VidPrevtyn Beta (SRD): Periodic safety update report assessment

10 May 2023 to 9 November 2023

This document consists of:

1. The PRAC assessment report of the VidPrevtyn Beta (SRD) periodic safety update report (PSUR) covering the period 10 May 2023 to 9 November 2023, and;
2. The VidPrevtyn Beta (SRD) 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/259328/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00011035/202311

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

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

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:	15 February 2024	15 February 2024
☐	PRAC Rapporteur's preliminary assessment report (AR)	15 April 2024	12 April 2024
☐	MS/PRAC members and MAH comments	15 May 2024	15 May 2024
☐	PRAC Rapporteur's updated assessment report following comments	30 May 2024	28 May 2024
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	13 June 2024	13 June 2024

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:

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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 2nd 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 May 2023 – 09 November 2023.

Vidprevtyn Beta was 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.

Vidprevtyn Beta was 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 was available as solution and emulsion for emulsion for injection. One dose (0.5 mL) containing five micrograms of recombinant SARS-CoV-2 S protein (B.1.351 strain) formulated with adjuvant system 03 adjuvant and administered intramuscularly.

The International Birth Date (IBD) of Vidprevtyn Beta is 10 November 2022 when it was first authorised in the EU. In addition, a marketing authorization was granted in the UK on 20 December 2022. During the period covered by this report, no marketing authorisation was granted.

Vidprevtyn Beta was marketed in 5 EU member states (Austria, France, Italy, Portugal and Slovenia) and 1 non-EU state (UK) and 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 was approximately 7,522 up to 09 November 2023. The total number of doses in England could be estimated to be approximately 2,112,460 up to 09 November 2023.

507,775 doses of VidPrevtyn Beta were administered during the current period and 2,144,734 doses were administered cumulatively. 283 cases with 754 ADRs were reported during the covered period, 783 cases with 1,980 ADRs were reported cumulatively.

A safety signal on allergic including anaphylactic reactions was identified during the reporting interval. The safety analysis was assessed via a type II variation and the PI was updated to include anaphylactic reactions and hypersensitivity (including rash, rash erythematous, urticaria, angioedema).

No new safety information was identified by the MAH and no actions were taken for safety reasons during this reporting interval. Nevertheless, the MAH requested to withdraw the marketing authorisation with a withdrawal effective date on 18 March 2024. The withdrawal decision is not based on the grounds provided in Articles 116 and 117 (i.e., not driven by quality, safety, efficacy or benefit/risk concerns). The European Commission decision to withdraw the Marketing Authorization of VidPrevtyn Beta has been adopted on 11 March 2024.

The MAH provided an addendum to the PSUR including all relevant information covering the period from 10 November 2023 to 18 March 2024 as previously agreed. No new safety findings were identified during that remaining marketing authorization period.

3. Recommendations

Based on the PRAC Rapporteur review of data on safety and efficacy, the PRAC is of the view that the reported data does not warrant an update to the product information.

The PRAC notes that the marketing authorisation of SARS-CoV-2, B.1.351 variant, prefusion Spike delta TM protein, recombinant was withdrawn on 18 March 2024 (adopted by the European Commission on 11 March 2024)

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

None

5. PSUR frequency and other changes to the EURD list

Based on the European Commission Decision issued on 11 March 2024 this product is currently withdrawn from the European market. No further PSUR submission is requested.

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 2nd single assessment of PSUR submitted for VidPrevtyn Beta (COVID-19 vaccine (recombinant, adjuvanted)), the covered period of this PSUSA is from 10 May 2023 to 09 November 2023.

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

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	10/05/2023 – 09/11/2023	10/11/2022-09/11/2023

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, Portugal and Slovenia.

During the period covered by this report, no MA for COVID-19 vaccine (recombinant, adjuvanted) was granted.

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.

Rapporteur assessment comment:

The information about marketing authorisation status is acknowledged. In addition, VidPrevtyn Beta has been marketed in the United Kingdom where vast majority of marketed doses was administrated.

After DLP of the current PSUR, ***the MAH requested to withdraw the marketing authorisation with a withdrawal effective date on 18 March 2024. The withdrawal decision is not based on the grounds provided in Articles 116 and 117 (i.e., not driven by quality, safety, efficacy or benefit/risk concerns). The European Commission decision to withdraw the Marketing Authorization of VidPrevtyn Beta has been adopted on 11 March 2024.***

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, 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 the safety reasons during the reporting period.

1.3.2. Changes to reference safety information

The EU SmPC for COVID-19 vaccine (recombinant, adjuvanted), version 01 dated 10 November 2022 was the RSI valid at the beginning of the PBRER period.

The RSI was revised on 21 September 2023 and the following amendments were made:

• Summary of Product Characteristics – Section 4.8 - Undesirable effects: Addition of "Anaphylactic reactions. Hypersensitivity (including rash, rash erythematous, urticaria, angioedema)" with frequency "Not known".

• Product Information Leaflet – Section 4 - Possible side effects: Addition of "Allergic reactions such as rash or hives or swelling of the face. Severe allergic reactions (anaphylaxis)" with frequency "Not known (cannot be estimated from available data)"

Of note, Sanofi has submitted to EMA on 28 September 2023 an update of section 4.8 of the SmPC to include additional safety data based on the safety reports from studies VAT00008 and VAT00002 Cohort 2 further to the extension of the safety database over 2000 and 3000 participants with six weeks safety follow-up. The procedure started on 16 October 2023 with an expected EMA Committee for Medicinal Products for Human Use (CHMP) opinion on the 14 December 2023.

Rapporteur assessment comment:

The section 4.8 of the SmPC and the section 4 of PIL were updated to include hypersensitivity and anaphylactic reactions during the covered period.

In addition, the variation II/0007/G has been approved recently. Within this variation, the section 4.8 was also updated, however only new information related to the studies VAT00002 and VAT00008 were included, no new adverse reactions were added.

1.3.3. Estimated exposure and use patterns

MAH / Product	Exposure in clinical trials (subjects)	Exposure post-marketing experience	
	Cumulative monovalent B.1.351	**Cumulative**	**Interval**
Vidprevtyn Beta	10 953	2 144 734	507 775

Clinical Trials

The cumulative exposure to COVID-19 vaccine (recombinant, adjuvanted), in interventional clinical trials sponsored by the MAH is estimated to be 22 303 participants. Actual exposure data from completed or open-label clinical trials 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 (MV) and bivalent (BiV).

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	1359
SARS-CoV-2 preS dTM Monovalent B.1.351	10 953
SARS-CoV-2 preS dTM Bivalent D614+B.1.351	1295
Placebo	1062
Two injections	
SARS-CoV-2 preS dTM Monovalent D614	12 300

SARS-CoV-2 preS dTM Bivalent D614+B.1.351	6060
Placebo/Placebo	10 784
Three injections	
SARS-CoV-2 preS dTM Monovalent D614	137
Total	
SARS-CoV-2 preS dTM Monovalent and Bivalent	**22 303**
Placebo	**4843**

Data as of 09-Nov-2023 from studies: VAT00001 (completed), VAT00002 (ongoing), and VAT00008 (ongoing). VAT00002 and VAT00008 participants may choose to receive one booster injection after a primary series vaccination. A subset of participants in VAT00002 received the D614 formulation as both primary series vaccination and booster injection. VAT00008 placebo participants may choose to receive a primary series vaccination (if unvaccinated) or one booster injection (if vaccinated) after meeting specific criteria. Therefore, participants in VAT00008 who received placebo in the first stage and received the vaccine during the crossover/booster phase are now counted in the vaccine row. Participants who received more than one treatment are counted in each of the treatments, as received injections.
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; preS dTM: Prefusion Spike Recombinant Protein

The cumulative exposure of COVID-19 vaccine (recombinant, adjuvanted) by demographic characteristics of age range, gender, and race/ethnicity is following:

Cumulative participant exposure to SARS-CoV-2 recombinant protein monovalent and bivalent vaccines in all clinical studies by age and sex group

Number of participants (monovalent and bivalent)

Age (years)	Male	Female	Total
18-55	1118	8354	19536
>=56	1461	1306	2767
Total	12643	9660	22303
18-25	2717	1636	4353
26-59	8901	7108	16009
60-74	909	825	1734
>=75	116	91	207

Race or Ethnicity	Number of Participants (monovalent and bivalent)
American Indian or Alaska Native	2881
Asian	8307
Black or African American	6623
Multiple	62
Native Hawaiian or other Pacific Islander	17
White	3061
Missing	1352
Total	22303
Hispanic or Latino	4438
Not Hispanic or Latino	17485
Missing	380

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. European Union/EEA 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 EU country and age group as of 09 November 2023 are presented in Table 2 (last update of EU tracker was on 05 October 2023).

