Appendix 6.4.2).

15.1.1.9 Sudden death

Based on the search of fatal outcomes, two cases reporting sudden death were reported on the period ([redacted], [redacted]) and are presented in Table 1 of fatal case reports in Appendix 6.3. Both cases had insufficient information for a comprehensive evaluation and the role of individual suspect vaccine cannot be assessed.

15.1.1.10 Gastro-intestinal disorders

Based on the MedDRA search strategy outlined in Appendix 6.4.1, one non-serious case report ([redacted]) of dyspepsia was reported. Based on medical review of this case report, no safety concern has been identified.

15.1.1.11 Coronary artery disease

Based on the MedDRA search strategy outlined in Appendix 6.4.1, one serious case of myocardial infarction ([redacted]) was reported from an HCP via[redacted]and involving a 78-year-old non-tobacco user [redacted], with ongoing chronic kidney disease, who experienced myocardial infarction one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Diagnosis was myocardial infarction with nonobstructive coronary arteries (MINOCA). There was medical history that relates to previous venous or arterial thromboses. The patient did not confirm or suspect autoimmune or inflammatory disease, including vasculitis. No hemorrhage was identified. As per reporter, this case report was not related to possible blood clots or low platelet counts or possible myocarditis or pericarditis. At time of reporting, the outcome was recovered/resolved. Further information regarding concomitant medication and tolerance, laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for Thrombosis/Thromboembolism (12).

Based on the medical review of the case report, no safety concern has been identified. In addition, no increased O/E ratio has been detected for coronary artery disease AESI. Refer to Appendix 6.4.2.

15.1.1.12 Thrombosis with thrombocytopenia syndrome

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of thrombosis with thrombocytopenia syndrome was reported, however, one case report ([redacted]) of deep vein thrombosis (DVT) and thrombocytopenia has been reported. It is presented below in Section 15.1.1.13 under "Thromboembolic AESIs (venous thromboembolism)".

15.1.1.13 Thromboembolic AESIs (venous thromboembolism)

Based on the MedDRA search strategy outlined in Appendix 6.4.1, six serious cases reported different types of thromboembolic AESIs, one reported pulmonary embolism ([redacted]), one reported DVT ([redacted]), three reported thrombosis ([redacted]), and one fatal case reported cerebral venous sinus thrombosis (CVST) ([redacted]) and were assessed against BCCD for thrombosis/thromboembolism (12):

- Case [redacted] reported pulmonary embolism from an HCP via [redacted] A 75-year-old [redacted] experienced pulmonary embolus (Diagnosed through Computerized Tomography [CT] pulmonary angiogram) five days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient had difficulty breathing and chest discomfort. Fibrin D dimer was not > 4000 (poorly documented but pathologic or imaging findings consistent with thromboembolism: diagnosed through CT pulmonary angiogram). At the time of reporting, the outcome was recovering (no information about corrective measurements was provided). Previous and current laboratory investigations including Fibrin D Dimer date (results which were reported as not > 4000 [Units not provided]), excluding alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case report meets BCCD level 1, considering diagnostic confirmation and experienced symptoms, however there is a lack of information on the patient's medical history, concomitant medications, and primary vaccination with COVID-19 vaccines.
- Case [redacted] reported DVT received from other HCP via [redacted] An 88-years-old [redacted] experienced DVT five days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The concomitant medications included allopurinol; aspirin; felodipine; folic acid; furosemide; glyceryl trinitrate; paracetamol; salbutamol; and beclomethasone dipropionate, formoterol fumarate, glycopyrronium bromide. At the time of reporting, the outcome was recovering. Further information regarding previous COVID-19 vaccinations, indication of reported concomitant medications including aspirin, medical history and risk factors, laboratory investigations and context for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case meets BCCD level 4 for thrombosis/thromboembolism.
- Thrombosis was reported in three cases ([redacted]) discussed below:

- Case [redacted] involving an 86-year-old [redacted] who experienced thrombus two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Symptoms were reported to be acute onset pain, paralysis, and numbness. A CT scan confirmed acute thrombus in right axillary artery. The patient had ongoing macular degeneration, hypertension and previous DVT/pulmonary embolism which constitutes a pre-existing risk factor. The patient had ongoing macular degeneration, hypertension and previous DVT/pulmonary embolism which constitutes a pre-existing risk factor. Further information regarding previous COVID-19 vaccinations, concomitant medications and other risk factors, complementary examination results and context for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be excluded. This case was assessed as BCCD level 1 for thrombosis/thromboembolism.
- Case [redacted] was reported from a consumer via [redacted] and referred to a [redacted] of an unknown age who experienced dyspnea, abdominal pain, and blood clots two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The concomitant medications included clopidogrel. The corrective treatment, outcome, and relevant details such as medical history was unknown. Further information on patient's age, weight, and body mass index (BMI), past medical history, thrombosis risk factors, current medications and current condition excluding alternative etiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for thrombosis/thromboembolism.
- Case [redacted] received from HCP via [redacted] reported in a 78-year-old [redacted] with past medical history of immunodeficiency and ongoing hypothyroidism, atrial fibrillation and cardiac failure who experienced a DVT and thrombocytopenia three days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient has been complaining of calf swelling since vaccination. The patient also felt sweaty and had dizziness with a fainting episode. The lowest patient's platelet count after vaccination was reported as "132" and no previous platelet counts were known. Anti- platelet factor 4 (PF4) antibodies identified was unknown. The patient was diagnosed with DVT. The patient's past medical history of immunodeficiency and current condition of could be a confounding factor. Further information on patient's weight and BMI, allergy history, thrombosis risk factors, immunodeficiency type, previous platelet counts, current laboratory findings, and concomitant medication excluding alternative etiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for thrombosis/thromboembolism.

- One fatal case of CVST ([redacted]) is presented in Table 1 of fatal cases in Appendix 6.3.

Based on the medical review of cumulative data, no safety concern has been identified.

In addition, no increased O/E ratio has been detected for venous thrombo-embolism (Refer to Appendix 6.4.2).

For CVST, no significant O/E ratio increase has been detected using a reporting rate of 100%. However, a significant O/E ratio increase has been detected using a reporting rate of 50% (meaning that only 50% of the cases were reported). This analysis presents limitation as it is based on only one event which makes this analysis unconclusive. In addition, this case has been assessed as BCCD level 4 for thrombosis/thromboembolism. This AESI will continue to be closely monitored (Refer to Appendix 6.4.2).

15.1.1.14 Stroke (hemorrhagic stroke and ischemic stroke)

Based on the MedDRA search strategy outlined in Appendix 6.4.1, six serious cases of stroke (all reported as cerebrovascular accident) were reported.

- Case [redacted] was reported from a consumer via [redacted] and referred to an 80-year-old [redacted] with no reported medical history who experienced cerebrovascular accident one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted) and was hospitalized. Past medications included cetirizine and topiramate. Patient's past vaccinations were not reported. Patient was reported as recovering. Further information regarding concurrent condition at the time of vaccination, previous vaccination, concomitant medication and tolerance, allergic history, laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case report was assessed as BCCD level 4 for thrombosis/thromboembolism (13).
- Case [redacted] was reported from a consumer via [redacted] involving an 85-year-old [redacted] who experienced stroke one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient also experienced confusional state, dysarthria, prosopagnosia, headache, and diarrhea of unknown duration after the vaccination. Concomitant medications included amlodipine; doxazosin; enalapril; tozinameran vaccine and elasomeran vaccine. The patient has not had a similar reaction to any other vaccine or medicine, any recent surgery or other trauma (eg, an accident). Reportedly, the patient had no history of blood clotting, irregular heart rhythm, deep venous thrombosis, lung, pulmonary embolism, brain (stroke) or coronary arteries (heart attack/myocardial infarction), intermittent claudication, any inflammatory or autoimmune diseases, eg, systemic lupus erythematosus (SLE), not any family problems with clots in blood vessels. Relevant investigations included CT head Scan; Blood Test; electrocardiogram (ECG); central nervous system (CNS)/neurological tests; magnetic resonance imaging (MRI); Ultrasound (results not reported). At time of reporting, the outcome was unknown. Further information on allergy history, medical condition at the time of vaccine and patient's laboratory investigation results precluding alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine

cannot be assessed. The case report was assessed as BCCD level 1 for thrombosis/thromboembolism.

- Case [redacted] was reported from a consumer via [redacted] and referred to a 76-year-old [redacted] with medical history of hypertension, who experienced stroke 28 hours after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Concomitant medications included bisoprolol; ezetimibe both for secondary prevention; pravastatin for blood cholesterol increased; ramipril for hypertension and aspirin for ADR not otherwise specified (NOS). Patient experienced facial droop on left side, left-sided weakness, and classic stroke symptoms. The patient underwent clot bursting treatment for the event. At time of reporting, the outcome was not recovered. Further information on allergy history, family history, past medication, laboratory investigation, previous laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. The case report was assessed as BCCD level 3 for thrombosis/thromboembolism.

- Case [redacted] was reported from a consumer via [redacted] and referred to an 87-year-old [redacted] with ongoing immunodeficiency, diabetes and chronic kidney disease, experienced stroke eight hours after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient's past medical history included anemia. Stroke was confirmed by scans. At time of reporting, the outcome was not recovered. The patient's medical history included anemia, immunodeficiency, diabetes, and chronic kidney disease. Further information on allergy history, family history, thrombosis risk factors and previous events, past or concomitant medication, stroke type (ischemic or hemorrhagic), current patient condition and previous laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. The case report was assessed as BCCD level 1 for thrombosis/thromboembolism.

- Case [redacted] was reported from HCP via [redacted] involving a 78-year-old [redacted] with medical history including "ongoing" transient ischemic attack (TIA), class III obesity, palpitations and hypertension, and the patient experienced stroke one day after vaccination with fifth dose of COVID-19 vaccine (recombinant, adjuvanted). Concomitant medications included atorvastatin for TIA; clopidogrel; diltiazem for palpitations; flucloxacillin for cellulitis; lansoprazole and ramipril for hypertension. As per reporter, this case report was related to possible blood clots or low platelet counts and not related to possible myocarditis or pericarditis. It was reported that platelet count was <150 - 109/L, D-dimer was > 4000 and anti-PF4 antibodies identified was unknown. The patient had not any previous reactions to medications, especially heparin or anticoagulants, history of, or current, malignancy. The patient had not confirmed or suspected autoimmune or inflammatory disease, including vasculitis. At time of reporting, the outcome was not recovered. Further information on etiology of palpitations, allergy history, family history, thrombosis risk factors and previous events, time elapsed since last TIA, current patient condition and previous laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this case. Based on the

reported information, the role of the individual suspect vaccine cannot be assessed. BCCD level 4 for thrombosis/thromboembolism.

- Case [redacted] was reported from a consumer involving an adult patient, of unknown age and gender experienced a stroke within minutes after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient's past medical history, medical treatment(s), vaccination(s) and family history were not provided. It was not reported if the patient received a corrective treatment for the event. Further information on patient's age, gender, past medical history, allergy history, current medications, condition at the time of reported event, laboratory investigation excluding alternative etiologies for the reported event, are needed to fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed. BCCD level 4 for thrombosis/thromboembolism.

Based on medical review of cumulative data, no safety concern has been identified nor pattern in thrombotic and thrombo-embolic events. In addition, no increased O/E ratio has been detected for ischemic and hemorrhagic stroke (Refer to Appendix 6.4.2).

15.1.1.15 Guillain- Barré syndrome

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of Guillain-Barré syndrome has been reported.

15.1.1.16 Immune thrombocytopenia

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of immune thrombocytopenia has been reported.

15.1.1.17 Microangiopathy and thrombotic microangiopathy

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of microangiopathy or thrombotic microangiopathy has been reported.

15.1.1.18 All Immune-mediated/autoimmune AESIs

Based on the MedDRA search strategy outlined in Appendix 6.4.1, three case reports of different immune-mediated/autoimmune AESIs were reported:

- One serious case report of myocarditis ([redacted]) that is also mentioned in Myocarditis/pericarditis section (See Section 16.3.1.1).
- One serious case report of gout ([redacted]) reported from an HCP via [redacted] referred to a 91-year-old [redacted] patient with no reported medical history who developed gout flare two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient's concomitant

medications included indapamide for renal hypertension. The patient's past vaccinations were not reported. The outcome was reported as not recovered. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded.

- One non-serious case report of vasculitis ([redacted]) that is also mentioned below in Single organ vasculitis section (See Section 15.1.1.21).

Based on medical review of the case reports, no safety concern nor pattern on immune-mediated/autoimmune AESIs has been identified.

15.1.1.19 Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multi-inflammatory Syndrome, Acute pancreatitis, Kawasaki disease, Sub-acute thyroiditis

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multi-inflammatory Syndrome, Acute pancreatitis, Kawasaki disease, Sub-acute thyroiditis has been reported.

15.1.1.20 Renal AESIs (including glomerulonephritis)

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of renal AESIs has been reported.

15.1.1.21 Single organ cutaneous vasculitis

Based on the MedDRA search strategy outlined in Appendix 6.4.1, one case report of single organ cutaneous vasculitis has been reported.

- One non-serious case [redacted] of vasculitis from an HCP via [redacted] involving an 86-year-old [redacted] with medical history of heparin-induced thrombocytopenia experienced vasculitis three days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Reportedly, the patient presented with purpuric rash over lower limbs (but platelet count was 110) which seemed to be possibly due to vasculitis or immune mediated. Patient was tested antineutrophil cytoplasmic antibody (ANCA) positive. Patient's past vaccinations were not reported. Information on corrective treatment not reported and outcome was reported as not recovered. Further information regarding patient's medical conditions at the time of vaccine, concurrent illness and previous vaccinations and tolerance are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. The case report was assessed as BCCD level 5 for Single Organ Cutaneous Vasculitis (14).

Based on the medical review of the case report, no safety concern was identified. In addition, no increased O/E ratio has been detected for single organ cutaneous vasculitis (Refer to Appendix 6.4.2).

15.1.1.22 Eye disorders (including optic neuritis)

Based on the MedDRA search strategy outlined in Appendix 6.4.1, a total of 16 case report of eye disorders were identified including nine serious cases and seven non-serious cases (no fatal outcome was reported). Of these, nine cases (56%) were reported as serious. Among these cases, four had another more likely explication (cases [redacted], [redacted], [redacted] and [redacted]), one had confounding factors for eye disorders onset (drug history including amitriptyline, which can cause eye disorders) and four did not provide medical and drug history, thus being not assessable for confounding factors.

- Case [redacted] was reported from an HCP via [redacted] and referred to a 93-year-old [redacted] with an unspecified ongoing food allergy experienced back pain, eye movement disorder, respiratory arrest, and erythema a couple of minutes after receiving COVID-19 vaccine (recombinant, adjuvanted). This case is presented under the Section 15.1.1.1 on Anaphylactic reactions.
- Case [redacted] reported from an HCP via [redacted] referred to a 90-year-old [redacted] with no reported medical history who developed retinal hemorrhage the same day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient's past vaccinations were not reported. The outcome was reported as not recovered. Based on the limited reported information regarding condition at the time of vaccination, concomitant disease or risk factor excluding other predisposing etiologies, the role of suspect cannot be assessed.
- Case [redacted] received from consumer via [redacted] and referred to an 81-years-old unknown gender patient experienced subconjunctival hemorrhage one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). At time of reporting, the outcome was recovering for the event. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded.
- Case [redacted] was reported by a consumer via [redacted] and involves 76-year-old [redacted] with no reported medical history was unable to see properly through left eye 15 minutes after receiving the vaccine. Patient's sight returned to normal within one hour of injection. Patient's past medications were not reported. No corrective treatment was reported, and the event outcome was recovered. Based on the limited information reported, the role of suspect cannot be assessed.
- Case [redacted] was received from consumer via [redacted] and referred to an 82-years-old [redacted] who experienced blurry vision, cold sweat, and sweating attack two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Three days after vaccination, the patient experienced lymphadenopathy. The first attack (blurry vision/loss of focus) lasted only about 10 secs and was followed by a cold sweat lasting five-10 minutes. Another attack (no vision impairment this time) of heavy sweating accompanied by slight nausea occurred two hours later and lasted for about 10-15 mins. The next day, lymph nodes were swollen and tender. The patient's past vaccination(s) included SARS-COV-2 vaccine on 09 April 2022 and Comirnaty on 21 December 2020. Concomitant medications included atorvastatin, ramipril, indapamide, and bisoprolol fumarate for hypertension. At time of reporting, the outcome was recovered for all the

events excepted swollen lymph nodes (recovering). Patient's hypertension could be confounding factor for event occurrence. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded.

- Case [redacted] reported from consumer via [redacted] and referred to a 76-year-old [redacted] with a medical history of renal neoplasm (removed) who experienced dry cough three days after, and lacrimation increased four days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient had ongoing hypertension, anemia, and sciatica on and off. Concomitant medications included amlodipine, losartan for hypertension; aspirin, paracetamol, phenylephrine hydrochloride for nasopharyngitis; ibuprofen for sciatica and folic acid supplements. Patient's past vaccinations were not reported. At time of reporting, the outcome was recovering. Further information on patient's allergy history, medical condition at the time of vaccination, previous vaccination and tolerance are needed to fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed.
- Case [redacted] was reported from a consumer via [redacted] and referred to an 82-year-old [redacted] with no reported medical history experienced dizziness, visual impairment, nausea, malaise, heart rate increased, wheezing same day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). The patient's past medical treatment included potassium and antihypertensives. Patient's past vaccinations were not reported. Outcome was reported as unknown. Further information regarding patient's medical history, allergy history, medical condition at the time of vaccination, previous vaccinations and tolerance are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.
- Case [redacted] reported from a consumer via [redacted] referred to a 77-year-old [redacted] with medical history of post-polio syndrome (poliomyelitis) developed dizziness, vertigo, blood pressure decreased, and vision blurred within an hour of vaccination with COVID-19 vaccine (recombinant, adjuvanted) vaccine. Concomitant medications included amitriptyline for myalgia; atorvastatin for TIA; clopidogrel and lansoprazole for gastroesophageal reflux disease. The patient's past vaccinations were not reported. Outcome was reported as not recovered for dizziness and unknown for rest of events. The patient's past four concomitant medication could be confounding factors. Further information on allergy history, patient's clinical condition at the time of vaccination, previous vaccinations and tolerance excluding alternative etiologies for the reported event are needed to fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed.
- Case [redacted] reported from consumer via [redacted] referred to a 77-year-old [redacted] with no reported medical history experienced tinnitus, ocular hypertension, parosmia and cluster headache one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient's past vaccinations were not reported. At time of reporting, the outcome was recovering for cluster headache and not recovered rest of the events. Further information on patient's past medical history, concomitant medication, concurrent conditions excluding alternative etiologies for the

reported event are needed to fully assess this case. Based on the limited reported information, the role of the individual suspect vaccine cannot be assessed.

- Seven non-serious cases of eye disorders were reported (44% of total). Median age of patients was 81.5 years. Four patients were female, one was male, and gender was not reported for two patients (Male/Female ratio: 0.25). Median time to eye disorders onset was 1.5 days (min: one day, max: four days). For three patients, time to symptom onset was not known. At time of reporting, three patients had recovered from the event, two were recovering, and two had not recovered. In one case of ocular itching there was a major confounding factor (pollen allergy). In four cases, medical and drug history was not provided. Two cases had a more likely explanation. In four cases, eye disorders were the only condition reported.

Based on medical review of cumulative data, no safety concern nor specific pattern has been identified.

15.1.1.23 Appendicitis

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of appendicitis has been reported.

15.1.1.24 Rhabdomyolysis

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of rhabdomyolysis has been reported.

15.1.2 Additional request from the EMA Committee for Medicinal Products for Human Use ASSESSMENT REPORT (10 November 2022):

15.1.2.1 Heavy Menstrual bleeding

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of heavy menstrual bleeding has been reported.

15.1.2.2 Swelling face/angioedema

In addition to Anaphylactic reactions specific analysis, MedDRA search strategy was conducted for SMQ: "*Angioedema*" (Narrow) and retrieved 17 cases including seven serious cases and 10 non-serious cases of swelling face/angioedema, none met BCCD level 1 or 2 for anaphylaxis. The serious cases are discussed below followed by a brief overview of the non-serious cases is presented:

- Case [redacted] was reported from a HCP via [redacted] involving a 79-year-old [redacted] with ongoing asthma and multiple allergies who developed swelling face and rash erythematous one hour after receiving COVID-19 vaccine (recombinant, adjuvanted). Patient's past medical history included anaphylactic reaction with Haemaccel. Patient's past vaccinations were not

reported. The patient took cetirizine on [redacted] own. The patient was hospitalized and recovered on the same day. Patient's ongoing asthma and multiple allergies with cats, dust, wool could be confounding factor for the events. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for anaphylaxis.

- Case [redacted] reported from an HCP via [redacted] involving a 90-year-old [redacted] who experienced lower lip angioedema two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient had urticaria rash to inside elbow. At time of reporting, the outcome was not recovered for the event. Insufficient information was provided for assessment. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded. This case was assessed as BCCD level 5 for anaphylaxis.
- Case [redacted] reported from [redacted] An 83-year-old patient of unknown gender experienced red neck, urticaria, rash (from neck down to breasts and on the back), ache and back pain one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Patient also experienced headache, fatigue, and asthenia six days after vaccination. At time of reporting, the patient was recovering from all the events excepted tiredness, feeling of total lack of energy, headache, ache (not recovered). Further information on allergy history, previous laboratory investigations; patient's medical history excluding alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.
- Case [redacted] reported from consumer via [redacted] A 76-year-old [redacted] with past medical history of myocardial infarction and hepatic steatosis, experienced allergy, hives two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Rash was like hives with large red lumps over most of body. On an unknown date, the patient developed lip swelling. Concomitant medications included generics bisoprolol for coronary heart disease. At time of reporting, the outcome was not resolved for the event allergy, and was unknown for the event lip swelling and hives. Further information on allergies, previous laboratory investigations to exclude alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.
- Case [redacted] reported from consumer via [redacted] A patient of an unknown age and gender experienced hives two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Concomitant medications included simvastatin for blood cholesterol increased; and nitrofurantoin and co-amoxyclav for urinary tract infection. At time of reporting, the outcome was not recovered. The patient's concomitant medications could be confounding factors. Further information on allergies, past medical history, patient's age, and gender to exclude alternative etiologies for the reported event are needed to fully assess this case. Based on the reported, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.

- Case [redacted] was reported from a consumer via [redacted]. A 78-year-old [redacted] experienced severe cutaneous AR, pruritus, urticaria and rash five days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Concomitant medications included amlodipine, atenolol, and losartan for hypertension; warfarin for atrial fibrillation; lansoprazole for Barrett's esophagus. Five days after the COVID booster injection, the patient experienced pruritus of entire upper arm which intensified rapidly over the next week to severe urticaria affecting both arms, backs of hands, left thigh, both feet and backs of upper left arm. Patient sought advice from local pharmacist on second day and obtained an antihistamine (Chlorpheniramine) which the patient has taken six times daily since then. Rash and itching persisted even after nine days. At time of reporting, the outcome was not recovered / not resolved. The patient's past three previous COVID vaccines and past medical history included immune thrombocytopenia. Further information on allergies, current condition precluding alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 5 for anaphylaxis.
- Case [redacted] reported from a consumer via [redacted] and referred to an unknown age [redacted] patient who developed pruritus, pharyngeal swelling, vaccination site bruising, vaccination site warmth and lymphadenopathy unknown duration after the vaccination. This case is already presented under Section 15.1.1.1 Anaphylactic reactions.

In addition, 10 non-serious cases (59% of total) were retrieved reporting facial swelling and angioedema during the period of this report. The median age of patients was 80 years (seven elderly/three adults). There were six males and four females reported in these cases (Male/Female ratio: 1.50). Median time to onset (TTO) of events was two days (min: the same day, max: four days). For four patients, time to symptom onset was not known. At time of reporting, the outcome was reported as not recovered/not resolved in five patients, recovering/resolving in three patients, recovered/resolved in one patient and unknown in remaining one case. In two cases there were confounding factors (such as co-suspect medications/ thyroid disorder) whereas remaining eight cases had insufficient information regarding the relevant case details such as onset latency, medical history, concomitant medications for a comprehensive evaluation. All these cases were assessed as BCCD level 5 for anaphylaxis.

Based medical review of cumulative data, a signal on Allergic including anaphylactic reactions has been opened on 17 May 2023 and has been validated on 14 June 2023 (Refer to Section 14).

15.1.2.3 Dizziness

Based on the MedDRA search strategy outlined in Appendix 6.4.1, 40 case reports of dizziness were reported cumulatively on the period: of these, 16 cases (40%) were reported as serious. Among these serious cases, one case had another more likely explanation, none had confounding factors for dizziness onset (drug history including anti-hypertensive, methotrexate, or endocrine treatment, which can cause dizziness; medical history including post-polio syndrome) and six did not provide medical and drug history, thus being not assessable for confounding factors. None of these cases reported a fatal outcome.

Of these 40 cases, dizziness as a standalone event was reported in only eight cases whereas the remaining cases had other associated AEs. Please refer to Appendix 6.4.3 for a detailed analysis.

Based on medical review of cumulative data, no safety concern nor specific pattern has been identified.

15.1.2.4 Paresthesia

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of paresthesia has been reported.

15.1.3 Specific requirement from the Medicines and Healthcare products Regulatory Agency dated 20 December 2022

15.1.3.1 Other peripheral and polyneuropathies

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of other peripheral and polyneuropathies has been reported.

15.1.3.2 Multiple sclerosis and other demyelinating disorders

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of multiple sclerosis and other demyelinating disorders has been reported.

15.1.3.3 Optic neuritis

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of optic neuritis was reported.

15.1.3.4 Myocardial infarction

Based on the MedDRA search strategy on coronary artery disease outlined in Appendix 6.4.1, one case of myocardial infarction ([redacted]) has been reported, it is presented above under coronary artery disease section (Refer to Section 15.1.1.11).

15.1.3.5 Encephalitis

Based on the MedDRA search strategy on meningoencephalitis outlined in Appendix 6.4.1, no case report of encephalitis has been reported.

15.1.3.6 Myasthenia gravis

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of myasthenia gravis has been reported.

15.1.3.7 Fibromyalgia

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of fibromyalgia has been reported.

15.1.3.8 Immune thrombocytopenic purpura/autoimmune thrombocytopenia

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case report of Immune thrombocytopenic purpura/autoimmune thrombocytopenia has been reported.

15.1.3.9 Post orthostatic tachycardia syndrome

Based on the MedDRA search strategy outlined in Appendix 6.4.1, no case of Post orthostatic tachycardia syndrome has been reported.

15.1.3.10 Seizures (including general convulsions and all other seizure presentations)

Based on the MedDRA search strategy outlined in Appendix 6.4.1, total of five cases reported seizures. All these cases were reported as serious with no fatal outcome being reported. Four of these cases were reported in the elderly population and the age group was unknown in remaining case. All these cases were assessed as per the BCCD for seizures as presented below (15):

- Case [redacted] reported from an HCP via [redacted] and referred to an 89-year-old [redacted] with no history of seizures who experienced seizures two days after receiving COVID-19 vaccine (recombinant, adjuvanted) vaccine and was hospitalized. Patient also experienced loss of consciousness of unknown duration after the vaccination. Patient's head CT was reported as normal. Patient had ongoing unspecified [redacted] and past vaccination included two COVID-19 mRNA vaccine BioNTech. The concomitant medications included carbomer for dry eye. The patient was treated with levetiracetam for generalized tonic-clonic seizure. The outcome was reported as not recovered for seizures and unknown for loss of consciousness. The patient's concurrent condition of dementia might be an expression of a common underlying confusion factor. Further information regarding patient's tolerance of previous vaccinations and other laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this case. Based on the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 2 for generalized convulsions.

- Case [redacted] reported from HCP via [redacted] and involving a 71-year-old [redacted] with ongoing immunodeficiency and Parkinson's disease who experienced respiratory arrest and seizures 10 minutes after vaccination with COVID-19 vaccine (recombinant, adjuvanted). Adrenaline was administered for query of anaphylaxis, patient was intubated and transferred to emergency and was discharged after 48 hours. Lorazepam and levetiracetam were given as corrective treatment for seizure. Patient's past vaccination(s) included COVID-19 Vaccine from AstraZeneca, Comirnaty and from Moderna. Further information on allergy history and previous laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD Level 4 for generalized convulsions.
- Case [redacted] reported from an HCP via [redacted] and involving a patient of unknown age and gender who experienced seizure the day of vaccination with COVID-19 vaccine (recombinant, adjuvanted). Further episode of hands twitching, and deterioration of consciousness were reported later. No history of chest pain, shortness of breath was reported. The patient was started on levetiracetam 250 mg and recovered. Further information on past medical history, concomitant medication excluding alternative etiologies for the reported event are needed to fully assess this case. Based upon the reported, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for generalized convulsions.
- Case [redacted] reported from consumer via [redacted] and involving an 81-year-old [redacted] who experienced unconscious and fits (non-epileptic) the day of vaccination with COVID-19 vaccine (recombinant, adjuvanted). It was not reported if the patient received a corrective treatment. The outcome was reported as recovered. Further information on allergy history, past medical history, concomitant medication, current condition excluding alternative etiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD level 4 for generalized convulsions.
- Case [redacted] reported from consumer via [redacted] and involving a 79-year-old [redacted] with no medical history who experienced seizure one day after vaccination with COVID-19 vaccine (recombinant, adjuvanted) and who was admitted to hospital for five days. Reportedly, patient lost consciousness completely, was unresponsive for around 10 mins, came round but took two-three hrs. All tests were clear for stroke/TIA/heart attack, bloods. Other laboratory investigations included blood test, CT, and ECG; results were not reported. At the time of reporting, the outcome was recovering for the event. The patient had no medical history. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded. This case was assessed as BCCD level 4 for generalized convulsions.

Based on medical review of the case reports, no safety concern has been identified. In addition, no increased O/E ratio has been detected for seizures. Refer to Appendix 6.4.2.