Table 2 – Number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in EU by country and age group through 09 November 2023

Country	EUROPE								Total
	Unknown	0-17	18-24	25-49	50-59	60-69	70-79	80+	
AUSTRIA	0	2	12	104	67	67	64	35	351
FRANCE	6881	0	0	0	0	0	0	0	6881
ITALY	53	0	3	48	20	51	23	14	212
PORTUGAL	6	0	1	21	14	17	15	3	77
SLOVENIA	0	0	0	0	1	0	0	0	1
Total	6940	2	16	173	102	135	102	52	7522

Of note, open access data on the Public Health France website are available: the cumulative number of doses administered during the 2023 French fall vaccination campaign categorized by COVID-19 vaccine type indicate 18 512 of COVID-19 vaccine (recombinant, adjuvanted) administered in France as per week 45.

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 available. The number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in England per age group as of 09 November 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 09 November 2023

Country	UK									Total
	Unknown	0-17	18-29	30-39	40-49	50-59	60-69	70-79	80+	
England	9	15	180	378	912	2 768	15 966	893 042	1 199 190	2 112 460[a]

a On 30-Nov-2023, a new update from the Department for Business, Energy & Industrial Strategy from UK government was available notifying 6240 doses have been administered in the UK during the Fall

campaign during the reporting interval. In total, 2 118 700 doses have been administered up to 09-Nov-2023 in the UK.

Based upon available data, 507 775 doses of COVID-19 vaccine (recombinant, adjuvanted) were administered worldwide for the current review period, with a total of 2 144 7343 doses administered cumulatively.

Post-approval use in special populations

The MAH does not have access to cumulative post-marketing 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 2 108 198 doses administered 60 years and older (Department for Business, Energy & Industrial Strategy from the UK government).

Use in the pregnancy and while breast-feeding is a missing information and is being studied in the scope of non-interventional studies with study identification (ID) VAT00012 and VAT00007 (not yet initiated). No exposure in these studies.

Use in the immuno-compromised subjects is a missing information and is being studied in the scope of externally sponsored collaborative (ESC) studies with study ID VAT00027, VAT00028 and 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]) is a missing information and is planned to be studied in the scope of a non-interventional study VAT00007 (not yet initiated).

Use in subjects with autoimmune or inflammatory disorders is a missing information and is planned to be studied in the scope of non-interventional study VAT00007 (not yet initiated).

Use in elderly: In the UK, country where most doses were administered, the indication 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 profile presented in this PBRER can be considered as reflecting the safety profile in this age group.

Rapporteur assessment comment:

Additional 8,004 subjects were exposed to monovalent B.1.351 formulation in the clinical trials during the reporting period. In the post-marketing period, the vast majority of doses were administrated in the UK and in the age groups of 70-79 years and 80+ years.

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	283	783	754	1 980

Rapporteur assessment comment:

1,073 SAEs were reported from the clinical trials cumulatively. Out of them 1,057 SAEs were blinded, and 14 SAEs were reported with the investigational product.

283 cases with 754 ADRs were reported during the covered period, 783 cases with 1,980 ADRs were reported cumulatively.

No new important safety information is identified.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Clinical trials

Completed clinical trials

VAT00001:

VAT00001 study was completed during the reporting period. The final data confirmed the interim data showing that a two-injection schedule of vaccination was necessary to induce neutralizing antibodies (Ab) and that the low-dose adjuvanted vaccine induced higher titers of neutralizing Abs compared to high-dose unadjuvanted protein-alone vaccine demonstrating the benefit of the adjuvant. In addition, the CoV2 preS dTM antigen adjuvanted with AS03 induced higher titers of neutralizing Abs compared to both the AF03 adjuvanted group and compared to the unadjuvanted groups with a two-injection schedule. However, even in the best performing vaccine group (two-injection schedule of high-dose + AS03), seroconversion rates at Day 36 [D] were below 90% in all adults with lower rates in older adults (82.4% in 50 years and older, 57.1% in 60 years and older). These results indicated the need for further optimization of the antigen formulation and dose, with doses higher than the effective high dose of 2.6 µg used in this study. Due to confounding effects, there was limited ability to meaningfully conclude on the durability of neutralizing Ab responses for longer term timepoints.

All vaccinations in the VAT00001 study occurred prior to the review period. The safety follow-up period of the study was completed prior to the review period. There were no clinically important emerging safety findings in this study completed during the reporting interval.

Ongoing clinical trials

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 5µg, 10µg, or 15µg 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 5µg 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 Adverse Events of Special Interest (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 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, 5 µg (D614 component) + 5 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 BiV vaccine. Thus, by design, the inclusion of the B.1.351 antigen with the D614 antigen in the BiV 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 AESI).

No safety concern was raised from the VAT00008 study for the MV or BiV vaccine formulations.

There was no new clinically important information arising from studies ongoing during the reporting interval and during the interval between the overlapping DSUR DLP (28 August 2023) and the PBRER DLP (09 November 2023)

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:

The clinical trial VAT00001 was completed during the reporting period. All subjects were vaccinated before the reporting period and the safety follow-up period was also completed before the period covered by the current PSUR. No important safety issues were identified.

Two clinical trials (VAT00002, VAT00008) were ongoing during the covered period. In the VAT00002 Phase II/III study supplemental cohorts were studied to address boost options. Supplemental Phase III Cohort 1 evaluated the parental strain (monovalent antigen D614) and Supplemental Phase III Cohort 2 evaluated 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 the stage 1 and bivalent formulation (5 microgram D614 antigen + 5 microgram B.1.351 antigen) in the stage 2. In the booster extension of the study monovalent B.1.351 antigen is 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, 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. Registration for the C-VIPER registry is currently open in several countries except in France.

As of the DLP, no participants vaccinated with COVID-19 vaccine (recombinant, adjuvanted) vaccine have been enrolled in VAT00012.

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

Rapporteur assessment comment:

One non-interventional study (VAT00012) designed to collect prospective safety data in pregnant women vaccinated with VidPrevtyn Beta was ongoing during the covered period, however, no participants were enrolled yet.

1.3.5.3. Other clinical trials and sources

During the reporting interval, two investigator-sponsored studies (VAT00013 and VAT00029, both sponsored by Assistance Publique Hopitaux 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 subunit 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.

An ancillary study of VAT00013 study has been launched to evaluate the immune response of a second booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine in comparison to mRNA Pfizer/BioNTech prototype vaccine in elderly participants (≥ 60 years of age) who received three doses of vaccination with mRNA vaccines.

VAT00029: This investigator-sponsored study is a randomized, single blinded-multicenter clinical trial to assess the immunogenicity and safety following a booster dose of the Sanofi-GSK Monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine compared to a BiV mRNA vaccine (Comirnaty Original/Omicron BA.4-5, BioNTech-Pfizer) in adults previously vaccinated with at least three doses of COVID-19 mRNA vaccine.

VAT00026: This phase II study 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 and during the interval between the overlapping DSUR DLP (28 August 2023) and the PBRER DLP (09 November 2023).

Rapporteur assessment comment:

2 investigator – sponsored studies (VAT00013, VAT00029) and 3 externally sponsored collaborative studies (VAT00026, VAT00027, VAT00028) were ongoing during the covered period. No important safety findings were identified.

1.3.5.4. Medication errors

During the reporting period, a total of 10 cases have been reported with medication error. All PTs within the Medication error SMQ reported with COVID-19 vaccine (recombinant, adjuvanted) by High Level Term (HLT) and PT are presented in Table 4.

The reported PTs within the Medication error SMQ reported with UNK MFR by HLT and PT are presented in Table 5.