15.1.4 FATAL CASES

A total of thirteen case reports with fatal outcome have been received during the period (including two cases that reported sudden death). Please refer to Appendix 6.3 for detailed analyses.

All cases are reported in elderly patients, some of them reported medical history that could give alternative explanation for the fatal outcome. Fatal outcome is mostly reported shortly after the vaccination, same day to one day in six case reports, two to six days in four case reports, 10-20 days in two patients and it was unknown in remaining one case. All case reports provided insufficient information on the patients' medical history, concurrent conditions, previous laboratory investigations, and no autopsy results excluding alternative etiologies for the reported event to fully assess the cases. No new safety concern was identified from the medical review of fatal cases.

In addition, no increased O/E ratio has been detected for fatalities (primary or sensitivity analyses) (excluding the case reported in a 28-year-old male). Refer to Appendix 6.4.2.

15.1.5 VACCINE FAILURE

Based on the MedDRA search criteria as outlined in Appendix 6.4.1, a total eight case reports of COVID-19 infection were reported, of which two were reported as serious case reports and are detailed below ([redacted] and [redacted]). No fatal outcomes or severe cases were being reported.

- One serious case [redacted] reported from a consumer via [redacted] and involving a 77-year-old [redacted] with medical history of atrial fibrillation, hypertension, and hypercholesterolemia, who experienced SARS-coronavirus-1 (CoV-1) infection (SARS) 14 days after vaccination with COVID-19 vaccine (recombinant, adjuvanted) and SARS-CoV-2 infection (COVID-19: confirmed by test) 15 days after vaccination. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as serious with the criteria of Medically significant, but the intensity of severity was not reported. This case was assessed as BCCD level 5 for VAED [11] and is detailed under Section 15.1.1.8 as Respiratory AESI.
- One serious case [redacted] received from consumer via [redacted] and involving an 86-year-old patient (unknown gender) with a medical history included atrial fibrillation with pacemaker fitted for heart, experienced COVID-19, coughing, flu, flu like symptoms and mucus discharge six days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). At the time of reporting, the outcome was recovering for all the events. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded. This case was assessed as serious with the criteria of medically significant with

disability, but the intensity of severity was not reported for the events. This case was assessed as BCCD level 5 VAED.

- Remaining six non-serious cases ([redacted], [redacted], [redacted], [redacted], [redacted], [redacted]) were all consumer-reported and were assessed as BCCD level 5 for VAED. The TTO ranged from few hours after the vaccination to few days in most cases except for two cases which reported respectively a TTO of four weeks ([redacted]) and of more than three months ([redacted]). The available information in all these cases was insufficient for a conclusive evaluation and the role of individual suspect vaccine could not be ascertained.

Based on medical review of cumulative data, no safety concern was identified.

16 SIGNAL AND RISK EVALUATION

16.1 SUMMARY OF SAFETY CONCERNS

The definitions of important identified and potential risks and missing information in GVP Module V Revision 2 apply in the context of risk management planning. The EU RMP is judged based on risk-benefit impact and the need for further risk minimization activities and/or further evaluation as part of a PV plan. Good Pharmacovigilance Practices Module VII is applicable for the purpose of risk classification in the PBRER. The definitions in GVP Module V are not used for the purpose of risk reclassification in the PBRER. For this reason, the lists of safety concerns reported in the PBRER, and the EU RMP may differ. Refer to Appendix 6.1 for the list of safety concerns specific to the EU RMP.

A summary of the safety concerns for COVID-19 vaccine (recombinant, adjuvanted) identified at the beginning of the reporting interval is presented in Table 6.

Table 6 - Summary of safety concerns at the beginning of the reporting interval

Important identified risks	None
Important potential risks	Vaccine-Associated Enhanced Disease including Vaccine-Associated Enhanced Respiratory Disease Myocarditis and Pericarditis
Missing information	Use in pregnancy and while breast-feeding Use in immunocompromised subjects Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders Interactions with other vaccines Long-term safety

16.2 SIGNAL EVALUATION

For an overview of all ongoing and closed signals refer to Section 15. This sub-section summarizes the results of evaluations of all signals closed during the interval period. Important identified and potential risks are characterized in Section 16.4.

Full text evaluation is provided in Appendix 5.3.

16.2.1 Signals categorized as a potential or identified risk

There were no new signals that were categorized either as "potential" or "identified" risk for COVID-19 vaccine (recombinant, adjuvanted) during the reporting period. Therefore, Appendix 5.3 is not applicable.

16.2.2 Signals adjudicated as not a safety issue

There were no signals that were adjudicated as "not a safety issue" for COVID-19 vaccine (recombinant, adjuvanted) during the reporting period. Therefore, Appendix 5.3 is not applicable.

16.3 EVALUATION OF RISKS AND NEW INFORMATION

16.3.1 New information on important potential risks

Utilizing the surveillance activities defined in Section 15, the MAH has determined that there was no new relevant safety information that would have an impact on the understanding and characterization of

the previously recognized potential risks. However, details regarding the new relevant safety information are included below.

16.3.1.1 Myocarditis/Pericarditis

- Source of new information: Cases retrieved from the reference interval from GPV Safety database
- Background relevant to the evaluation: For more details on this risk, see also Section 16.4.
- Method(s) of evaluation including data sources, search criteria, and analytical approaches: The GPV Safety database was searched for the following MedDRA PTs: "*Autoimmune myocarditis*", "*Eosinophilic myocarditis*", "*Giant cell myocarditis*", "*Hypersensitivity myocarditis*", "*Immune-mediated myocarditis*", "*Lupus myocarditis*", "*Myocarditis*, "*Myocarditis post infection*", "*Radiation myocarditis*". In addition, O/E analyses are conducted based on the methodology and recommendations described by Mahaux et al. (16).
- Results: From the review of the GPV safety database, one case of myocarditis was retrieved for COVID-19 vaccine (recombinant, adjuvanted) during the reference period. In addition, no increased O/E ratio has been detected for myocarditis/pericarditis (Refer to Appendix 6.4.2 and Section 16.4).
- Discussion: One serious case report of myocarditis ([redacted]) was reported from consumer via [redacted] in an elderly patient of unknown gender two days after vaccination. An 81-year-old and unknown gender patient experienced positional dizziness and myocarditis two days after vaccination with COVID-19 vaccine (recombinant, adjuvanted). At time of reporting, the outcome was not recovered. Further information on patient underlying disease condition, past medical and drug history, concomitant medications, description of the reported symptoms, complementary investigations and results excluding alternative etiologies for the reported event are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. This case was assessed as BCCD (17) level 4 for myocarditis.
- Conclusion: Based on medical review of cumulative data supported by O/E analysis, no safety concern has been identified.

16.3.1.2 Vaccines-Associated Enhanced Disease including Vaccine-Associated Enhanced Respiratory Disease

There were no cases that reported VAED/VAERD (Refer to Section 15.1.5 for Vaccination Failure and Section 15.1.1.3 for COVID-19 AESIs).

16.3.2 New information on important identified risks

There are no important identified risks for COVID-19 vaccine (recombinant, adjuvanted). Therefore, this section is not applicable.

16.3.3 New information on other potential risks not categorized as important

Utilizing the surveillance activities defined in Section 15, the MAH has not identified any new safety information during the reporting interval that would have an impact on the understanding and characterization of the previously recognized potential risk(s) not categorized as important.

16.3.4 New information on other identified risks not categorized as important

There are no identified risks not categorized as important for COVID-19 vaccine (recombinant, adjuvanted), therefore this section is not applicable.

16.3.5 Update on missing information

Utilizing the surveillance activities defined in Section 15, the MAH has not identified any new safety information during the reporting interval that would have an impact on the understanding and characterization of missing information.

Use in pregnancy and while breast-feeding

No case reports of use in pregnancy were reported.

Two systematic review and meta-analysis were published in relation to pregnancy. One concerning pregnancy outcome following COVID-19 vaccination with BNT162b2, Moderna, ChAdOx1 and Janssen vaccines (8) and the second in relation to pregnancy outcome and risk of pregnancy related complications in COVID-19 vaccinated pregnant population that found no increased risks in pregnant women or neonates of vaccinated women compared to non-vaccinated, and no significant effects on maternal-fetal complications (9) (see Section 11).

Use in immunocompromised subjects

One literature article presented the use of a protein-based COVID-19 vaccine (SpikoGen) in patients undergoing kidney transplant receiving immunosuppressive therapy (7). The observed safety profile in this patient population was similar to the previously known safety profile of the vaccine and no SAEs reported (see Section 11).

Use in frail subjects with unstable health conditions and co-morbidities (eg, Chronic Obstructive Pulmonary Disease, diabetes, chronic neurological disease, cardiovascular disorders)

No significant information about the use with unstable health conditions and co-morbidities was identified.

Use in subjects with autoimmune or inflammatory disorders

No significant information about the use with autoimmune or inflammatory disorders was identified.

Interactions with other vaccines

No information about the use with other vaccines was identified.

Long-term safety

No new information is available from postmarketing sources since the vaccine has been only approximately five months on the market.

16.4 CHARACTERIZATION OF RISKS

The MAH routinely screens multiple data sources to identify new safety information on the list of safety concerns. Data sources routinely screened to identify relevant new safety information are listed in Section 15. Any data received during the reporting interval that may change the current understanding of the risks are reported in Section 16.3.

16.4.1 Important identified and potential risks

Table 7 - Important potential risk: Vaccine-Associated Enhanced Disease including Vaccine-Associated Enhanced Respiratory Disease

Potential risk	Vaccine-Associated Enhanced Disease including Vaccine-Associated Enhanced Respiratory Disease
Potential mechanism	This potential risk has not been described with any SARS-CoV-2 vaccine from any other late phase Clinical Studies nor in animal models with SARS-CoV-2 infection. Historically, cellular immunopathology associated to either Th2 or inflammatory T cell responses has been observed after viral challenge in some animal models administered SARS-CoV-1 (murine, ferret and non-human primate models) or MERS-CoV (mice model) early-stage vaccine candidates (18) (19). No similar observations were reported for any of the SARS-CoV-2 vaccines, in animal models or in humans. This potential risk has been included based on these animal data with these related beta coronaviruses. Historically, disease enhancement in vaccinated children following infection with natural virus has been observed with an inactivated respiratory syncytial virus vaccine

Potential risk	Vaccine-Associated Enhanced Disease including Vaccine-Associated Enhanced Respiratory Disease
	(20). Vaccine-associated disease enhancement in humans has been described for two investigational formalin inactivated vaccines; against Respiratory Syncytial Virus and measles, and one licensed vaccine, the tetravalent live attenuated dengue vaccine (21) (18). Two different mechanisms have been identified to trigger disease enhancement. • Antibody Dependent Enhancement is the result of vaccine-elicited antibodies that do not effectively neutralize the virus because of low affinity, wrong specificity, or inadequate concentration. Virus-Ab complexes can gain entry to cells via Fc-receptor-mediated uptake and lead to a more severe disease. • A second mechanism involves triggering of allergic inflammation, characterized by Th2 biased immune response over Th1 (18), (22) The molecular mechanism for this phenomenon, sometimes termed ADE, VAERD, or Immune Enhancement of viral infection, is also not fully understood. In the context of coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the Th cell response (23), (24), (25), (18).
Evidence source(s) and strength of evidence	A theoretical concern with coronavirus vaccines is VAED (18), (19), (22), (11). This is the potential (hypothetical) increased disease severity in naive vaccinees (11) upon exposure to wild-type virus (26). This disease enhancement of viral infection is also not fully understood. Mostly in the context of non-clinical beta coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the Th cell response (23), (24), (25). Animal models of SARS-CoV-2 infection have not shown evidence of VAED disease after immunization (27). Available data for other COVID-19 vaccines from different platforms do not indicate a risk of vaccine enhanced disease (27), (28), (29), (30). However, considering limited long-term safety data and in the absence of effectiveness data, the available evidence is not yet fully sufficient to rule out VAED including VAERD as a safety concern. Thus, it remains an important potential risk. No safety concern has been identified from postmarketing setting as of PBRER DLP.
Characterization of the risk	Vaccine-Associated Enhanced Disease including VAERD is a theoretical safety concern based on the currently available information for COVID-19 vaccines. Within the Clinical Studies for CoV2 preS dTM-AS03 (B.1.351), active surveillance (phone calls with the study participants) and passive surveillance (study participants instructed to contact the site if the experience COVID-19-like illness symptoms or have a positive COVID-19 test from any other source) for COVID-19-like illness was implemented. For the VAT00008 phase III stage 1 and stage 2 efficacy study, a harm monitoring with regards to symptomatic and severe COVID-19 cases was implemented.

Potential risk	Vaccine-Associated Enhanced Disease including Vaccine-Associated Enhanced Respiratory Disease
	These provisions within the Clinical Studies allow detection of any evidence of VAED including VAERD caused by CoV2 preS dTM-AS03 (B.1.351). No evidence of VAED including VAERD was found based on review of available data from clinical studies. • Of note, in D614 containing vaccines (Monovalent) formulation and specifically in VAT00008 stage 1, an increased number of Omicron symptomatic COVID-19 cases in the naive vaccine group compared to the naive placebo group was observed. When scrutinizing this observation, there was no increase in severe outcomes, hospitalization, or mortality in the naive vaccinees. The clinical presentation (intensity of symptoms as measured in three intensity grades, number of symptoms per omicron case and the duration of symptoms) was similar in the naive vaccine and placebo groups. No evidence of an increased viral load (naive vaccinees versus naive placebo recipients) was found. Most likely explanation for the observation is a lack of efficacy of the Monovalent D614 formulation against Omicron (lower level of neutralizing antibodies for this variant, additionally a long period between administration of the two doses of the study vaccine in VAT00008 stage 1 and the start of the Omicron wave (approximately five months after study start). In VAT00008 stage 2, no increased number of Omicron cases in the vaccine group were reported as compared to the placebo group. This was not seen neither in Booster formulations. In addition, VAED including VAERD might not apply to booster vaccine if referring to Brighton definition (VAED including VAERD risk would concern only SARS-CoV-2 seronegative individuals or individuals with unknown serostatus and no previous COVID-19 infection) (11).
Risk factors and risk groups	Individuals with lower neutralizing antibodies titers or those with waning immunity (22), (11), (31).
Preventability	This risk remains unpredictable and may depend on the immune response of the patient (18), (32). Potential risk may be decreased with an efficacious vaccine generating an adequate immune response is expected to mitigate this theoretical risk. Clinical study participants are informed of this theoretical risk during the informed consent process. Occurrence of COVID-19 cases and especially severe COVID-19 cases are monitored in the Clinical Studies and in postmarketing setting. This will allow early detection of any evidence of VAED including VAERD.
Impact on the benefit-risk balance of the product	Available data for mRNA COVID-19 vaccines Pfizer/BioNTech and Moderna (28), (29), for an adenovirus-vectored vaccine (Janssen) (30) as well as for a protein adjuvanted vaccine (33) do not indicate a risk of vaccine enhanced disease. As VAED including VAERD is a theoretical (hypothetical) safety concern there is no deleterious impact on the benefit-risk balance anticipated for this product.
Public health impact	No public health impact is identified currently.

ADE: Antibody Dependent Enhancement; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; Fc: Fragment Crystallizable; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; mRNA: Messenger Ribonucleic Acid; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Th: T-helper; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine-Associated Enhanced Respiratory Disease; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point; Ab: Antibody; AS03: Adjuvant System 03; SARS-CoV-1: Severe Acute Respiratory Syndrome Coronavirus-1.

Table 8 - Important potential risk: Myocarditis and Pericarditis

Potential risk	Myocarditis and Pericarditis
Potential mechanism	Myocarditis is a rare disease with an estimated annual incidence prior to COVID-19 vaccine pandemic of 16 per 100 000 persons in the general population. The true incidence may be higher, as signs and symptoms vary, and it therefore can be challenging to make the diagnosis. Viruses are the primary cause of myocarditis, including amongst others adeno- and enteroviruses. Severe acute respiratory syndrome coronavirus 2 has been associated with myocarditis as well, and multiple cases have been described since the outbreak of the COVID-19 pandemic (34). The majority of patients are young, healthy males (35). Based on systematic review, males are notably more likely to develop myocarditis and pericarditis following COVID-19 vaccination than females (85% versus 15%). The higher prevalence of this condition among males can be explained based on the role played by variations in hormone signaling. Testosterone has the ability to suppress anti-inflammatory immune cells while promoting a more aggressive Th 1 cell immunological response. Estrogen, on the other hand, inhibits pro-inflammatory T cells, resulting in a reduction in cell-mediated immune responses. However, further research is required to explore the exact phenomenon (36). Several mechanisms have been hypothesised to account for COVID-19 mRNA vaccine associated myocarditis including autoimmunity triggered by molecular mimicry (35), (36), immune-mediated pathology (37), pro-inflammatory cascade (38).
Evidence source(s) and strength of evidence	Myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines, mainly in males under the age of 40 years within 14 days after a second dose. However, cases have also been reported in older males, in females, and following other doses. There are limited data on the risk of myocarditis following third and subsequent booster doses. However, the risk after the third dose seems to be lower than following the second dose (39). The observed risk is highest in males 12 to 17 years of age. While some cases required intensive care support, available data from short-term follow-up suggest that symptoms resolve in most individuals with conservative management. Information is not yet available about potential long-term sequelae (40), (41). The risk of myocarditis is greater after SARS-CoV-2 infection than after COVID-19 vaccination and remains modest after sequential doses including a booster dose of Pfizer BioNTech mRNA vaccine. An increased risk of myocarditis is observed at 1-7 days (IRR 21.08, 95% CI 15.34, 28.96), 8-14 days (IRR 11.29, 95% CI 7.70, 16.57), 15-21 days (IRR 5.36, 95% CI 3.24, 8.89) and 21-28 days (IRR 3.08, 95% CI 1.65, 5.75) following a positive test (37). Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of NOVAVAX COVID-19 vaccine, which is manufactured using a protein/adjuvant platform and a different AS than the CoV2 preS dTM vaccine. Considering limited safety data, the available evidence is not yet fully sufficient to rule out myocarditis and pericarditis as a safety concern. Thus, it is added as an important potential risk. No safety concern has been identified from postmarketing setting as of PBRER DLP.

Potential risk	Myocarditis and Pericarditis
Characterization of the risk	No case of myocarditis and pericarditis has been observed in ongoing clinical studies with CoV2 preS dTM (B.1.351) vaccine. However, based on potential risk from other COVID-19 vaccines, participants of ongoing clinical studies with CoV2 preS dTM (B.1.351) vaccine are advised to seek immediate medical attention and notify study site staff if symptoms compatible with myocarditis and pericarditis occur following vaccination. Participants with events of myocarditis and pericarditis will be discontinued from further vaccination and followed for subsequent visits as per the protocol for safety, immunogenicity, and efficacy endpoints. The most important published cohort studies to date demonstrate that myocarditis is a very rare side effect after COVID-19 mRNA vaccination, with an incidence of approximately 1-4 cases per 100 000 vaccinated persons (34). The risk of myocarditis is greater after SARS-CoV-2 infection than after COVID-19 vaccination and remains modest after sequential doses including a booster dose of Pfizer BioNTech mRNA vaccine. An increased risk of myocarditis is observed at 1-7 days (IRR 21.08, 95% CI 15.34, 28.96), 8-14 days (IRR 11.29, 95% CI 7.70, 16.57), 15-21 days (IRR 5.36, 95% CI 3.24, 8.89) and 21-28 days (IRR 3.08, 95% CI 1.65, 5.75) following a positive test (37). The observed risk is highest in males 12 to 17 years of age. While some cases required intensive care support, available data from short-term follow-up suggest that symptoms resolve in most individuals with conservative management. Information is not yet available about potential long-term sequelae (40), (41). Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of the NOVAVAX COVID-19 vaccine, which is manufactured using a protein/adjuvant platform and a different AS than the CoV2 preS dTM vaccine (42). In the placebo-controlled safety dataset of NOVAVAX COVID-19 vaccine (participants 12 years of age and older) with 30 058 subjects receiving active vaccine and 19 892 subjects receiving placebo, two cases of myocarditis were reported following exposure to NOVAVAX COVID-19 vaccine and one case was reported following exposure to placebo. In the post-crossover phase of studies, three cases of myocarditis were reported. The Sponsor assessed the causality as not related for the five cases occurring after exposure to COVID-19 vaccine with all cases attributed to alternative etiologies, including reasonable infectious and/or non-infectious causes. There were no cases of myocarditis and pericarditis assessed as related by the Sponsor.
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk (35), (36).
Preventability	As the mechanism is not fully understood, preventative measures cannot be defined at this time.
Impact on the benefit-risk balance of the product	Balanced with the risk of death and illness seen with COVID-19 itself, the vaccine has a favorable risk-benefit balance.
Public health impact	Myocarditis and pericarditis are events which may be serious or non-serious and are generally mild but may be potentially life-threatening. Most vaccine-associated myocarditis events have been mild and self-limiting (37). Balanced with the risk of death and illness

Potential risk	Myocarditis and Pericarditis
	(including myocarditis) seen with COVID-19 itself, the impact on the risk-benefit balance of the vaccine is considered as minimal (34).

CI: Confidence Interval; CoV-2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; IRR: Incidence Rate Ratio; mRNA: Messenger Ribonucleic Acid; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Th: T-helper; AS: Adjuvant System; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point.

16.4.2 Missing information

Table 9 - Missing information: Use in pregnancy and while breast-feeding

Missing Information	Use in pregnancy and while breast-feeding
Evidence source(s) and strength of evidence	Pregnant or breast-feeding women are excluded from Clinical Studies (phase II/III and phase III). A pregnancy test is systematically being performed in these women before each study vaccine administration and the vaccine or placebo dose is not injected in case of a positive pregnancy test. Use of CoV2 preS dTM-AS03 (B.1.351) in pregnancy and while breast-feeding is considered as missing information until sufficient evidence is available. Safety data with other vaccine manufactured with the same platform and safety data with other AS03 adjuvanted vaccines administered during pregnancy have shown no evidence of an increased risk of adverse outcomes in the mother or child (43). A DART study has been conducted in rabbits. Results do not indicate any findings that could raise suspicion of a safety concern in human. There were no vaccine-related effects on mating performance or fertility in female rabbits, or on embryo-fetal (including teratogenicity) and early post-natal development of the offspring. From ongoing Clinical Studies (VAT00001, VAT00002, and VAT00008) and due to exclusion criteria, only limited number of pregnancy exposures were reported. No safety concern was identified. No pregnancy exposure has been reported from postmarketing setting as of PBRER DLP.
Anticipated risk/consequence of the missing information	It is not yet known whether CoV2 preS dTM-AS03 (B.1.351) could cause any fetal harm when administered to a pregnant woman or if any detrimental effects could occur when administered in breast-feeding women. Use in pregnancy and while breast-feeding is a missing information for COVID-19 vaccine (recombinant, adjuvanted) and will be studied in VAT00012 (C-VIPER, sponsor Pregistry, LLC) with the objective to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with a COVID-19 vaccine. In general, it is recognized that the anticipated risk and consequence of vaccination in pregnant and breast-feeding women is low and only considered for some live attenuated vaccines (44). Preliminary findings in pregnant persons who received mRNA COVID-19 vaccines did not show obvious safety signals. However, more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes (45), (46).

Missing Information	Use in pregnancy and while breast-feeding

COVID-19: Coronavirus Disease-2019; DART: Developmental and Reproductive Toxicity; mRNA: Messenger Ribonucleic Acid; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point: C-VIPER: COVID-19 Vaccines International Pregnancy Exposure Registry; CoV-2 preS dTM: CoV-2 prefusion Spike delta TM; AS03: Adjuvant System 03.

Table 10 - Missing information: Use in immunocompromised subjects

Missing Information	Use in immunocompromised subjects
Evidence source(s) and strength of evidence	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in immunocompromised patients is not yet known as these populations have been excluded from some phase II/III Clinical Studies. This population is included in phase III Clinical Study allowing the participation of individuals with a range of medical conditions including immunocompromised state. In the phase II/III study (VAT00002) and in the phase III study (VAT00008), participants with a controlled HIV infection could be included. Use in immune-compromised subjects for COVID-19 vaccine (recombinant, adjuvanted) is being studied or will be studied in VAT00027 Booster effects Booster effects with autoimmune treatments in participants with poor response to initial COVID-19 Vaccine (sponsored by the NIAID), VAT00028 Safety and Immunogenicity of a dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine in kidney transplant recipients with a persistently low SARS-CoV-2 Ab titer (sponsored by the NIAID) and VAT00007 Post-Authorization, observational study to assess the safety of COVID-19 vaccine (recombinant, adjuvanted) using routinely collected secondary data in Europe through VAC4EU. Not initiated. No safety concern has been identified as of PBRER DLP.
Anticipated risk/consequence of the missing information	The immunogenicity of the vaccine may be reduced in patients with immunocompromised conditions. This is not a safety risk per se outside of a potential decrease of efficacy in case of severe impairment of immune function.

CoV-2 preS dTM: CoV-2 prefusion Spike delta TM; HIV: Human Immunodeficiency Virus: NIAID: National Institute of Allergy and Infectious Diseases; COVID-19: Coronavirus Disease-2019; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-2; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point; Ab: Antibody; AS03: Adjuvant System 03.

Table 11 - Missing information: Use in frail subjects with unstable health conditions and co morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

Missing Information	Use in frail subjects with unstable health conditions and co morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
Evidence source(s) and strength of evidence	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in frail patients is not yet known even though elderly population and individuals with co-morbidities (31) or high-risk conditions were represented in Clinical Studies: Individuals with co-morbidities (31) or high risk conditions are considered to be associated with an increased risk of severe COVID-19 (cancer, chronic kidney disease, COPD, obesity (BMI of 30 or higher), heart conditions such as heart failure, coronary artery disease or cardiomyopathies, sickle cell disease, thalassemia, type 1 or type 2 diabetes mellitus, moderate-to-severe asthma, cerebrovascular disease, cystic fibrosis, hypertension/high

Missing Information	Use in frail subjects with unstable health conditions and co morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
	blood pressure, neurologic conditions, hepatic disease, pulmonary fibrosis and smoking). In addition, individuals with immunocompromised state from solid organ transplant, immunocompromised state from other causes (blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of immunosuppressors) are planned to be enrolled in phase III Clinical Study (VAT00008). From VAT00008 and VAT00002, no safety concern for the study vaccine was identified when comparing the safety profile in participants with high-risk medical condition (as defined in the study protocol) with participants without high-risk medical condition group. Individuals with unstable acute or chronic illness are part of the exclusion criteria in the Clinical Studies. Use in frail subjects with unstable health conditions and co-morbidities (eg, COPD, diabetes, chronic neurological disease, CVD) will be studied in VAT00007 Post-Authorization, observational study to assess the safety of COVID-19 vaccine (recombinant, adjuvanted) using routinely collected secondary data in Europe through VAC4EU. No safety concern has been identified as of PBRER DLP including in elderly population.
Anticipated risk/consequence of the missing information	The vaccine has been studied in participants with stable chronic diseases (eg, patients with hepatic impairment and patients with cardiovascular impairment), however it has not been studied in frail participants with severe co-morbidities that may compromise immune function due to the condition or treatment of the condition. This is not a safety risk per se outside of a potential decrease of efficacy in case of severe impairment of immune function.

COPD: Chronic Obstructive Pulmonary Disease; CoV-2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; HIV: Human Immunodeficiency Virus; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point; CVD: Cardiovascular Disorders; BMI: Body Mass Index; AS03: Adjuvant System 03.

Table 12 - Missing information: Use in subjects with autoimmune or inflammatory disorders

Missing Information	Use in subjects with autoimmune or inflammatory disorders
Evidence source(s) and strength of evidence	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in subjects with autoimmune or inflammatory disorders is not fully known even if individuals with autoimmune or immune-inflammatory diseases could be included in Clinical Studies: Participants with stable clinical conditions under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) could be enrolled in phase II/III (VAT00002) and phase III (VAT00008) at the discretion of the investigator. Individual with auto-immune or immune-inflammatory disease are part of the target population. Use in subjects with autoimmune or inflammatory disorders for COVID-19 vaccine (recombinant, adjuvanted) will be studied in VAT00007 Post-Authorization, observational study to assess the safety of COVID-19 vaccine (recombinant, adjuvanted) using routinely collected secondary data in Europe through VAC4EU. No safety concern has been identified as of PBRER DLP.
Anticipated risk/consequence of the missing information	Individuals with autoimmune or inflammatory disorders may experience a different outcome than achieved in healthy individuals administered vaccines.

Missing Information	Use in subjects with autoimmune or inflammatory disorders

CoV-2 preS dTM: CoV-2 prefusion Spike delta TM; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point; AS03: Adjuvant System 03.

Table 13 - Missing information: Interactions with other vaccines

Missing Information	Interactions with other vaccines
Evidence source(s) and strength of evidence	Receipt of any vaccine in the 30 days preceding the first study vaccination, except for influenza vaccination, is part of the exclusion criteria in the Clinical Studies. From phase II/III and phase III Clinical Studies (VAT00002 and VAT00008), influenza vaccination could be received at any time in relation to study intervention and influenza vaccination is part of concomitant medications that are collected. Vaccination with CoV2 preS dTM-AS03 (B.1.351) together or in close temporal connection with other vaccines is likely to occur later in a postmarketing setting. No safety concern has been identified as of PBRER DLP.
Anticipated risk/consequence of the missing information	From phase II/III and phase III Clinical Studies (VAT00002 and VAT00008), influenza vaccination could be received at any time in relation to study intervention and influenza vaccination is part of concomitant medications that are collected.

CoV-2 preS dTM: CoV-2 prefusion Spike delta TM; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point; AS03: Adjuvant System 03.

Table 14 - Missing information: Long-term safety

Missing Information	Long-term safety
Evidence source(s) and strength of evidence	Despite extensive experience with the manufacturing platform and AS03 adjuvant, there is limited long-term safety data available with CoV2 preS dTM-AS03 (B.1.351). One year safety follow-up has been completed for participants who received CoV2 preS dTM AS03 (B.1.351) as a booster in the VAT00002 Cohort 2 main arm. Analysis of this long-term follow-up did not identify any safety concern. Vaccines targeting SARS-CoV-2 are a new class of vaccines, with first vaccines authorized in 2020 and 2021. No safety concern has been identified as of PBRER DLP.
Anticipated risk/consequence of the missing information	The long-term safety data of CoV2 preS dTM-AS03 (B.1.351) is limited, however safety follow-up is ongoing in the phase II/III (with supportive data from phase I/II) and phase III study Clinical Studies. Based on currently available information, there is no evidence of any potential risks with late onset after vaccination.