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 with COVID-19 vaccine (recombinant, adjuvanted)

Medication Error description	PT for Medication Error	Count of events of Medication Error
Children of 5 and 11 years-old received the vaccine.	*Product administered to patient of inappropriate age*	2
A child and an elderly patient received COVID-19 vaccine (recombinant, adjuvanted) instead of Pfizer vaccine against COVID-19	*Wrong product administrated*	2
Medication error reported by a consumer: for him, this reaction "occurred as a result of a mistake made in the administration of the vaccine since when the vaccination was administered it was painful,	*Medication error*	1

compared to the first 5 COVID-19 vaccinations		
Patient mistakenly received COVID-19 vaccine (recombinant, adjuvanted) vaccine as primary dose	*Product use in unapproved indication*	1
Incorrect placement of COVID-19 vaccination (confirmed by rheumatologist).	*Wrong technique in product usage process*	1
Vaccine administered the month of the expiry date or just after.	*Expired product administered*	1
Patient received his COVID-19 vaccine (recombinant, adjuvanted) less than four months after his previous COVID-19 vaccine dose.	*Inappropriate schedule of product administration*	1
Pharmacist ordered COVID-19 vaccine (recombinant, adjuvanted) doses in Oct-2023, that patient received expired the same month.	*Product dispensing error*	1
Patient received lower volume than recommended.	*Incorrect dose administered*	1

Table 5 • Most frequently reported medication errors reported during the interval with UNK MFR

Medication Error description	PT for Medication Error	Count of events of Medication Error
According to "documentation", two vaccines were administered to the elderly patients: COVID-19 vaccine (recombinant, adjuvanted) and Efluelda®. The patient thinks it is a documentation error because patient only has one arm available for vaccination (patient has a plaster on a vaccination site).	*Transcription medication error*	1

Out of the 10 cases of medication errors reported during the review period, three (one serious and two non-serious) were reported with AEs (30 %) and seven cases had no reported AEs (70 %). The three cases associated with AEs are described for the assessment of interval medication error cases reporting AEs (Table 6).

Table 6 - Interval medication error cases reporting adverse events

Case ID Seriousness	Medication Error PT	PT(s) of reported AE(s)	Suspected vaccine	Comment
[redacted] Serious	Wrong technique in product usage process	*Polymyalgia rheumatica* *Pain in extremity*	COVID-19 vaccine (recombinant, adjuvanted)	Case reported by a consumer. A 79-year-old patient reported pain in extremity and wrong technique in product usage process the day of vaccination with COVID-19 Vaccine (dose 5). Severe left upper arm pain was due to incorrect placement of COVID-19 vaccination (confirmed by rheumatologist). The patient also experienced polymyalgia rheumatica on the same day. Hospital report states that polymyalgia was possibly triggered by the COVID-19 vaccine. As per reporter this reaction occurred was not a result of a mistake made in the administration of the vaccine. At time of reporting, the outcome was not recovered for the events polymyalgia and pain in extremity.
[redacted] Non-Serious	Medication error	*Erythema* *Somnolence* *Injection site mass* *Arthralgia* *Injection site pain* *Asthenia*	COVID-19 vaccine (recombinant, adjuvanted)	Case reported by a consumer. An 82-year-old patient with ongoing arthritis, experienced redness, sleepiness, injection site mass, injection site pain, feeling of total lack of energy and reported medication error the day of vaccination (6th dose). Patient also reported pain in hip, five days after vaccination. As per reporter "this reaction occurred as a result of a mistake made in the administration of the vaccine since when the vaccination was administered it was painful, compared to the first five COVID-19 vaccinations." At time of reporting, the outcome was not recovered/ not resolved for all events. *MAH comment: Although the pain during vaccination might have been linked with a vaccination technique, there is no evidence to conclude on any error and any link between the applied vaccination technique and the symptoms reported except for Injection site pain.*
[redacted] Non-Serious	Wrong product administered	Rhinorrhoea, Pain, Pyrexia	COVID-19 vaccine (recombinant, adjuvanted)	Case reported by a physician, who is also the patient. The patient of unknown age experienced fever, runny nose and body aches an unknown date after vaccination. At time of event, patient had prostate cancer, Parkinson's disease, bone marrow dysplasia, polyneuropathy, diabetes mellitus, Myelodysplastic syndrome and sleep apnea syndrome (device assisted). The patient already had symptoms (fatigue, dizziness) before vaccination. The patient was supposed to receive Pfizer COVID-19 vaccine but the day of vaccination, the pharmacy called him back and told him that there was an error, and he would receive VidPrevtyn Beta®.

	Patient does not think symptoms are related to the vaccine but to repeated infections that te patient gets very regularly because of his sleep apnea device. At time of reporting, the outcome was unknown for the event.

There were no relevant safety findings on patterns of medication errors and potential medication errors identified which would require specific risk minimization measures (RMMs) 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:

10 cases of medication error were reported during the covered period. Out of them, adverse events were reported in 3 cases. No significant safety finding on pattern of the medication errors was identified.

1.3.5.5. Nonclinical data

No significant findings have been identified during the reporting interval.

Rapporteur assessment comment:

The information is acknowledged.

1.3.5.6. 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.

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 AESI 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 studies

After MAH's proposal in the last PBRER to implement a focused strategy for literature screening, PRAC agreed to focus the scientific literature search strategy on the vaccines of the same or similar platform. During the reporting period, five publications identified from the scientific (including non-clinical) and medical literature contained relevant safety findings summarized hereafter.

Class-related articles for other protein-based and protein nanoparticle vaccines:

Altman N, Berning AA, Mann SC, Quaife RA, Gill E, Auerbach SR, et al. Vaccination-Associated Myocarditis and Myocardial Injury. Circulation Research. 2023 May 12;132(10):1338–57.

The article discussed SARS-CoV-2 vaccine–associated myocarditis of various platforms, including protein-based vaccine (NVX-CoV2373 – adjuvanted recombinant spike protein vaccine, NUVAXOVID®). Five (5) cases of temporally related myocardial injury that clinically could have been myocarditis, plus one case of pericarditis were reported in Phase 3 clinical trials with Nuvaxovid within ten days of vaccine receipt, versus one case of possible myocarditis in the placebo arm that occurred 72 days post-vaccination. It was reported that the risk of myocarditis after the Nuvaxovid and mRNA vaccines may be similar, and that mRNA-induced immune activation as a major mechanism of vaccine-associated myocarditis is therefore not supported.

MAH comment: From the data provided in the article, it seems that mRNA-induced immune activation may not be the only mechanism of vaccine-associated myocarditis. Genetic variation in ACE2 leading to differences in S protein binding affinity may explain a similar degree of infrequent myocarditis case reports between mRNA and recombinant protein-based vaccines.

Rapporteur assessment comment:

The authors discussed the potential biological mechanism of myocarditis following immunisation with mRNA covid-19 vaccines and following Nuvaxovid. Myocarditis is a listed ADR of mRNA vaccines and Nuvaxovid. No important safety finding was identified.

Wilkinson B, Patel KS, Smith K, Walker R, Wang C, Greene AM, et al. A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for the NOVAVAX® COVID-19 Vaccine (NVX-CoV2373), a recombinant spike protein vaccine with Matrix-M adjuvant to prevent disease caused by SARS-CoV-2 viruses. Vaccine. 2023 Oct 26;41(45):6762–73.

The authors presented NOVAVAX COVID-19 Vaccine (NVX-CoV2373, Nuvaxovid), a recombinant spike protein vaccine with Matrix-M adjuvant, in the Brighton Collaboration (BC) standardized template with key considerations for a benefit/risk assessment to prevent disease caused by SARS-CoV-2 viruses. Clinical data in over 31 000 adult and adolescent participants administered Nuvaxovid has demonstrated that in primary two-dose vaccination there was a well-tolerated response to Nuvaxovid and high vaccine efficacy against mild, moderate or severe COVID-19. Similarly, for the booster vaccination (six months after primary vaccination), there was a high vaccine efficacy (substantial increases in humoral antibodies against both the prototype strain and all evaluated variants, similar to or higher than the antibody levels observed in phase 3 studies), and a well-tolerated safety profile in both primary and booster vaccination. In regard to the AESI of Myocarditis/pericarditis, two events of myocarditis in the Nuvaxovid group, and one event in the placebo group were reported in the pre-crossover period (risk difference of zero (95% CI, 0.02–0.02). In the post-crossover from placebo to active vaccine, two events of pericarditis and one

event of myocarditis were reported for Nuvaxovid, and one event of myocarditis for placebo (risk difference of 0 (95% CI, 0.02–0.05) for myocarditis and 0.02 (95% CI, 0.00–0.08) for pericarditis).