CoV2 preS dTM: CoV-2 prefusion Spike delta TM; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-2; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point; AS03: Adjuvant System 03.

16.5 EFFECTIVENESS OF RISK MINIMIZATION

No effectiveness evaluation is established for COVID-19 vaccine (recombinant, adjuvanted) since there are no RMM beyond routine.

17 BENEFIT EVALUATION

17.1 IMPORTANT BASELINE EFFICACY AND EFFECTIVENESS INFORMATION

The approved indications for COVID-19 vaccine (recombinant, adjuvanted), is presented in Section 2.

The mechanism of action consists of the induction of immune responses against the antigens contained in the vaccine. The S glycoprotein of SARS-CoV-2 associated with AS03 adjuvant stimulates neutralizing and other functional S-specific antibodies, as well as cellular immune responses directed against the S antigen, which may contribute to protection against COVID-19 (47).

Epidemiology:

Epidemiological data collected since the beginning of the pandemic have shown that individuals of any age can acquire infection of SARS-CoV-2, however, there is an uneven distribution of infections per defined age group. According to data published by the WHO, people aged 30 to 39 years have the highest amount of confirmed and probable cases, followed by 20 to 29, 40 to 49 and 50 to 59 years age groups respectively. This age-based distribution, however, does not correlate across gender-based distribution, with infections occurring at similar rates between males and females (47).

Globally, till 09 May 2023, there have been 766 029 927 confirmed cases of COVID-19, including 6 928 795 deaths, reported to WHO (48). Although all regions have reported substantive numbers of cases, the greatest cumulative numbers of confirmed cases to date have been in Europe (>276 million cases), the Western Pacific (>203 million cases) and the Americas (>178 million cases) (48).

Key risk factors for severe COVID-19 disease include but not limited to CVD, diabetes, chronic respiratory disease, COPD, hypertension, malignancies, obesity, chronic kidney disease, cerebrovascular disease and stroke, with higher risk of severity and mortality ranging 1.14 to 7.1 times higher in these risk groups (49). Older age (particularly ≥65 years) is a recognized risk factor for more severe COVID-19 disease and death, with populations aged 65 to 74 years at five times higher risk of hospitalization and 90 times higher risk of death than population aged 18 to 29 years old in the US (50).

New and emerging variants are playing an important role in local and global epidemiology.

Omicron has established itself as the dominant SARS-CoV-2 lineage globally. In early 2022, a large number of Omicron-descendent sub-lineages emerged (BA.1, BA.2, BA.3, BA.4, BA.5), with ECDC categorizing these sub-lineages separately to better distinguish their relative impacts to the

epidemiological situation. Amongst these sub-lineages, BA.2, BA.4 and BA.5 consistently circulated in the EU/EEA until late 2022. The current epidemiological situation is hallmarked by a highly diverse landscape of co-circulating BA.2 and BA.5 descendent variants, which have different properties to their parental lineages and require individual assessment (51).

Efficacy data/Immunogenicity data:

Efficacy of CoV2 preS dTM-AS03 (B.1.351 strain) vaccine has been inferred by immuno-bridging of immune responses to an authorized COVID-19 vaccine, for which VE has been established.

The clinical immunogenicity of CoV2 preS dTM-AS03 (B.1.351 strain) vaccine given as a booster injection is being evaluated in two clinical studies: VAT00013 (Study 1) in COVID-19 mRNA vaccine-primed participants and VAT00002 Cohort 2, Beta arm (Study 2) that included participants primed with various types of COVID-19 vaccines.

Immunogenicity results from Study VAT00013

This is a randomized, single-blinded multicenter investigator-initiated clinical study conducted in France, which evaluated the immune response induced by a booster dose of either CoV2 preS dTM-AS03 (B.1.351 strain) vaccine, or Pfizer COVID-19 mRNA vaccine or Sanofi investigational booster vaccine (protein-based adjuvanted COVID-19 vaccine, D614, 5 µg) in individuals previously vaccinated with two doses of Pfizer COVID-19 mRNA vaccine. The per-protocol analysis population included 217 participants 18 years of age and older primed with two doses of COVID-19 mRNA vaccine three to seven months prior to receiving CoV2 preS dTM-AS03 (B.1.351 strain) vaccine (N = 67), COVID-19 mRNA vaccine (N = 76) and Sanofi investigational booster D614 vaccine (N = 74). The mean age was 40.6 years (range 18 to 73 years). The mean duration between the second dose of the primary series and the booster dose was 174 days and was comparable across groups.

Among this per-protocol population, samples from prior to vaccination and 28 days after booster of 114 participants (54 from CoV2 preS dTM-AS03 [B.1.351 strain] vaccine and 60 from Pfizer COVID-19 mRNA vaccine and 48 from Sanofi investigational booster D614 vaccine) were tested by Pseudovirus Neutralization Assay. The Geometric Mean Titers (GMT) of neutralizing antibodies 28 days after CoV2 preS dTM-AS03 (B.1.351 strain) vaccine or Pfizer COVID-19 mRNA vaccine booster in COVID-19 mRNA vaccine-primed participants were compared.

Superiority of GMT against Omicron BA.1 was demonstrated for CoV2 preS dTM-AS03 (B.1.351 strain) vaccine group in comparison with Pfizer COVID-19 mRNA vaccine group.

Non-inferiority of seroresponse rate against Omicron BA.1 and D614G strains for CoV2 preS dTM-AS03 (B.1.351 strain) vaccine compared to Pfizer COVID-19 mRNA vaccine was demonstrated with seroresponse rate defined as a four-fold or greater rise in serum neutralization titer 28 days post-booster dose relative to pre-booster dose.

Across all variants tested, the levels of neutralizing Ab titers 28 days post-booster dose observed in CoV2 preS dTM-AS03 (B.1.351 strain) vaccine group were higher than in Pfizer COVID-19 mRNA vaccine group, with the GMT ratio between 1.43 and 2.53 (52), (53), (54).

Immunogenicity results from Study VAT00002 (Cohort 2, Beta arm)

CoV2 preS dTM-AS03 (B.1.351 strain) vaccine given as a booster is being evaluated in an ongoing multicenter phase 3 clinical study in participants 18 years of age and older in Australia, France, Honduras, Spain, UK, and United States. Per-protocol analysis population included 615 participants who received CoV2 preS dTM-AS03 (B.1.351 strain) vaccine 4 to 10 months after receiving primary vaccination with 2 doses of Pfizer COVID-19 mRNA vaccine (nucleoside modified) (n = 325) or Moderna COVID-19 mRNA Vaccine (nucleoside modified) (n = 93), AstraZeneca COVID-19 Vaccine (ChAdOx1-S [recombinant]) (n = 94), Sanofi investigational primary vaccine (protein-based adjuvanted COVID-19 vaccine, D614, 5 to 15 µg of antigen dose) (n = 72), or with one dose of Janssen COVID-19 vaccine (Ad26.COV2-S [recombinant]) (n = 31).

In per-protocol analysis population receiving CoV2 preS dTM-AS03 (B.1.351 strain) vaccine booster, the mean age of participants was 46.0 years (range 18 to 93 years); 435 (70.7%) were 18 to 55 years of age 180 (29.3%) were 56 years of age and older, 78 (12.7%) were 65 years of age and older. Among them, 47.0% were male, 53.0% were female, 67.6% were White, 11.7% were Black or African American, 3.4% American Indian or Alaska Native, and 2.9% were Asian.

Immunogenicity was assessed by measuring neutralizing Ab titers (ID50) against a pseudo virus expressing the SARS-CoV-2 S protein from a USA_WA1/2020 isolate with the D614G mutation and B.1.351 variant using a SARS-CoV-2 Pseudo virus Neutralization Assay.

A booster response to CoV2 preS dTM-AS03 (B.1.351 strain) vaccine was demonstrated regardless of the vaccine used for primary vaccination with the Geometric Mean Titers Ratio (GMTR [GMTR], fold increase) 14 days post-booster relative to pre-booster against B.1.351 strain ranging from 38.5 to 180, and from 14.5 to 148 for D614G strain (55).

17.2 NEWLY IDENTIFIED INFORMATION ON EFFICACY AND EFFECTIVENESS

No new relevant efficacy and/or effectiveness findings in approved indications were identified during the reporting interval.

Vaccine failure is discussed in detail in Section 15.1.5.

Based on the review of the data received for Vaccine failure/VAED, a total of eight cases (two serious and six non-serious) that reported COVID-19 after vaccination. All were consumer reported cases with a BCCD level 5 assessment. These cases did not have sufficient data for a comprehensive evaluation; However, based on the limited information available, no cases reported VAED/VAERD (see also

Section 16.3.1.2) and no cases reported lack of efficacy. Based on the medical review of cumulative safety data, no information on changes in the therapeutic environment could be identified that could impact efficacy and/or effectiveness or lead to vaccine failure.

17.3 CHARACTERIZATION OF BENEFITS

No new relevant efficacy findings in approved indications were identified during the reporting interval, and the efficacy profile of COVID-19 vaccine (recombinant, adjuvanted), is unchanged.

The data available from the studies performed for this vaccine remain the reference information on the robustness of the immune response elicited by the vaccine. No new immunogenicity data that would put these conclusions in question have been made available during the reporting period.

18 INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

18.1 BENEFIT-RISK CONTEXT - MEDICAL NEED AND IMPORTANT ALTERNATIVES

The novel coronavirus, SARS-CoV-2, was first detected in Wuhan city, Hubei province, China, in December 2019 caused an initial outbreak of severe respiratory illness in the local population. This outbreak rapidly escalated until on 20 January 2020 the WHO first declared the outbreak as a Public Health Emergency of International Concern until 11 March 2020, when the status was changed, and a pandemic was declared.

Globally, till 09 May 2023, there have been 766 029 927 confirmed cases of COVID-19, including 6 928 795 deaths, reported to WHO (48). Although all regions have reported substantive numbers of cases, the greatest cumulative numbers of confirmed cases to date have been in Europe (>276 million cases), the Western Pacific (>203 million cases) and the Americas (>178 million cases) (48).

Geographical variations have been observed in the burden of disease at the country level, mostly due to differences in timing and stringency of non-pharmaceutical interventions implemented. Differences of practices in testing/reporting of cases and healthcare management for severe cases may have had an impact on the number of reported cases globally (56).

Coronavirus disease-2019 symptoms may vary from mild to severe, with approximately 33% to 55% of known cases to be asymptomatic (varies by variant) (57), (58). The risk of transmission from an asymptomatic appears to be less than that from an individual with symptoms. Nevertheless, asymptomatic, or pre-symptomatic individuals are less likely to isolate themselves from other people, and the extent to which transmission from such individuals contributes to the pandemic is uncertain. Centers for Disease Control and Prevention (CDC) modelling study estimated that 59% of transmission

could be attributed to individuals without symptoms: 35% from pre-symptomatic individuals, and 24% from those who remained asymptomatic (59).

Symptoms appear on average four to five days after infection, though the usual range is between two to 14 days. Preliminary data shows the incubation period for Omicron to be 2.9 to 3.2 days (60). Most reported symptoms include fever, fatigue, muscle ache, cough, and shortness of breath, which can progress to pneumonia. Mild acute disease tends to resolve within approximately two weeks, whereas severe cases can last 36 weeks. Longer term sequalae in some cases, otherwise known as "long-COVID" or "post-acute COVID syndrome", in which symptoms such as headaches, fatigue, myocarditis, and dyspnea can last for weeks or even months after the acute phase (61), (53). Older adults and people who have severe underlying medical conditions (eg, heart/lung disease, diabetes, or conditions affecting the immune system, such as immunosuppression) have been observed to be at higher risk for developing more serious complications from COVID-19 (62).

New and emerging variants are playing an important role in local and global epidemiology. As of September 2022, the only variant of concern (VOC) defined by WHO and ECDC is Omicron, with ECDC specifying four sub-lineages of Omicron; BA.1, BA.2, BA.4 and BA.5 (53), (52). The Omicron variant has a substantial growth advantage, due in part to a combination of immune escape and intrinsic high transmissibility and has rapidly become the predominant strain worldwide (63).

Multiple antivirals and therapeutic treatments that target severe COVID-19 have been authorized. The antiviral treatment, remdesivir, has been approved by both the FDA and European Commission (EC). The EC has also authorized other treatments: anakinra, regdanvimab, tocilizumab, baricitinib, casirivimab/imdevimab, tixagevimab/cilgavimab, sotrovimab and ritonavir. Most therapeutic options, however, are still in early stages of research (64).

Following the introduction of the first SARS-CoV-2 vaccines in December 2020, vaccination is reducing burden of disease. The WHO has issued emergency use listing (EUL) for multiple COVID-19 vaccines while in Europe, the EC has granted MA to different types of COVID-19 vaccines such mRNA vaccines, viral vector vaccines, recombinant protein vaccine and inactivated, adjuvanted vaccine from different manufacturers. However, waning of vaccine-induced protection is a growing concern with many studies reporting a decrease in vaccine effectiveness after six months (63), (65), (66). Antibody levels are demonstrated to decrease over time after the second dose of the COVID-19 vaccination, therefore, protection against the Beta variant is expected to provide good coverage against other circulating variants.

COVID-19 vaccine (recombinant, adjuvanted) which is indicated as a booster for active immunisation to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine demonstrates positive results with a good safety profile (67), (68), (3).

18.2 BENEFIT-RISK ANALYSIS EVALUATION

18.2.1 Methodology

The current benefit-risk evaluation, pivotal studies, and all postmarketing data. New information that has become available during the reporting interval, including newly identified risks described in Section 16.4.2 and newly identified efficacy data described in Section 17.2, has been assessed to determine whether it affects the previously established benefit-risk profile of COVID-19 vaccine (recombinant, adjuvanted) in the approved indication(s).

A structured systematic approach was applied to COVID-19 vaccine (recombinant, adjuvanted) as a booster for active immunization to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine based on literature articles including published epidemiological studies, labeling documents, sponsored and unsponsored clinical trials and postmarketing data in order to evaluate the benefit-risk profile of COVID-19 vaccine (recombinant, adjuvanted). Results presented on benefits and risks sections were retrieved from the most up-to-date information regarding the clinical efficacy/effectiveness and safety of COVID-19 vaccine (recombinant, adjuvanted).

The data presentations are based on a descriptive framework developed for benefit-risk decision-making in drug development and post-approval settings. The approach is meant to facilitate identification of critical issues regarding benefits and risks and improve transparency of the assumptions used by the MAH to evaluate the benefit-risk profile.

The steps from the framework were used to define the main problem to be addressed, ie, the context in which a decision had to be made, to determine key benefits and key risk outcomes to construct a value tree, and to identify the data sources.