However, myocarditis/pericarditis was classified as an important identified risk for Nuvaxovid, based on reports received in the post-authorization setting.

MAH comment: Myocarditis/pericarditis is considered an important potential risk for COVID-19 vaccine (recombinant, adjuvanted) and is closely monitored through both routine and additional pharmacovigilance (PV) activities.

Rapporteur assessment comment:

The authors discuss an efficacy and safety profile of Nuvaxovid including a listed ADR of myocarditis. No important safety issue was identified.

Song JY, Choi WS, Heo JY, Kim EJ, Lee JS, Jung DS, et al. Immunogenicity and safety of SARSCoV- 2 recombinant protein nanoparticle vaccine GBP510 adjuvanted with AS03: interim results of a randomised, active-controlled, observer-blinded, phase 3 trial. EClinicalMedicine. 2023 Oct 1;64:102140.

The authors presented the interim results of a phase three multinational study for GBP510 (SKYCOVIONE®) vaccine adjuvanted with AS03 (GBP510/AS03) compared with ChAdOx1-S in healthy adults aged ≥18 years, up to six months after the second dose. GBP510 is a recombinant protein vaccine consisting of self-assembling, two-component nanoparticles displaying SARS-CoV-2 spike receptor-binding domains (receptor binding domain [RBDs] adjuvanted with AS03. A total of 4036 participants were randomized to receive two-doses of GBP510/AS03 (n = 3039) or ChAdOx1-S (n = 997). In the safety analysis, the proportion of participants with AEs after any vaccination was higher with GBP510/AS03 versus ChAdOx1-S for solicited local AEs (56.7% versus 49.2%) but was similar for solicited systemic AEs (51.2% versus 53.5%) and unsolicited AEs (13.3% versus 14.6%) up to 28 days after the second vaccination. A total of six cases reporting AESIs were reported, three in the GBP510/AS03 group (acute kidney injury, rapidly progressive glomerulonephritis, and cutaneous vasculitis) and three in the ChAdOx1 S group (acute pancreatitis, anaphylactic reaction, and psoriasis). No safety concerns were identified during follow-up for six months after the second vaccination. Additionally, five pregnancies were reported in the GBP510/AS03 group and two in the ChAdOx1-S group; all individuals gave birth without any abnormal outcomes or SAEs.

MAH comment: The interim findings of this study suggested that GBP510/AS03 met the superiority criterion for neutralizing antibodies and non-inferiority criterion for seroconversion rate compared with ChAdOx1-S and showed a clinically acceptable safety profile.

Rapporteur assessment comment:

In this article, the interim results of a phase III study with a candidate covid vaccine Skycovione adjuvanted with ASO3 were presented. Skycovione was compared with Vaxzevria in healthy subjects of age 18 years and older. The proportion of participants which experienced solicited local AEs was higher with Skycovione, however it was similar for solicited systemic AEs and unsolicited AEs. No significant safety finding was identified.

Sanofi-Sponsored studies published during the reporting interval:

Of note, the following two articles were published during the reporting period, presenting the results of the Sanofi sponsored studies with two different SARS-CoV-2 recombinant protein vaccines with AS03 adjuvant:

de Bruyn G, Wang J, Purvis A, Ruiz MS, Adhikarla H, Alvi S, et al; VAT00002 booster cohorts study team. 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: a phase 3, parallel-group study. EClinicalMedicine. 2023 Jul 22;62:102109.

MAH Comment: This publication refers to the Sanofi sponsored phase III study VAT00002 (Supplemental Cohorts). It presents the interim analyses up to 14 days post-last vaccination for immunogenicity and over a median duration of five months for safety. 549-RSP-COVID-19_NS / 561-RSP-COVID-19-bi vaccine boosters demonstrated acceptable safety and elicited robust neutralizing antibodies against multiple variants, regardless of priming vaccine.

Dayan GH, Rouphael N, Walsh SR, Chen A, Grunenberg N, Allen M, et al. Efficacy of a monovalent (D614) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant in adults: a phase 3, multi-country study. eClinicalMedicine. 2023 Oct 1;64:102168.

MAH comment: This publication refers to the Sanofi sponsored phase III study parallel, international randomized, double-blind, placebo-controlled study for the prototype MV (D614) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant. The vaccine was well-tolerated with an acceptable safety profile and some level of protection against the Delta strain in participants regardless of prior infection, comparable to vaccine efficacy with other D614-based COVID-19 vaccines.

Rapporteur assessment comment:

The articles discuss the clinical trials VAT00002 and VAT00008, which are already presented above.

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

The following significant changes were proposed to the RSI after the DLP of the report following final PRAC updated assessment report dated 30 November 2023 to include "dizziness" to the Adverse Reactions section of the EU SmPC and PIL with frequency "rare". The approval of the EU SmPC and PIL including this update was granted on 14 December 2023.

Rapporteur assessment comment:

The ADR of dizziness was recommended to be included to the PI with rare frequency within the previous PSUSA procedure.

The information is acknowledged.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Important identified risks	None
Important potential risks	Vaccine-associated enhanced disease including vaccine associated enhanced respiratory disease Myocarditis and pericarditis
Missing information	Using 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 Interaction with other vaccines Long-term safety

2.2. Signal evaluation

- Tabular overview of signals: new, ongoing or closed during the reporting interval 10/05/2023 to 09/11/2023.

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Allergic including anaphylactic reactions	**05/2023**	**closed**	**08/2023**	**Aggregate PV data**	**Internal qualitative review of weekly Line Listing resulting in signal detected.**	**Aggregate review of internal PV database**	Label Evaluation

Allergic including anaphylactic reactions

There was one signal that was categorized as identified risk (non-important) for COVID-19 vaccine (recombinant, adjuvanted) during the reporting interval. This signal of "Allergic including anaphylactic reaction" was mentioned in Section 14 Late-breaking information of the previous PBRER DLP 09 May 2023 and the conclusion, classification and full safety analysis reported were already submitted to EMA on 03

August 2023 through a Type II variation. The updated RSI was submitted (procedure EMEA/H/C/005754/II/0006) and approved to include anaphylactic reactions and allergic reactions (including rash, rash erythematous, urticaria, angioedema) as listed AEs for COVID-19 vaccine (recombinant, adjuvanted).

Based on medical review of cases of allergic including anaphylactic reactions reported after the use of COVID-19 vaccine (recombinant, adjuvanted), the cumulative weight of evidence is sufficient to support a causal association between allergic including anaphylactic reactions and COVID-19 vaccine (recombinant, adjuvanted). A labeling change evaluation was deemed necessary to include anaphylactic as listed adverse events for COVID-19 vaccine (recombinant, adjuvanted) and was performed through an RSI update. Overall, the benefit-risk ratio of the COVID-19 vaccine (recombinant, adjuvanted) remains favorable in its approved indication under the current recommended conditions of use.

Rapporteur assessment comment:

The MAH provided a safety evaluation report concerning allergic and anaphylactic reactions, which is not reproduced in the AR.

The causal relationship between VidPrevtyn Beta and allergic including anaphylactic reactions was established within the procedure EMEA/H/C/005754/II/0006 and the PI was already updated.

2.3. Evaluation of risks and safety topics under monitoring

Rapporteur assessment comment:

No case reports of the following AESI were reported during the covered period: Guillain-Barré syndrome, Acute Disseminated Encephalomyelitis, Transverse myelitis, Bell's palsy, Narcolepsy, Type 1 Diabetes mellitus, Microangiopathy and thrombotic microangiopathy, Stress cardiomyopathy, Single organ cutaneous vasculitis, Disseminated intravascular coagulation, Cerebral venous sinus thrombosis, Thrombosis with thrombocytopenia syndrome, Neurological AESIs (Neuropathies/Polyneuropathies, Demyelinating disorders including Multiple Sclerosis and Optic neuritis), Meningoencephalitis/encephalitis, Dermatological AESIs (including Chilblains, Erythema Multiforme, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis), Multisystem inflammatory syndrome, Sudden death, Vaccination failure, Sub-acute thyroiditis/auto-immune thyroiditis, Kawasaki disease, Musculoskeletal AESIs (including Rhabdomyolysis and Fibromyalgia), Appendicitis, Gastrointestinal disorders, Heavy menstrual bleeding, Post-orthostatic tachycardia syndrome, Pregnancy related AESIs.