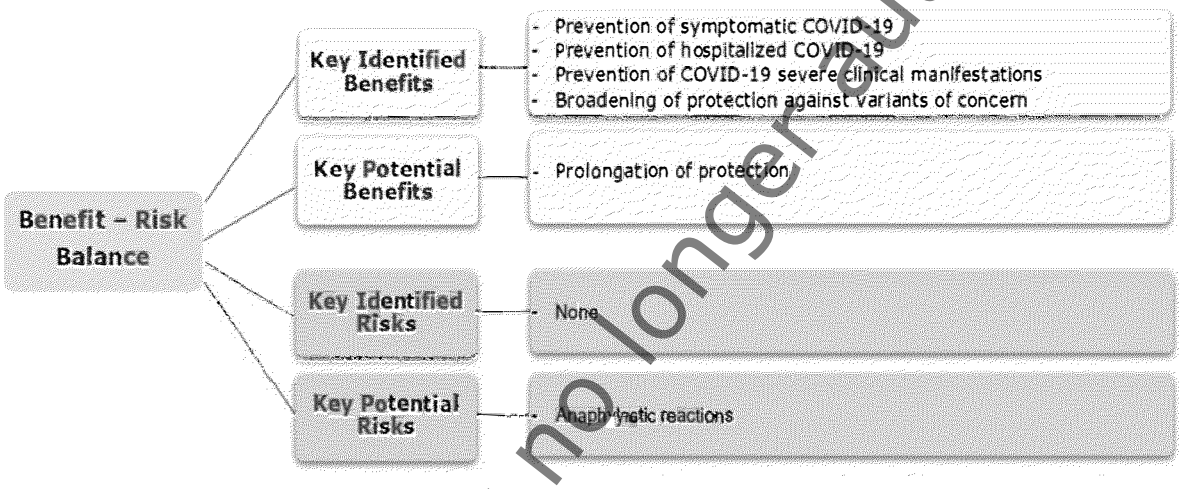
The descriptive framework emphasizes relevant metrics to enable a comprehensive discussion of benefit-risk while providing complete transparency into the origin and format of the source data. Key benefits are defined by favorable effects that contribute importantly to the overall benefit-risk evaluation and that are important for the patient (clinically important, relevant, intense, or durable). The key risks are defined by unfavorable effects that contribute importantly to the overall benefit-risk evaluation, and not necessarily include all important risks described in Section 16. The selection was based on medical judgment (clinically important risks because of their severity, frequency, duration, toxicity, irreversibility, or inability to be predicted or prevented). They may also include those that are considered for risk minimization activity beyond labeling. Key benefits and key risks of COVID-19 vaccine (recombinant, adjuvanted) were organized in a hierarchic manner to construct a “Value Tree”.

The data presentation consists of a descriptive benefit risk framework table and a “Value Tree” for the approved indications developed for benefit-risk decision-making in drug development and post-approval settings.

18.2.2 Benefit-risk evaluation

A Value Tree providing a concise, visual representation of the key benefits and key risks considered in the overall benefit-risk assessment is presented below (see Figure 1).

Figure 1 - Value Tree for Benefit-Risk Assessment as a booster in active immunization to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine



Of note, Anaphylactic reactions are being re-assessed part of the signal that has been opened on Allergic including anaphylactic reactions; signal has been validated on 14 June 2023 and on 26 June 2023, signal of allergic including anaphylactic reactions was confirmed as an identified risk. The weighted cumulative evidence was considered sufficient to support a causal association between COVID-19 vaccine (recombinant, adjuvanted) and allergic including anaphylactic reactions that should be reflected in the RSI (refer to Section 14 for further information).

The Benefit-Risk Assessment tables (Table 15, Table 16, Table 17, and Table 18) presented below provides an overall summary and assessment of the key decision factors that were considered for the benefit-risk assessment of COVID-19 vaccine (recombinant, adjuvanted) as a booster in active immunization to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine.

Table 15 - Benefit-Risk Assessment table - Analysis of condition

Evidence and Uncertainties	Conclusions and Reasons
The 2019-20 coronavirus pandemic is an ongoing pandemic of COVID-19, caused by SARS-CoV-2, protein-enveloped RNA virus. Globally, till 09 May 2023, there have been 766 029 927 confirmed cases of COVID-19, including 6 928 795 deaths, reported to WHO. (48). A fifth coronavirus wave declared mid-Nov 2021 followed by the emergence of a new variant (Omicron) that was first reported to WHO from South Africa (B.1.1.529). There have been subsequent peaks (both cases and hospitalizations) through to mid- May 2023 (69) due to emerging Omicron sub-lineages with higher transmissibility and immune escape (13) (17). As of 09 May 2023, seven sub-lineages of Omicron have been classified as VOCs by the CDC; B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5) (70). As of today, it is estimated that 95% or more of the population in EU and US are non-naive for COVID-19 (vaccinated or with previous infection) (71). On the 05 May 2023, WHO chief declares end to COVID-19 as a global health emergency. The head of the UN WHO has declared "with great hope" an end to COVID-19 as a public health emergency, stressing that it does mean the disease is no longer a global threat (72). **Evidence** Most common clinical presentation includes fever, cough, anosmia and shortness of breath. Severity varies from mild symptoms to severe conditions that can lead to a fatal outcome and long-term sequelae. The mean SARS-CoV-2 incubation period is estimated to be six days (73), and infectiousness is estimated to last for one-9.5 days (depending on the variant) (74). 25% of asymptomatic SARS-CoV-2 infections (75). Antibody persistence demonstrated up to eight months after COVID-19 infection and up to six months after the second mRNA vaccine dose (76). A study from Italy (77) showed that > 98% of infected subjects had antibodies up to nine months later. **New emerging variants:** Emergence of new variants (Alpha, Beta, Gamma, Delta, Omicron variants including XBB lineages) with changes in transmissibility, severity, and risk of reinfection: highly transmissible VOCs emerged and are spreading globally.	COVID-19 is a life threatening and disabling disease with true unmet need for patients. Vaccine access varying by regions/countries. Coverage rates for at least one dose of vaccine vary from >90% in UAE, Portugal, and Brunei, to < 3% in Burundi, Haiti, and DRC (82). There is an unmet medical need for individuals to have access to a COVID-19 vaccine that confers protection against circulating variant strains. No authorized COVID-19 vaccine has yet demonstrated efficacy against Omicron variant. Benefit-risk assessment is driven by efficacy in non-naive population. Emergence of new variants with changes in transmissibility, severity, increasing the risk of reinfection and possible SARS-CoV-2 potential of becoming endemic and seasonal triggers the need for booster vaccination(s).

Evidence and Uncertainties	Conclusions and Reasons
Some variants have become dominant strains within one-four months (78) (79) (80). **Uncertainties** There is some data indicating COVID-19 will become an endemic, with opportunistic infections and seasonal pic of burden. New variants are emerging at an unprecedented rate and are generating waves of infection out of season. Influential factors to determine seasonality are still unknown (81).	

COVID-19: Coronavirus Disease-2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; WHO: World Health Organization; UAE: United Arab Emirates; DRC: Democratic Republic of the Congo; CDC: Centers for Disease Control and Prevention; VOC: Variant of Concern; US: United States; EU: European Union; UN: United Nation; mRNA: Messenger Ribonucleic Acid.

Table 16 - Benefit-Risk Assessment table - Current Treatment Options

Evidence and Uncertainties	Conclusions and Reasons
As of 09 May 2023, 380 vaccine candidates have been reported around the world (348 in clinical development and 32 in use) (83). Only three COVID-19 vaccines approved or authorized for emergency use by US FDA: Comirnaty (Pfizer-BioNTech COVID-19 Vaccine), Spikevax (Moderna COVID-19 Vaccine), and NOVAVAX COVID-19 Vaccine. In addition to the above vaccines, COVID-19 Vaccine Valneva and VAXZEVRIA® (COVID-19 Vaccine AstraZeneca) are approved for use in Europe by the EMA. Non-vaccine pre-exposure prophylaxis: currently only one non-vaccine pre-exposure prophylaxis is approved by FDA under EUA. EVUSHELD® (tixagevimab co-packaged with cilgavimab) is for emergency use in those who are not currently infected with SARS-CoV-2 and have not had a known recent exposure, have moderate to severe immune compromise or vaccination with any available vaccine is not recommended. Post-exposure treatments: currently only one drug treatment for use in COVID-19 [Remdesivir] approved by FDA and 14 treatments authorised for emergency use (EUA-FDA) (84). During this public health emergency [Ritonavir-boosted nirmatrelvir (PAXLOVID®), molnupiravir, and certain anti-SARS-CoV-2 mAbs received EUA from the FDA for the treatment of COVID-19] CTAP (85). Recommendations for treating non-hospitalized patients (listed in order of preference (86).	Widespread vaccine deployment in many countries reduced burden of disease and burden on healthcare system (88). COVID-19 vaccine (Recombinant, Adjuvanted) has the potential of playing a key role as universal booster regardless of the COVID-19 vaccine use as primary vaccination in countries with high vaccine coverage and high seropositivity rates worldwide, as well as in countries with low vaccine coverage because of more simple handling conditions (no ultracold storage requirements). Current standard of care for patients acquiring serious COVID-19 is mainly supportive.

Evidence and Uncertainties	Conclusions and Reasons
Antivirals for COVID-19 should be used by people at risk for developing severe COVID-19 if recently tested positive for coronavirus, had mild to moderate symptoms for no more than five days and are not yet hospitalized. Ritonavir-boosted nirmatrelvir (PAXLOVID) (inhibiting an enzyme needed to process some viral proteins into their final, functional form) (in adults and pediatric patients 12 + and > 40kg). Remdesivir with/without Dexamethasone or in combination with Baricitinib (Cytokine inhibitor) with an FDA authorization (in adults and pediatric patients 12+ and > 40kg). For use when neither of the preferred therapies (above) are available or ttherapeutic management of hospitalized individuals with COVID-19. Recommended use of each therapeutic is based on the medical status of the patient, in patients who do not require supplemental oxygen but are at an increased risk of developing severe disease. Bebtelovimab: Monoclonal Ab for treatment that retains activity against Omicron (in adults and pediatric patients aged 12+ and > 40kg). Molnupiravir introducing mutations into the viral genome during viral replication. Full course of treatment with molnupiravir could suppress the virus in less than 36 h (adults only) (87). Other therapies such as tocilizumab (Ab against Interleukin 6) used in patients (aged two years and older) receiving corticosteroid medicines and requiring supplemental oxygen or mechanical ventilation. Baricitinib (Olumiant) is authorised for emergency use as treatment in hospitalised pediatric and adult patients (aged two and above) requiring supplemental oxygen, mechanical ventilation, or ECMO. Coronavirus disease-2019 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorised in patients with immunosuppressive disease or receiving immunosuppressive treatment (84). Currently approved drugs by the FDA: **ACTEMRA®** (Tocilizumab) is approved for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or IMV, or ECMO. **VEKLURY®** (Remdesivir) is approved for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least three kilograms) who are: hospitalized, or not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death. **PAXLOVID** (nirmatrelvir and ritonavir) is approved for the treatment of mild-to-moderate COVID-19 in adults who are at	

Evidence and Uncertainties	Conclusions and Reasons
high risk for progression to severe COVID-19, including hospitalization or death. Paxlovid is not approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19. In the case of COVID-19 infection, the immune system can become hyperactive which may result in worsening of disease. Immune modulators can help suppress this hyperinflammation. **KINERET®** (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma suPAR. **OLUMIANT®** (baricitinib) is approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or IMV, or ECMO. It is authorized for the treatment of COVID-19 in pediatric patients two to less than 18 years of age requiring supplemental oxygen, IMV, or ECMO. **ACTEMRA** (tocilizumab) is authorized for the treatment of COVID-19 in hospitalized pediatric patients two to less than 18 years of age who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or IMV, or ECMO. **GOHIBIC®** (vilobelimab) is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving IMV or ECMO. Monoclonal antibodies.	

US: United States; FDA: Food and Drug Administration; EUA: Emergency Use Authorization; mAb; CTAP: Coronavirus Treatment Acceleration Program; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; ECMO: Extracorporeal Membrane Oxygenation; suPAR: Soluble Urokinase Plasminogen Activator Receptor; IMV: Invasive Mechanical Ventilation; COVID-19: Coronavirus Disease-2019; EMA: European Medicines Agency; Ab: Antibody.

Table 17 - Benefit-Risk Assessment table - Benefit

Evidence and Uncertainties	Conclusions and Reasons
Individual level key identified benefits • Prevention of symptomatic COVID-19 • Prevention of hospitalized COVID-19 • Prevention of COVID-19 severe clinical manifestations • Broadening of protection against VOCs **B.1.351 Containing vaccines (Monovalent and Bivalent)** **Clinical evidence: Booster** **VAT00002 Phase III Supplemental Cohort 2** • **Monovalent:** The primary objectives were evaluated in Pfizer mRNA-primed younger adult (18-55 year) age	Robust immunogenicity results in booster vaccination (VAT00002 supplemental cohorts) in adults 18 years and older (all age groups).

Evidence and Uncertainties	Conclusions and Reasons
stratum. The first Co-primary immunogenicity endpoint was non-inferiority of the post-booster B.1.351 titer to the prototype strain vaccine post-primary D614G titer. The GMT ratio was 1.96, and the lower bound of the 98.3% CI of 1.96, exceeding the threshold for success of 0.67, thus the objective was met. The second Co-primary endpoint was superiority of the post-booster to pre-booster titer. The GMT ratio was 35.4, with a lower bound of 26.7, exceeding the threshold for success of two, thus the objective was met. • **Bivalent:** The primary objectives were evaluated in Pfizer mRNA-primed younger adult (18-55 year) age stratum. The post-booster B.1.351 and D614G titers were non-inferior to the prototype strain vaccine post-primary D614G titer (GMT ratio 1.39 and 2.34, respectively). The lower bound of the 98.3% CI for each comparison exceeded the threshold for success of 0.67, thus non-inferiority was concluded. The second Co-primary endpoint was superiority of the post-booster B.1.351 and D614G titer to corresponding pre-booster titer. The GMT ratio for B.1.351 was 34.2 and for D614G was 14.4, each with a lower CI bound exceeding the threshold for success of two, thus the objective was met. • **VAT013 Investigator-Sponsored Study:** study was conducted to assess the immunogenicity and safety of three booster vaccine options: CoV2 preS dTM-AS03 (D614), CoV2 preS dTM-AS03 (B.1.351), and Pfizer/BioNTech. The results showed showed the higher immune response elicited by CoV2 preS dTM-AS03 (B.1.351) vaccine than that elicited by the CoV2 preS dTM-AS03 (D614) booster vaccine or the approved Pfizer/BioNTech booster vaccine across a range of variants, including D614G, Beta, Delta, Omicron BA.1, Omicron BA.4/5, Omicron BQ.1.1, and XBB.1.	
Clinical Evidence: Primary series Study undertaken in real-word setting of high SARS-CoV-2 seropositivity in participants. Global study to span all VOCs including Alpha, Gamma, Mu, Delta, and Omicron: Circulation of variants during the conduct of the study predominantly Delta and Omicron (others in order of predominance: non-VOCs, Alpha, Gamma, Mu, and Lambda). **Bivalent B.1.351/D614** **VAT00008 phase III study (stage 2):** Vaccine efficacy for the prevention of symptomatic COVID-19 disease was 64.7% (95% CI: 46.6; 77.2) meeting the primary efficacy objective (ie, to obtain a point estimate of VE > 50%, as calculated by the	Significant VE demonstrated to prevent symptomatic COVID-19, including COVID-19 caused by Omicron.