Considering the MAH has requested to withdraw the marketing authorisation of VidPrevtyn Beta with a withdrawal effective date on 18 March 2024, the PRAC Rapp does not request further monitoring of AESI.

2.3.1. Acute aseptic arthritis

2 case reports of potential Acute aseptic arthritis have been reported during the reporting period and cumulatively. Both case reports are presented below.

- Case [redacted] reported from a consumer via [redacted] involved an 80-year-old patient of unknown gender with no reported medical history who developed arthritis 2 days after receiving VidPrevtyn Beta (no information about the symptoms and the joints affected). Concomitant medications included quinine for muscle spasms. Relevant laboratory test results included blood test (negative for

polymyalgia), X-ray for hips and knees (results awaiting) and SARS-CoV-2 test (negative). Past vaccinations were not reported. Outcome was reported as not recovered. Further information on medical history, concurrent conditions at the time of vaccination, past or concomitant medication, current and previous laboratory investigations excluding alternative etiologies 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.

- [redacted] reported from a consumer via [redacted] involved a patient of unknown age and gender, with reported medical history of COVID-19 and ongoing high blood pressure, who experienced arthritis and fatigue 3 days after VidPrevtyn Beta vaccination (no information about the symptoms and the joints affected). Five days following the vaccination, the patient experienced lower respiratory tract infection, and on the next day the patient felt hot. Past vaccinations were not reported. The outcome was reported as recovered. Further information on patient's medical history relevant to arthritis, clinical condition at the time of vaccination, past or concomitant medication and laboratory investigations excluding alternative etiologies 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. Based on the medical review of the case reports, no safety concern has been identified.

  In addition, no increased O/E ratio has been detected for this AESI.

Rapporteur assessment comment:

2 cases of aseptic arthritis were reported during the covered period. Both cases were reported by the consumers who developed arthritis 2 – 3 days after vaccination with VidPrevtyn. No information about the symptoms and their duration were reported as well as no results of the examinations were provided. Outcome was reported as not recovered in one case. The limited information precludes any further assessment of the cases. Of note, arthralgia is a listed ADR of VidPrevtyn Beta.

2.3.2. Rheumatoid arthritis

3 case reports of potential Rheumatoid arthritis (including flare of rheumatoid arthritis) have been reported during the reporting period and cumulatively.

- Case [redacted] reported from a consumer involved a 75-year-old female with ongoing rheumatoid arthritis who experienced a fall, a flare up of rheumatoid arthritis, dizziness, dyspnea, myalgia, arthralgia, malaise, chills, vaccination site pain, fatigue, vaccination site swelling and vaccination site warmth on an unknown date after vaccination with VidPrevtyn Beta. The patient's past vaccinations were not reported. Outcome was reported as unknown. Further information regarding medical history, treatment history, concurrent condition during vaccination, latency between vaccination and event, current condition, details and date of the history of falling and past rheumatoid arthritis flares 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 (nurse) via [redacted] involved a 77-year-old patient of unknown gender with ongoing rheumatoid arthritis who experienced pain at vaccination site, flare up of arthritis symptoms (knees swelling and wrists painful) and extreme fatigue an unknown time after VidPrevtyn Beta vaccination (5th dose). Past vaccinations were unspecified; however, it was mentioned that the patient did not have side effects with previous vaccines. Outcome was reported as unknown for all events. Further information on injection site procedure, medical history, family history, past or concomitant medication and laboratory investigations excluding alternative etiologies 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.

- Case [redacted] reported from a healthcare professional via [redacted] involved a 75-year-old female, with ongoing rheumatoid arthritis who experienced flare of rheumatoid arthritis the same day after vaccination with VidPrevtyn Beta. Patient had a medical history of bronchiectasis, hepatic cyst, cholelithiasis, uterine leiomyoma and ovarian cyst. The patient was treated with codeine for pain, ferrous fumarate, hydroxychloroquine and prednisolone for rheumatoid arthritis. The outcome was reported as recovering /resolving for the event. Approximately 4 months after the vaccination, the patient underwent various laboratory tests including urine (blood urine absent, glucose urine absent, nitrite urine absent, protein urine absent, negative leukocyte test), increased c-reactive protein, abnormal liver function test. No other information was provided. The patient had ongoing condition of rheumatoid arthritis which could play a confounding role for the event. Further information on lifestyle history, family history, past medications, concomitant medications and results of other laboratory investigations are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

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

Rapporteur assessment comment:

3 cases describing flare up of rheumatoid arthritis were reported during the covered period and cumulatively. 2 cases were reported by the HCPs (the MAH specified a nurse as a consumer) and 1 case report was reported by a consumer. No information about dynamics of the rheumatoid arthritis, previous flare ups, results of the examinations and the laboratory results were provided. TTO was provided only in 1 case, the patient experienced flare up at the day of vaccination. O/E ratio is not increased. Based on the cases, the causal relationship between rheumatoid arthritis and VidPrevtyn Beta cannot be established.

2.3.3. (Idiopathic) thrombocytopaenia including Immune thrombocytopaenia and thrombotic thrombocytopenic purpura

2 case reports of potential Idiopathic thrombocytopenia including thrombocytopenia and thrombotic thrombocytopenic purpura have been reported during the reporting period and cumulatively. Both case reports are presented below.

- Case [redacted] reported from an HCP via [redacted] involved a 78-year-old female with past medical history including immunodeficiency, hypothyroidism, atrial fibrillation and cardiac failure, who experienced a blood clot and thrombocytopenia 3 days after vaccination with VidPrevtyn Beta. Patient complained of calf swelling since vaccination. Later she felt sweaty, dizzy and fainted. The lowest patient's platelet count after vaccination was 132 (no measurement units were reported, but probably G/L) and no previous platelet counts are known. D-dimer was "high" but not >4000 ng/mL. Anti-PF4 antibodies dosage was unknown. As per reporter, this case report was not related to possible myocarditis or pericarditis. The diagnosis was suspected deep vein thrombosis. The patient's past medical history of immunodeficiency and current condition of atrial fibrillation and cardiac failure could be confounding factors. Further information on patient's weight and body mass index (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. The case was assessed as BCCD level 4 for thrombosis/thromboembolism.

- Case [redacted] from a pharmacist via [redacted] involved an 86-year-old male who experienced thrombocytopenic purpura 11 days after vaccination with VidPrevtyn Beta. Concomitant medication included dabigatran. The patient was admitted in emergency department and first platelet count was 3 G/L. He was then administered idarucizumab and following (date unknown) platelet count rose to 10 G/L. Patient was then discharged on oral prednisolone, with dabigatran prescription suspended. The patient was not tested for COVID-19 since having the vaccine. At time of reporting, the outcome was recovering for the event. The patient was treated with dabigatran, which may represent a confounding factor. Further information regarding medical history, dabigatran dose and indication, current medications, other risk factors, infectious checkup, complementary 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 excluded. The case has been assessed against the BCCD for thrombocytopenia (2) as level 2.

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

Rapporteur assessment comment:

2 HCP cases of thrombocytopenia and thrombocytopenic purpura were reported during the covered period.

In the first case, a patient experienced thrombocytopaenia (the lowest count was 132) and venous thrombosis. No results of ultrasonography were provided however, the symptoms and the value of D-dimer are suggestive of venous thrombosis. Anti-PF4 antibodies result is not known.

The second case is confounded by the simultaneous use of dabigatran and the lack of information about medical history, previous counts of thrombocytes, laboratory results excluding alternative aetiologies e.g. viral infection precludes any meaningful assessment.

O/E ratio is not increased. Based on the cases, the causal relationship between immune thrombocytopaenia and VidPrevtyn Beta cannot be established.

2.3.4. Heart failure

3 case reports of potential Heart failure have been reported during the reporting period and cumulatively. All case reports are presented below.

- Case [redacted] reported from a consumer involved a 78-year-old male with no reported medical history, who had aches, headache and was fatigued on the same day after vaccination with VidPrevtyn Beta. Patient experienced arrhythmia, malaise, congestive heart failure and COVID-19 an unknown time after vaccination. The patient's past vaccinations and concomitant medications were not reported. Information on corrective treatment not reported and outcome was reported unknown for all events. Further information regarding concurrent condition during vaccination, time to symptoms onset, previous vaccinations tolerance, allergic history, medical and drug history (especially from the cardiological point of view), laboratory investigations (including results of SARS-CoV-2 test) 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. See also Section 13 Arrhythmia.
    - Case [redacted] reported from a consumer via [redacted] involved a 75-year-old male, with reported medical history of immunodeficiency, nephrolithiasis, renal surgery 4 months ago, COVID-19 approximately 9 months ago, hernia repair and thyroid disorder treated conservatively,

who experienced dyspnea, cardiac arrest and respiratory disorder 4 days after vaccination with VidPrevtyn Beta vaccine and was hospitalized. Five days after vaccination, the patient experienced inflammatory marker increased, atrial fibrillation, lung consolidation, pneumonia and sepsis. Congestive cardiac failure was reported 24 days post vaccination. The patient also developed pleural effusion and left ventricular dysfunction an unknown time after vaccination. Relevant laboratory test results included echocardiogram that indicated atrial fibrillation and heart failure, ejection fraction was 35%. The patient was never diagnosed with atrial fibrillation previously. He was fit and strong with no respiratory problems. He never experienced any reaction to previous vaccinations for flu, COVID-19, pneumonia, or any other vaccination. His past medical treatment included simvastatin and fenofibrate. The patient was treated with apixaban, bisoprolol, eplerenone, furosemide, dapagliflozin, candesartan and digoxin. The outcome was reported as unknown for the event pleural effusion and left ventricular dysfunction, recovering for all others. Further information on concomitant medication and current condition precluding 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 was also retrieved for Anaphylaxis (assessed as BCCD level 5 – not a case of anaphylaxis) and for arrhythmia See also Sections 33 Anaphylactic reactions and 13 Arrhythmia.

- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old male with reported medical history of COVID-19 positive approximately 1 year and 1 month before vaccination who experienced dyspnoea and chest pain 3 days after receiving VidPrevtyn Beta vaccine. Patient also experienced fatigue, palpitations, syncope, dilated cardiomyopathy, cardiac failure, left ventricular dysfunction, pneumonia, insomnia, gastrointestinal pain, abdominal distension, peripheral swelling and myocarditis on an unknown date after the vaccination. Before experiencing symptoms, the patient had consultation with a hospital doctor regarding a pharyngeal pouch and its surgery and the patient was advised to wait due to the risks involved. The symptoms of breathlessness were misdiagnosed as a lung infection and treated with antibiotics for two weeks without improvement. The patient was hospitalized and treated for cardiac failure with acetylsalicylic acid, bumetanide, bisoprolol, atorvastatin, candesartan and dapagliflozin. The patient was also treated with doxycycline. The patient underwent various laboratory investigations including angiogram, chest X-ray, computerised tomogram (CT) and ultrasound scan (results unknown for all of these exams). Echocardiogram showed small right ventricular ectopic event and troponin level was unknown, but the diagnosis was dilated cardiomyopathy. Outcome was reported as recovering for dyspnoea and unknown for rest of the events. Patient's past vaccinations included unspecified SARS-CoV-2 vaccine and he had a minor reaction to first COVID vaccination that lasted one evening (feeling of extreme tiredness only) and did not experience any reaction to the previous mRNA COVID booster vaccinations. Further information on medical history, concomitant medication, current condition, details of the events and the results of previous and latest 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 has been assessed against BCCD for myocarditis as level 4 (3). See also Section 16.3.1.1 Myocarditis/Pericarditis in the body of the document.

Additionally, one case report ([redacted]) from a literature article from [redacted] (Winchester J. Acute or chronic? Failing left ventricle in a 34 year old. Journal of the Intensive Care Society. 2023;24(1):114-5) reported left ventricular failure as well as dilated cardiomyopathy, sinus tachycardia, pulmonary oedema, pleural effusion and suspect myocarditis in a 34-year-old male on an unknown date after receiving a COVID-19 vaccine from an unknown manufacturer. He was treated with

angiotensin-converting-enzyme (ACE) inhibitors and beta-adrenergic blockade and recovered. See also Sections 13 Arrythmia and 15 Myocarditis.

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

Rapporteur assessment comment:

3 cases of heart failure were reported during the covered period and cumulatively. All of them were reported by the consumers. 2 case reports are unassessable due to lack of information as TTO, medical history, concomitant medication, laboratory results and investigations, therapy and outcome. The last case report is confounded by sepsis, which preceded occurrence of heart failure in a patient with not specified immunodeficiency and no information about laboratory results and results of further investigations were provided. In addition, the MAH provided one literature case of heart failure without specification of COVID-19 vaccine and other considerable details. O/E ratio is not increased. Based on the cases, the causal relationship between heart failure and VidPrevtyn Beta cannot be established.

2.3.5. Arrhythmia

6 case reports of potential Arrythmia have been reported during the reporting period and 12 case reports have been reported cumulatively. All case reports are presented below.

- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old male with history of prostate problems who experienced coldness in the evening of the vaccination, chest pain in the next day, heart racing and irregular pulse after vaccination with VidPrevtyn Beta. Pneumonia was diagnosed via X-ray. COVID-19 virus test was reported as positive on an unknown date. Outcome was reported as not recovered for coldness, chest pain, heart racing and irregular pulse and was recovering for pneumonia. Pneumonia was in a context of COVID-19 test positive shortly after COVID-19 vaccination cannot be considered as vaccination failure. Further information regarding concurrent conditions, previous vaccinations, concomitant medication and tolerance and investigations for the reported event are needed to fully assess this case.
- Case [redacted] reported from HCP via [redacted] involved an unknown elderly patient who reported atrial fibrillation, dyspnoea, palpitations and tachycardia. The case is unassessable due to insufficient information provided.
- Case [redacted] reported from a consumer via [redacted] involved an 84-year-old patient of unknown gender with no reported medical history who developed cardiac flutter, dizziness, dyspnoea, wheezing, headache, malaise, injection site pain and fatigue same day after vaccination with VidPrevtyn Beta. Patient's past vaccinations were not reported. The outcome was reported as recovering. Although this seems an allergic reaction to the vaccination, 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.
- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old female with ongoing multiple sclerosis who experienced irregular heart rate, pain in extremity and malaise on the same day after vaccination with VidPrevtyn Beta. Past medications included beta interferon. Patient's past vaccinations were not reported. The outcome was reported as not recovered. Although this seems to be an allergic reaction to the vaccination, 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 upon the reported information, the role of the individual suspect vaccine cannot be assessed.

- Case [redacted] reported from an HCP via [redacted] involved a 78-year-old female, with past medical history of thrombocytopenia (approximately 5 years ago), who experienced atrial fibrillation (confirmed by electrocardiogram) on the day of vaccination with VidPrevtyn Beta. Concomitant medications included amlodipine, atorvastatin and ramipril for hypertension. Last electrocardiogram (ECG) performed 2 months before the vaccination, did not show any sign of atrial fibrillation. The patient's past vaccinations included flu vaccine and Comirnaty 6 months before this vaccination. At time of reporting, the outcome was not recovered for the event. Based on the limited information provided regarding this case, causal role of the company suspect product cannot be excluded. Case will be re-evaluated post further update on the patient's underlying disease conditions, past medical and drug history, concurrent illnesses. Also, patient's past medical history included thrombocytopenia and change of medication for hypertension which could be confounding factor for the event occurrence.

- Case [redacted] received from a consumer via [redacted] involved an 80-year-old female who experienced shortness of breath, heart racing and irregular heart rate 2 days after vaccination with VidPrevtyn Beta. It was not reported if the patient received a corrective treatment. The outcome was reported as recovered. Further information on allergy history, previous laboratory investigations and autopsy results, patient's 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.