Evidence and Uncertainties	Conclusions and Reasons
IRR, with the lower bound of the 95% CI > 30%; modified Full Analysis Set post-dose two: all participants regardless of serostatus at baseline). Vaccine efficacy 72.5% (95% CI: 49.5; 86.0) for prevention of Omicron symptomatic COVID-19 disease (all participants regardless of serostatus at baseline). Vaccine efficacy in the younger adult population (18-59 years): 67.3% (49.7;79.3) for prevention of symptomatic COVID-19 (87 cases in Placebo group vs. 29 in Vaccine group). Limited number of participants and cases in the older adult population precludes a definitive conclusion in this age group. Vaccine efficacy in the older adults (60+ years): -47.7% (-1668.0; 83.1) (two cases in Placebo group vs. three in Vaccine group). **Uncertainty:** Duration of the follow-up time (median follow-up of approximately three months) precludes evaluation of the durability of the efficacy. **Non-clinical evidence:** Growing body of evidence indicating that induction of Ab, particularly neutralizing Ab to the S protein of SARS-CoV-2 may be associated with protection against COVID-19 (89) (90) (91). **Emerging variants: Need for broadened protection** Using monovalent Beta vaccine as a booster (third dose) in primed NHPs (mRNA-primed study CoV2-07_NHP and subunit-primed study CoV2-08_NHP), neutralizing Ab titers were detected at high levels in all animals against Alpha, Beta, Gamma, Delta, Mu, and Omicron BA.1. **Duration of immunity:** Moderate Ab decline during the first two to three months after primary immunization with the Beta monovalent and D614/Beta bivalent followed by stabilization in NHPs up to six months, high and robust S-specific memory B cells were detected in all animals (CoV2-06_NHP). In primed NHPs, the booster effect on D614 and variant neutralizing Ab titers was prolonged up to six months (in both mRNA- and subunit-primed macaques), and S-memory B cells responses were increased especially in the NHP with low responses after the primary vaccination (mRNA-primed study CoV2-07_NHP and subunit-primed study CoV2-08_NHP). **Uncertainties** • Correlate of Protection: Immune response that allows prediction of the degree of protection against infection or disease: work ongoing, no correlate established yet.	Non-clinical data supports S protein of SARS-CoV-2 as appropriate target.

Evidence and Uncertainties	Conclusions and Reasons
• Efficacy against infection and disease in at-risk groups (eg, immunocompromised subjects) and special population (eg, pregnant women). • Efficacy against new emergent variants. • Duration of vaccination effect (including Ab persistence of adjuvanted vaccine) ie, long term effectiveness (duration of follow-up in VAT00008 stage 1 at primary analysis: In average five months; VAT00008 stage 2: Approximately three months). • Effectiveness among individuals primed with another COVID-19 vaccine in general. Effectiveness in individuals of 60 years age and older due to limited number of participants in this age group	Immunocompromised participants allowed to be included into the phase III Clinical Study VAT00008. Pregnancy exposures in VAT00002 and VAT00008 to be followed and assessed. Postmarketing data to be assessed through pregnancy registry (VAT00012). Exploratory analysis of VAT00008 will be efficacy by SARS-CoV-2 variant. Duration of protection will be monitored in post-authorization effectiveness study(ies).

COVID-19: Coronavirus Disease-2019; mRNA: mRNA: Messenger Ribonucleic Acid; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; GMT: Geometric Mean Titers; CI: Confidence Interval; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; VOC: Variant of Concern; VE: Vaccine Efficacy; IRR: Incidence Rate Ratio; Ab: Antibody; NHP: Non-Human Primates; S: Spike.

Table 18 - Benefit-Risk Assessment table - Risk and Risk Management

Evidence and Uncertainties	Conclusions and Reasons
Key potential risk for COVID-19 Vaccine (recombinant, adjuvanted) not considered as Important Potential Risk:	
• Anaphylaxis: Class-effect for all vaccines (even not adjuvanted). Anaphylaxis is monitored as an AESI within the Clinical Studies (primary series and booster vaccinations). No safety concern identified with regards to anaphylaxis based on review of available Pivotal Clinical Studies data (B.1.351 or bivalent B.1.351/D614) including VAT00008 Open label extension.	No safety concern identified with regards to anaphylaxis based on review of available study data (primary series and booster vaccinations). Based on medical review of postmarketing case reports, a signal has been opened on Allergic including anaphylaxis reactions after PBRER DLP on 17 May 2023 (refer to Section 14 for additional information).
Based on medical review of postmarketing safety data, a signal on Allergic including anaphylactic reactions has been opened on 17 May 2023 (after PBRER DLP). Refer to Section 14 for additional information on this signal.	No safety concern on myocarditis/pericarditis identified as of PBRER DLP.
Key potential risk for COVID-19 Vaccine (recombinant, adjuvanted) considered as Important Potential Risk:	No safety concern on VAED including VAERD identified as of PBRER DLP.
• Myocarditis/Pericarditis: No safety concern identified during the clinical development and from postmarketing setting.	
• VAED including VAERD Class-effect for all COVID-19 vaccines. No safety concern identified from postmarketing setting.	No validated safety signal identified from pivotal Clinical Studies neither in the overall population nor in subgroups (older adults, individuals with high-risk medical conditions).
Uncertainty:	

Evidence and Uncertainties	Conclusions and Reasons
No increased risk of thrombosis identified in the placebo-controlled VAT00008 study. • Limited safety database to assess very rare events (eg, anaphylaxis) including those identified for other COVID-19 vaccines in postmarketing setting (other platforms). **AS03 adjuvanted vaccines Evidence** • Strongly characterized adjuvant (pandemic Influenza vaccines) • Clinical data: acceptable safety profile - Consistent with Literature review. • Higher reactogenicity compared to placebo with increase in general symptoms after AS03-adjuvanted flu vaccines compared to non-adjuvanted/placebo (92) (43). **Baculovirus platform Evidence** • Strongly characterized protein manufacturing platform (Baculovirus) 23 million doses of recombinant flu vaccines distributed in adults up to June 2022 with no safety concern. Other COVID-19 vaccine Evidence: Other COVID-19 AS03 adjuvanted vaccines demonstrated an acceptable safety profile (93), (94). **Uncertainties** • Effects with any new antigen/adjuvant association: potential Immune Mediated Diseases including risk of Narcolepsy derived from the use of Adjuvanted PANDEMRIX® vaccine (AH1N1 pdm09 - AS03 GSK) • Limited safety data in pregnant and breast-feeding women, in immunocompromised subjects, in frail subjects with unstable health conditions and co-morbidities (eg, COPD, diabetes, chronic neurological disease, CVD), in subjects with autoimmune or inflammatory disorders. • Long term safety	Extensive AS03-adjuvanted flu vaccines and Baculovirus platform experiences in clinical and postmarketing setting with no safety concern. Similar profile of SAE, AESI, MAAE, unsolicited AE between the vaccine and placebo groups observed in both participants with and without a high-risk medical condition. From postmarketing safety data up to PBRER DLP 09 May 2023 and with more than 1.6 million doses administered: • A signal on Allergic including anaphylactic reactions has been opened on 17 May 2023 (after PBRER DLP). • No other safety concern has been identified (and in particular concerning VAED including VAERD, increased risk of thrombosis, myocarditis, pericarditis, thrombosis with thrombocytopenia, narcolepsy or other AESIs) Extensive exposure of elderly patients in the UK with more than 99% of doses administered in 60 years of age and older without any safety concern by age group (below 70 years old and above 70 years old). Risk management includes early reinforced postmarketing surveillance. • Safety in immunocompromised patients is part of phase II/III Supplemental Cohorts (VAT00002) and III (VAT00008) and of VAT00027 booster effects with autoimmune treatments in participants with poor response to initial COVID-19 Vaccine (sponsored by the NIAID). Enrollment in this trial is ongoing. • VAT00028 Safety and Immunogenicity of a dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine in kidney transplant recipients with a persistently low SARS-CoV-2 Ab titer (sponsored by the NIAID). Enrollment in this trial is ongoing. • Long term safety including AESIs will be monitored during pivotal Clinical Studies follow-up and in PASS. Proposed Risk Management Strategy considered adequate to document the risk management system set-up for the COVID-19 vaccine (recombinant, adjuvanted) and to ensure a safe use of the vaccine in real-life setting.

Evidence and Uncertainties	Conclusions and Reasons

COVID-19: Coronavirus Disease-2019; AESI: Adverse Event of Special Interest; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine-Associated Enhanced Respiratory Disease; UK: United Kingdom; AS03: Adjuvant System 03; SAE: Serious Adverse Event; MAAE: Medically Attended Adverse Event; AE: Adverse Event; NIAID: National Institute of Allergy and Infectious Diseases; GSK: GlaxoSmithKline; COPD: Chronic Obstructive Pulmonary Disease; PASS: Post-Authorization Safety Studies; CVD: Cardiovascular Disorders.

Benefit-Risk conclusion

Available data as of today for COVID-19 vaccine (recombinant, adjuvanted) including immunogenicity and safety data in individuals 18 years of age and older from VAT00002 supplemental cohorts 2 (monovalent B.1.351 and bivalent B.1.351/D614 booster), efficacy and safety data from VAT00008 Stage 2 with bivalent primary vaccination in individuals 18 through 59 years (limited sample size and number of COVID-19 cases did not allow to demonstrate efficacy in older age group) supported by VAT00013 clinical study where the level of neutralizing Ab titers were high and greater than the approved Pfizer/BioNTech booster vaccine containing D614 strain and by VAT00008 booster extension (monovalent B.1.351 formulation) allow to conclude a positive Benefit/Risk of a COVID-19 vaccine (recombinant, adjuvanted) in individuals 18 years of age and older. The anticipated benefits that may be afforded outweigh the potential risks associated with COVID-19 vaccine (adjuvanted, recombinant) as booster given in adults from 18 years and older.

Postmarketing safety data up to PBRER DLP with more than 1.6 million doses administered in postmarketing setting are supportive of this conclusion.

19 CONCLUSIONS AND ACTIONS

Based on the evaluation of the cumulative safety data and the benefit-risk analysis during the reporting interval, the benefit-risk balance of COVID-19 vaccine (recombinant, adjuvanted) in the approved indication remains positive in the currently approved conditions of use.

20 REFERENCES

1. Goepfert PA, Fu B, Chabanon AL, Bonaparte MI, Davis MG, Essink BJ, et al. Safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations in healthy adults: interim results of a randomised, placebo-controlled, phase 1-2, dose-ranging study. Lancet Infect Dis. 2021 Sep;21(9):1257-70.

2. De Rosa SC, Cohen KW, Bonaparte M, Fu B, Garg S, Gerard C, et al. Whole-blood cytokine secretion assay as a high-throughput alternative for assessing the cell-mediated immunity profile after two doses of an adjuvanted SARS-CoV-2 recombinant protein vaccine candidate. Clin Transl Immunology. 2022 Jan 11;11(1):e1360.

3. Sridhar S, Joaquin A, Bonaparte MI, Bueso A, Chabanon AL, Chen A, et al. Safety and immunogenicity of an AS03-adjuvanted SARS-CoV-2 recombinant protein vaccine (CoV2 preS dTM) in healthy adults: interim findings from a phase 2, randomised, dose-finding, multicentre study. Lancet Infect Dis. 2022 May 1;22(5):636-48.

4. de Bruyn G, Wang J, Purvis A, Sanchez Ruiz M, Adhikarla H, Alvi S, et al. Safety and immunogenicity of a variant-adapted SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant as a booster in adults primed with authorized vaccines. medRxiv. 2022:2022-12.

5. Dayan GH, Rouphael N, Walsh SR, Chen A, Grunenberg N, Allen M, et al. VAT00008 study team. Efficacy of a bivalent (D614 + B.1.351) SARS-CoV-2 Protein Vaccine. medRxiv [Preprint]. 2023 Jan 13:2022.12.05.22282933.

6. Macias Saint-Gerons D, Ibarz MT, Castro JL, Fores-Martos J, Tabares-Seisdedos R. Myopericarditis Associated with the Novavax COVID-19 Vaccine (NVX-CoV2373): A Retrospective Analysis of Individual Case Safety Reports from VigiBase. Drugs Real World Outcomes. 2023 Jun;10(2):263-70.

7. Nafar M, Mostafaloo N, Firouzan A, Poorrezagholi F, Samadian F, Dalili N, et al. Immunogenicity and Safety of SpikoGen, an Adjuvanted Recombinant SARS-CoV-2 Spike Protein, as a Heterologous Third Booster Dose in Kidney Transplant Patients: A Single-arm Clinical Trial. Clin. Ther. 2022 Dec 1;44(12):1566-76.

8. Cole C, Tsakiroglou M, Waitt C. Communication is crucial: Lessons from COVID-19 vaccination and pregnancy. Br J Clin Pharmacol. 2023 Feb;89(2):582-93.

9. Tormen M, Taliento C, Salvioli S, Piccolotti I, Scutiero G, Cappadona R, et al. Effectiveness and safety of COVID-19 vaccine in pregnant women: A systematic review with meta-analysis. BJOG. 2023 Mar;130(4):348-57.

10. Gold MS, Amarasinghe A, Greenhawt M, Kelso JM, Kochhar S, Yu-Hor Thong B, et al. Anaphylaxis: Revision of the Brighton collaboration case definition. Vaccine [Internet]. 2022 Nov 24 [cited 2022 Dec 26];41:2605-14. Available from: https://reader.elsevier.com/reader/sd/pii/S0264410X22014256?token=E42DFE8E03152BFB02375CECC49B7EDDF9B73A795FB68ED61DE0C34732C64A461840912FEAB195B2C5A8FA8BA40D7F1D&originRegion=eu-west-1&originCreation=20221226125620

11. Munoz FM, Cramer JP, Dekker CL, Dudley MZ, Graham BS, Gurwith M, et al. Brighton Collaboration Vaccine-associated Enhanced Disease Working Group. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2021 May 21;39(22):3053-66.

12. Gollamudi J, Sartain SE, Navaei AH, Aneja S, Kaur Dhawan P, Tran D, et al. Thrombosis and thromboembolism: Brighton collaboration case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2022 Oct;40(44):6431-44.

13. World Health Organization (WHO). Update on Omicron [Internet]. [Updated 2021 Nov 28; cited 2023 Jun 15]. Available from https://www.who.int/news/item/28-11-2021-update-on-omicron

14. Zanoni G, Girolomoni G, Bonetto C, Trotta F, Hausermann P, Opri R, et al. Single organ cutaneous vasculitis: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016 Dec 12;34(51):6561-71.

15. Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004 Jan;22(5-6):557-62.

16. Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiol Drug Saf. 2016 Feb;25(2):215-22.