- Case [redacted] reported from a consumer via [redacted] involved an 80-year-old male who experienced atrial fibrillation 5 days after vaccination with VidPrevtyn Beta. After the vaccination the patient felt achy, nauseous and slightly dizzy for several days and then, on day 5, he suffered from a new and severe episode of atrial fibrillation with very high heart rate and chaotic pulse. The patient's heart did not return to normal until approximately 5pm on day 6. As per reporter, this case report was not related to possible myocarditis or pericarditis. A corrective treatment (heart monitoring and administration of drugs) was received for the event. At the time of reporting, the outcome was recovered with sequelae. Based on the limited information provided regarding this case, the causal role of the company suspect product cannot be excluded. Case will be re-evaluated post further update on the patient's underlying disease conditions, past medical and drug history, concurrent illnesses and concomitant medications.

- Case [redacted] reported from a consumer involved a 78-year-old male, with no reported medical history, who had aches, headache and was fatigued on the same day after vaccination with VidPrevtyn Beta. The patient experienced arrhythmia, malaise, congestive heart failure, and COVID-19 an unknown time after vaccination. The patient's past vaccinations and concomitant medications were not reported. Information on corrective treatment not reported and outcome was reported unknown for all events. Further information regarding concurrent condition during vaccination, time to symptoms onset, previous vaccinations tolerance, allergic history, medical and drug history (especially from the cardiological point of view), laboratory investigations (including results of SARS-CoV-2 test) 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. See also Section 11 Heart failure.

- Case [redacted] reported from an HCP via [redacted] involved an 81-year-old female with no reported medical history, who experienced paroxysmal atrial fibrillation 7 days after the administration of VidPrevtyn Beta vaccine. Reportedly, the patient attended Accident and emergency department and complained of lightheadedness on an unknown date after vaccination.

The outcome was reported as recovered. Further information on patient's medical and drug history (especially from the cardiological point of view), clinical condition at the time of vaccination, concomitant medications 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.

- Case [redacted] reported from an HCP via [redacted] involved a male of unknown age with medical history of COVID-19 who experienced upper abdominal pain on the same day of VidPrevtyn Beta vaccine administration. The patient was in bed for a week then collapsed and was admitted to hospital for another week with fatigue, dyspnea, syncope, dizziness, cough, orthostatic hypotension after an unknown latency post-vaccination. He was diagnosed with uncontrolled atrial fibrillation and acute kidney injury. Concomitant medications included atenolol, aspirin and a statin. Corrective treatment was edoxaban and bisoprolol for atrial fibrillation. Outcome was reported as recovering for atrial fibrillation and unknown for the other events. As per reporter, this case report was not related to possible blood clots or low platelet counts and was related to possible myocarditis or pericarditis. Further information on patient's medical and drug history, concurrent conditions at the time of vaccination, allergy history, laboratory investigation and imaging exams 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. The case report was assessed as BCCD level 4 for myocarditis/pericarditis (3). See also Section 24 Acute kidney injury.
- Case [redacted] reported from a consumer via [redacted] involved a 75-year-old male with reported medical history of immunodeficiency, nephrolithiasis and renal surgery 4 months ago, COVID-19 approximately 9 months ago, hernia repair and thyroid disorder treated conservatively, who experienced dyspnea, cardiac arrest and respiratory disorder 4 days after vaccination with VidPrevtyn Beta and was hospitalized. Five days after vaccination, the patient experienced inflammatory marker increased, atrial fibrillation, lung consolidation, pneumonia and sepsis. Congestive cardiac failure was reported 24 days post vaccination. The patient also developed pleural effusion and left ventricular dysfunction an unknown time after vaccination. Relevant laboratory test results included echocardiogram that indicated atrial fibrillation and heart failure, ejection fraction was 35%. The patient was never diagnosed with atrial fibrillation previously. He was fit and strong with no respiratory problems. He never experienced any reaction to previous vaccinations for flu, COVID-19, pneumonia, or any other vaccination. His past medical treatment included simvastatin and fenofibrate. The patient was treated with apixaban, bisoprolol, eplerenone, furosemide, dapagliflozin, candesartan and digoxin. The outcome was reported as unknown for the event pleural effusion and left ventricular dysfunction, recovering for all others. Further information on concomitant medication and current condition precluding 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 per BCCD for anaphylaxis as not a case of anaphylaxis (level 5). See also Sections 33 Anaphylactic reactions and 11 Heart failure.
- Case [redacted] reported from a consumer via [redacted] involved a 77-year-old male with ongoing hypertension and hypercholesterolaemia who experienced fatigue, paraesthesia, dry mouth, irregular heartbeat, dysphonia, disturbance in attention and anxiety within 24 hours of VidPrevtyn Beta vaccination. Concomitant medication included bendroflumethiazide and losartan for hypertension and simvastatin for hypercholesterolaemia. Past vaccinations were not reported. The outcome was reported as not recovered for all the events. Further information on patient's clinical condition at the time of vaccination, injection site and localization of paraesthesia, past medication, previous vaccinations and tolerance, and laboratory investigation 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. See also Section 29 Paresthesia.

Additionally, one case report ([redacted]) from a literature article from [redacted] (Winchester J. Acute or chronic? Failing left ventricle in a 34 year old. Journal of the Intensive Care Society. 2023;24(1):114-5) reported sinus tachycardia as well as dilated cardiomyopathy, left ventricular failure, pulmonary oedema, pleural effusion and suspect myocarditis in a 34-year-old male on an unknown date after receiving a COVID-19 vaccine from an unknown manufacturer. He was treated with ACE inhibitors and beta-adrenergic blockade and recovered. See also sections 11 Heart failure and 15 Myocarditis.

Based on the medical review of the case reports, no safety concern has been identified. In addition, increased O/E ratio has been detected for this AESI (Refer to Appendix 6.3.2).

Rapporteur assessment comment:

6 cases of arrhythmia were reported during the covered period and 12 cases were reported cumulatively. 8 cases were reported by patients and 4 cases were reported by HCPs. Most of the patient case reports does not include information about results of investigations, concomitant medications. Medical history was not reported in 5 cases. It is not fully clear if the patients attended a physician to establish a diagnosis of arrhythmia or if they only experienced palpitations in some cases. Pneumonia was established in one patient, which was COVID-19 positive. In one cases, cardiac failure and atrial fibrillation was reported in a patient with not specified immunodeficiency who experienced sepsis. Regarding the HCP cases, medical history of patients was not provided in 3 cases. In the last case, a patient suffered from hypertension, which is a known risk factor for occurrence of atrial fibrillation.

O/E ratio is not increased. Based on the cases, the causal relationship between arrhythmias and VidPrevtyn Beta cannot be established.

2.3.6. Coronary artery disease (including Myocardial infarction)

1 case report of potential Coronary artery disease (including Myocardial infarction) were reported in the period, 2 case reports have been reported cumulatively. The case reported in the reporting period is presented below.

- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old male with medical history of gout, Barrett's oesophagus, tendonitis, inflammatory bowel disease and ongoing type 2 diabetes mellitus and arthritis, who experienced malaise 2 days after vaccination with VidPrevtyn Beta. His health deteriorated in the following days, and he experienced hyperhidrosis and decreased appetite (latency: 3 days), liver injury (latency: 4 days), dizziness, disorientation, hypervolaemia (latency: 19 days), myocardial infarction (latency: 20 days), dyspnoea and asthenia an unknown time after vaccination. Relevant laboratory test results included echocardiogram (no results available), scan (shadow on liver, heart not working as it should, due to excess fluid built up and suspected mild heart attack due to fluid). Concomitant medications included, pregabalin, metformin, linagliptin, lansoprazole, fexofenadine, atorvastatin, allopurinol and ferrous fumarate. The patient's past vaccinations included 5 COVID-19 Vaccines including one from Moderna. Patient was treated with 2 saline drips and vitamin K injections for liver injury. The outcome was recovering for malaise, asthenia, dyspnoea, hypervolaemia, myocardial infarction, recovered for hyperhidrosis, decreased appetite, not recovered for the event liver damage and unknown for dizziness and disorientation. Patient's ongoing condition of type 2 diabetes mellitus might be a contributing factor. Further information on current condition

at time of vaccination and laboratory investigations results (especially liver function tests and cardiac enzymes level) 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. See also Section 23 Acute liver injury.