17. European Centre for Disease Prevention and Control. Assessment of the further spread and potential impact of the SARS-CoV-2 Omicron variant of concern in the EU/EEA, 19th update - [Internet] [Updated 2022 Jan 27; cited 2023 Jun 15]. ECDC: Available from https://www.ecdc.europa.eu/en/publications-data/covid-19-omicron-risk-assessment-further-emergence-and-potential-impact

18. Lambert PH, Ambrosino DM, Andersen SR, Baric RS, Black SB, Chen RT, et al. Consensus summary report for CEPI/BC March 12-13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. Vaccine. 2020 Jun 26;38(31):4783-91.

19. Haynes BF, Corey L, Fernandes P, Gilbert PB, Hotez PJ, Rao S, et al. Prospects for a safe COVID-19 vaccine. Sci Transl Med. 2020 Nov 4;12(568):eabe0948.

20. Openshaw PJ, Culley FJ, Olszewska W. Immunopathogenesis of vaccine-enhanced RSV disease. Vaccine. 2001 Oct 15;20 Suppl 1:S27-31.

21. Safety Platform for Emergency Vaccines (SPEAC). Priority List of COVID-19 Adverse events of special interest: Quarterly update December 2020 Version 1.2 [Internet]. [updated 2020 Dec 23; Cited 2023 Jun 15]. Available from: https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020-review_final.pdf

22. Graham BS. Rapid COVID-19 vaccine development. Science. 2020;368(6494):945-6.

23. Tseng CT, Sbrana E, Iwata-Yoshikawa N, Newman PC, Garron T, Atmar RL, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. PLoS One. 2012;7(4):e35421.

24. Yasui F, Kai C, Kitabatake M, Inoue S, Yoneda M, Yokochi S, et al. Prior immunization with severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) nucleocapsid protein causes severe pneumonia in mice infected with SARS-CoV. J Immunol. 2008;181(9):6337-48.

25. Czub M, Weingartl H, Czub S, He R, Cao J. Evaluation of modified vaccinia virus Ankara based recombinant SARS vaccine in ferrets. Vaccine. 2005;23(17-18):2273-9.

26. Smatti MK, Al Thani AA, Yassine HM. Viral-Induced Enhanced Disease Illness. Front Microbiol. 2018; 9:2991.

27. Francica JR, Flynn BJ, Foulds KE, Noe AT, Werner AP, Moore IN, et al. Protective antibodies elicited by SARS-CoV-2 spike protein vaccination are boosted in the lung after challenge in nonhuman primates. Sci Transl Med. 2021 Aug 18;13(607):eabi4547.

28. Vaccines and Related Biological Products Advisory Committee Meeting, FDA Briefing Document Pfizer-BioNTech COVID-19 Vaccine, 2020 Dec 10, Cited date 2023 Jun 15, Available from https://www.fda.gov/media/144245/download

29. Vaccines and Related Biological Products Advisory Committee Meeting, FDA Briefing Document Moderna COVID-19 Vaccine, 2020 Dec 17, Cited 2023 Jun 15, Available from https://www.fda.gov/media/144434/download

30. Vaccines and Related Biological Products Advisory Committee Meeting, FDA Briefing Document, Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19, 2021 Feb 26, Cited 2023 Jun 15, Available from https://www.fda.gov/media/146217/download

31. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals [Internet]. [Updated date 2023

Feb 09; cited date 2023 Jun 15]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

32. Vogel AB, Kanevsky I, Che Y, Swanson KA, Muik A, Vormehr M, et al. A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates. BioRxiv. 2020 Sep 8:2020-09.

33. European Medicines Agency. Novavax Inc. EU Risk Management Plan, Nuvaxovid (COVID-19 Vaccine (Recombinant, Adjuvanted) [Internet]. [cited 2022 Feb]. Available from: https://www.ema.europa.eu/documents/rmp-summary/nuvaxovid-epar-risk-management-plan_en.pdf

34. Klamer TA, Linschoten M, Asselbergs FW. The benefit of vaccination against COVID-19 outweighs the potential risk of myocarditis and pericarditis. Neth Heart J. 2022 Apr;30(4):190-7.

35. Pillay J, Gaudet L, Wingert A, Bialy L, Mackie AS, Paterson DI, et al. Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following covid-19 vaccination: living evidence syntheses and review. BMJ. 2022 Jul 13;378:e069445.

36. Fatima M, Ahmad Cheema H, Ahmed Khan MH, Shahid H, Saad Ali M, Hassan U, et al. Development of myocarditis and pericarditis after COVID-19 vaccination in adult population: A systematic review. Ann Med Surg (Lond). 2022 Apr;76:103486.

37. Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. 2022 Feb;28(2):410-22.

38. Mormile R. Myocarditis and pericarditis following mRNA COVID-19 vaccination in younger patients: is there a shared thread? Expert Rev Cardiovasc Ther. 2022 Feb;20(2):87-90.

39. Marschner CA, Shaw KE, Tijmes FS, Fronza M, Khullar S, Seidman MA, et al. Myocarditis Following COVID-19 Vaccination. Cardiology Clinics. 2022 Aug 1;40(3):375-88.

40. Lane S, Yeomans A, Shakir S. Reports of myocarditis and pericarditis following mRNA COVID-19 vaccination: a systematic review of spontaneously reported data from the UK, Europe and the USA and of the scientific literature. BMJ Open. 2022 May 25;12(5):e059223.

41. Oster ME, Shay DK, Su JR, Gee J, Creech CB, Broder KR, et al. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. JAMA. 2022 Jan 25;327(4):331-40.

42. Twentyman E, Wallace M, Roper LE, Anderson TC, Rubis AB, Fleming-Dutra KE, et al. Interim Recommendation of the Advisory Committee on Immunization Practices for Use of the Novavax

COVID-19 Vaccine in Persons Aged ≥ 18 years-United States, July 2022. Morb Mortal Wkly Rep. 2022 Aug 5;71(31):988-92.

43. Tavares F, Nazareth I, Monegal JS, Kolte I, Verstraeten T, Bauchau V. Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: A prospective cohort study. Vaccine. 2011 Aug 26;29(37):6358-65.

44. Interim Clinical Considerations for Use of COVID-19 Vaccines in the United States [Internet]. [cited 2023 May 13]. Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

45. Kachikis A, Englund JA, Singleton M, Covelli I, Drake AL, Eckert LO. Short-term Reactions Among Pregnant and Lactating Individuals in the First Wave of the COVID-19 Vaccine Rollout. JAMA Netw Open. 2021 Aug 2;4(8):e2121310.

46. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al; CDC v-safe COVID-19 Pregnancy Registry Team. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med. 2021 Jun 17;384(24):2273-82.

47. EU-Risk Management Plan for VidPrevtyn® Beta (COV2 PRES DTM-AS03 [B.1.351]); version 1.0, dated 10 Nov 2022.

48. World Health Organization. WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2023 May 19]. Available from: https://covid19.who.int/

49. Sanofi. EU-Risk Management Plan.; version 1.0.

50. Serotracker. Seroprevalence Estimates by Country [Internet]. [cited 2023 May 21]. Available from: https://serotracker.com/en/Analyze

51. European Centre for Disease Prevention and Control. Communicable Disease Threats Report, week 9, 27 February - 5 March 2023, Week 8. [Internet]. [cited 2023 May 25]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/communicable-disease-threats-report-3-march-2023.pdf

52. Tracking of hCOV19 Variants. [Internet]. [cited 2023 May 19]. Available from: https://gisaid.org/hcov19-variants/

53. World Health Organization. Tracking SARS-CoV-2 variants [Internet]. [cited 2023 May 19] Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

54. Sanofi. 2.5 Clinical Overview – Addendum (COVID-19): VAT00013. [VV-CLIN-0638481]

55. Sanofi. Brief Interim Clinical Study Report: VAT00002; version 1.0.

56. Rahmandad H, Lim TY, Sterman J. Behavioral dynamics of COVID-19: estimating underreporting, multiple waves, and adherence fatigue across 92 nations. Syst Dyn Rev. 2021 Jan-Mar;37(1):5-31.

57. European Centre for Disease Prevention and Control. Assessment of the further spread and potential impact of the SARS-CoV-2 Omicron variant of concern in the EU/EEA, 19th update - 27 January 2022. ECDC: Stockholm; 2022. [Internet]. [cited 2023 May 19]. Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-omicron-risk-assessment-further-emergence-and-potential-impact

58. Byambasuren O, Cardona M, Bell K, Clark J, McLaws ML, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. J Assoc Med Microbiol Infect Dis Can. 2020 Dec;5(4):223-34.

59. Johansson MA, Quandelacy TM, Kada S, Prasad PV, Steele M, Brooks JT, et al. SARSCoV-2 Transmission From People Without COVID-19 Symptoms. JAMA Netw Open. 2021 Jan 4;4(1):e2035057.

60. World Health Organization. Contact tracing and quarantine in the context of the Omicron SARS-CoV-2 variant Interim guidance, 17 February 2022. [Internet]. [cited 2023 May 19]. Available from: https://apps.who.int/iris/bitstream/handle/10665/351949/WHO-2019-nCoV-Contact-tracing-and-quarantine-Omicron-variant-2022.1-eng.pdf?sequence=1&isAllowed=y

61. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-42.

62. European Centre for Disease Prevention and Control. SARS-CoV-2 variants of concern as of 17 May 2023. [Internet]. [cited 2023 May 19] Available from: https://www.ecdc.europa.eu/en/covid-19/variants-concern

63. World Health Organization. Weekly epidemiological update on COVID-19 - 11 January 2022. [Internet]. [cited 2023 May 19]. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---11-january-2022

64. Bellino S. COVID-19 treatments approved in the European Union and clinical recommendations for the management of non-hospitalized and hospitalized patients. Ann Med. 2022 Dec;54(1):2856-60.

65. UK Health Security Agency. COVID-19 vaccine surveillance report: Week 4. 27 January 2022. [Internet]. [cited 2023 May 19]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1050721/Vaccine-surveillance-report-week-4.pdf

66. Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet. 2022 Mar 5;399(10328):924-44.

67. Press Release: Sanofi-GSK next-generation COVID-19 booster delivers strong immune response against variants of concern including Omicron. 2022. [Internet]. [cited 2023 May 19]. Available from: https://www.sanofi.com/en/media-room/press-releases/2022/2022-06-13-05-30-00-2460833

68. Launay O, Cachanado M, Luong Nguyen LB, Ninove L, Lachatre M, Ben Ghezala I, et al. Immunogenicity and safety of Beta-adjuvanted recombinant booster vaccine. N Engl J Med. 2022 Jul 28;387(4):374-6.

69. Our World in Data. Number of COVID-19 patients in hospital per million [Internet]. [cited 2023 Jun 21]. Available from: https://ourworldindata.org/grapher/current-covid-hospitalizations-per-million

70. Centers for Disease Control and Prevention (CDC). SARS-CoV-2 Variant Classifications and Definitions [Internet] [Updated 2023 Mar 20; cited 2023 Jun15]. Available from https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html

71. https://serotracker.com/en/Analyze

72. United Nations, WHO chief declares end to COVID-19 as a global health emergency, [Internet]. [Updated date 2023 May 05; cited date 2023 Jun 19]. Available at https://news.un.org/en/story/2023/05/1136367

73. Cheng C, Zhang D, Dang D, Geng J, Zhu P, Yuan M, et al. The incubation period of COVID-19: a global meta-analysis of 53 studies and a Chinese observation study of 11 545 patients. Infect Dis Poverty. 2021 Sep 17;10(1):119.

74. Byrne AW, McEvoy D, Collins AB, Hunt K, Casey M, Barber A, et al. Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases. BMJ Open. 2020 Aug 5;10(8):e039856.

75. Alene M, Yismaw L, Assemie MA, Ketema DB, Mengist B, Kassie B, et al. Magnitude of asymptomatic COVID-19 cases throughout the course of infection: A systematic review and meta-analysis. PLoS One. 2021 Mar 23;16(3):e0249090.

76. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. Medrxiv. 2021 Sep 21:2021-09.

77. Dorigatti I, Lavezzo E, Manuto L, Ciavarella C, Pacenti M, Boldrin C, et al. SARS-CoV-2 antibody dynamics and transmission from community-wide serological testing in the Italian municipality of Vo'. Nat Commun. 2021 Jul 19;12(1):4383.

78. Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L, et al. Transmission of SARS-CoV-2 Lineage B. 1.1. 7 in England: Insights from linking epidemiological and genetic data. MedRxiv. 2021 Jan 4:2020-12.

79. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021 Apr 9;372(6538):eabg3055.

80. Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L, et al. Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England. Nature. 2021 May;593(7858):266-9.

81. Fontal A, Bouma MJ, San-José A, López L, Pascual M, Rodó X. Climatic signatures in the different COVID-19 pandemic waves across both hemispheres. Nat Comput Sci. 2021 Oct;1(10):655-65.

82. Our World in Data. Coronavirus (COVID-19) Vaccinations - Statistics and Research [Internet]. [cited 2023 Jun 21]. Available from: https://ourworldindata.org/covid-vaccinations

83. World Health Organization, COVID-19 vaccine tracker and landscape [Internet]. [Updated 2023 Mar 30; cited 2023 Jun 19]. Available at https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

84. Emergency Use Authorization [Internet]. [Updated 2023 Jun 02; cited 2023 Jun 15]. Available from https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

85. Coronavirus Treatment Acceleration Program (CTAP) [Internet]. [Updated 2023 May 12; cited 2023 Jun 15]. Available from https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap#:~:text=Use%20Authorization%20Transparency-,What%20is%20CTAP%3F,)%20for%20COVID%2D19%20therapeutics

86. Therapeutic Management of Nonhospitalized Adults With COVID-19 [Internet]. [Updated 2023 Apr 20; Cited 2023 Jun 15]. Available from https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

87. Coronavirus (COVID-19) Update: FDA Authorizes New Monoclonal Antibody for Treatment of COVID-19 that Retains Activity Against Omicron Variant [Internet]. [Updated 2022 Feb 11; cited 2023 Jun 15]. Available from https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains

88. Centers for Disease Control and Prevention (CDC). Science Brief: COVID-19 Vaccines and Vaccination [Internet]. [Updated 2021 Sep 15; cited 2023 Jun 15]. Available from https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

89. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Mar 13;367(6483):1260-3.

90. Pallesen J, Wang N, Corbett KS, Wrapp D, Kirchdoerfer RN, Turner HL, et al. Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. Proc Natl Acad Sci U S A. 2017 Aug 29;114(35):E7348-57.

91. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat. med. 2021 Nov;27(11):2032-40.

92. Cohet C, van der Most R, Bauchau V, Bekkat-Berkani R, Doherty TM, Schuind A, et al. Safety of AS03-adjuvanted influenza vaccines: A review of the evidence. Vaccine. 2019;37(23):3006-21.

93. Ward BJ, Gobeil P, Séguin A, Atkins J, Boulay I, Charbonneau PY. et al. Phase 1 trial of a candidate recombinant virus-like particle vaccine for Covid-19 disease produced in plants. MedRxiv. 2020 Nov 6:2020-11.

94. Richmond P, Hatchuel L, Dong M, Ma B, Hu B, Smolenov I, et al. Safety and immunogenicity of S-Trimer (SCB-2019), a protein subunit vaccine candidate for COVID-19 in healthy adults: a phase 1, randomised, double-blind, placebo-controlled trial. Lancet. 2021 Feb 20;397(10275):682-94.