Of note, case [redacted] reported in the previous PBRER was followed-up to obtain all available details including clinical course, results of the performed examinations and diagnosis, however, no new follow-up information has been received for this case report.

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

Rapporteur assessment comment:

1 consumer case was reported during the covered period. No information about laboratory tests and other examinations was provided.

The MAH tried to follow-up a case ([redacted]) reporting myocardial infarction with non-obstructive coronary arteries however, no new information was obtained. O/E ratio is not increased. Based on the available information, the causal relationship between coronary artery disease and VidPrevtyn Beta cannot be established.

2.3.7. Myocarditis/Pericarditis

One case reporting potential Myocarditis was reported during the reference period, 2 case reports have been received cumulatively.

Myocarditis/pericarditis is considered an important potential risk.

- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old male with medical history of COVID-19 positive approximately one year and one month before vaccination who experienced dyspnea and chest pain three days after receiving VidPrevtyn Beta. The patient also experienced fatigue, palpitations, syncope, dilated cardiomyopathy, cardiac failure, left ventricular dysfunction, pneumonia, insomnia, gastrointestinal pain, abdominal distension, peripheral swelling and myocarditis on an unknown date after the vaccination. Before experiencing the symptoms, the patient had consultation with a hospital doctor regarding a pharyngeal pouch and its surgery and the patient was advised to wait due to the risks involved. The symptoms of breathlessness were misdiagnosed as a lung infection and treated with antibiotics for two weeks without improvement. The patient was hospitalized and treated for cardiac failure with acetylsalicylic acid, bumetanide, bisoprolol, atorvastatin, candesartan and dapagliflozin. The patient was also treated with doxycycline. The patient underwent various laboratory investigations including angiogram, chest X-ray, computerized tomogram and ultrasound scan (results unknown for all of these exams). Echocardiogram showed small right ventricular ectopic event and troponin level was unknown, but the diagnosis was dilated cardiomyopathy. The outcome was reported as recovering for dyspnea and unknown for the rest of the events. Patient's past vaccinations included unspecified SARS-CoV-2 vaccine and patient had a minor reaction to the first COVID vaccination that lasted one evening (feeling of extreme tiredness only) and did not experience any reaction to the previous mRNA COVID booster vaccinations. Further information on medical history, concomitant medication, current condition, details of the events and the results of previous and latest 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 has been assessed against the BCCD for myocarditis as level 4.

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

Of note, despite efforts to obtain the follow-up information for the case report of myocarditis ([redacted]) presented in the previous PBRER, no new follow-ups have been received for this case report.

Two case reports of potential myocarditis have been reported with a COVID-19 vaccine from an unknown manufacturer:

One case report ([redacted]) from a literature article from [redacted](Winchester J.Acute or chronic? Failing left ventricle in a 34 year old. Journal of the Intensive Care Society. 2023;24(1):114-5) reported a suspect myocarditis as well as dilated cardiomyopathy, sinus tachycardia, left ventricular failure, pulmonary oedema, and pleural effusion in a 34-year-old male on an unknown date after receiving a COVID-19 vaccine from an unknown manufacturer. A potential diagnosis of vaccination-associated myocarditis was considered, but in view of the low troponin, the presentation was felt most likely to represent decompensated chronic dilated cardiomyopathy. He was treated with ACE inhibitors and beta-adrenergic blockade and recovered. See also sections 11 Heart failure and 13 Arrhythmia. Although this literature report was published in April 2023, it includes the abstracts from the Intensive Care Sociate State of the Art (SOA) 2022 Congress, conducted in Belfast from 28 June to 01 July 2022; therefore any use of VidPrevtyn Beta in this patient can be reasonable excluded.

The other case report ([redacted]) was reported from a study in a literature article from[redacted] (Aprile M, Cutore L, Sambataro D, Sambataro G, Colaci M. Adverse events after vaccination for SARSCOV2 in a case series of fibromyalgia patients versus healthy controls. Annals of the Rheumatic Diseases 2023 ;82 Suppl 1:1916-7) presenting a case report of myocarditis in a patient with fibromyalgia. No details about the patient, latency or outcome are available. This literature report was published in May 2023 and originated from a study with 6-month follow-up; it is therefore highly unlikely that this participant could have received VidPrevtyn Beta.

Rapporteur assessment comment:

One consumer case was reported during the covered period where dilatated cardiomyopathy, left ventricular dysfunction and several ADRs from other organ systems were reported. No laboratory results and conclusions of other investigations were provided. This case is unassessable.

The MAH provided information that no further information was obtained for the case of myocarditis ([redacted]) reported in the previous period despite of their effort. The information is acknowledged.

In addition, the MAH discussed two cases of myocarditis from the literature article, where not specified COVID-19 vaccines where administrated. O/E ratio is not increased. Based on the available information, the causal relationship between myocarditis/pericarditis and VidPrevtyn Beta cannot be established.

2.3.8. Venous thromboembolism (including Pulmonary embolism and Deep vein thrombosis)

11 case reports of potential Venous thromboembolism (including Pulmonary embolism, Deep vein thrombosis and stroke) were reported in the reporting period, 23 case reports were reported cumulatively.

Of note, to ensure a broad review of all potential Venous thromboembolism events, "SMQ (N) Embolic and thrombotic events, venous" has been updated by integrating the SMQ (N) "Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous" in the search strategy for retrieving all potential case reports. They have been assessed against the BCCD for thrombosis/thromboembolism. Therefore, 13 cases included in this analysis are also included in the O/E analysis for haemorrhagic stroke and ischemic stroke.

The following case reports have been reported during the reporting period and cumulatively:

- 1 case report of Pulmonary embolism (2 case reports cumulatively),

- 1 case report of Deep vein thrombosis (2 case reports cumulatively),

- 1 case of Pulmonary thrombosis (1 case report cumulatively),

- 1 case of Monoparesis (1 case report cumulatively),

- 7 cases of different stroke types (13 case reports cumulatively):

- 4 cases of Cerebrovascular accident (10 case reports cumulatively)

- 1 case of Cerebral ischemia (1 case reports cumulatively)

- 1 case of Hemorrhagic stroke (1 case reports cumulatively)

- 1 case of Cerebral infarction (1 case reports cumulatively).

Additionally, 1 case of potential Cerebral venous sinus thrombosis (none during the reporting period) and 3 case reports of potential Thrombosis (none during the reporting period) have been reported cumulatively.

Seven (7) cases of stroke retrieved by the MedDRA search strategy for Venous thromboembolism (including Pulmonary embolism and Deep vein thrombosis) reported during the reporting period are presented in Section 19 Stroke. The remaining 4 case reports of potential Venous thromboembolism (including Pulmonary embolism and Deep vein thrombosis) reported during the reporting period are presented below.

- Case [redacted] reported from an HCP via [redacted] involved a 96-year-old female with medical history of deep vein thrombosis and lower respiratory tract infection, who experienced infectious pleural effusion 4 days after receiving VidPrevtyn Beta. Reportedly, the patient also had lower respiratory tract infection 5 days after the vaccination and dyspnoea, pulmonary embolism and peripheral swelling on an unknown date after the vaccination. The patient's past medical treatment included anticoagulants. Concomitant medications included bimatoprost, escitalopram, and mirtazapine. The outcome was reported as recovered with sequelae for infectious pleural effusion and unknown for others. Further information regarding allergy history, time of respiratory and thrombotic symptoms onset, results of imaging studies and previous laboratory investigations (with particular regard to D-dimer and platelets count) precluding 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 was assessed as BCCD level 3 for thrombosis/thromboembolism.

- Case [redacted] reported from a consumer via [redacted] involved an 82-year-old female with no reported medical history who experienced pulmonary thrombosis and infection 6 days after receiving VidPrevtyn Beta vaccine. Reportedly, the patient also had dyspnoea and was diagnosed with pulmonary embolism. Concomitant medications included omeprazole, atorvastatin, losartan and indapamide. The outcome was reported as recovering. Further information regarding concurrent condition during vaccination, tolerance, allergic history, medical history, thrombosis risk factors, laboratory investigations (in particular, D-dimer dosing and platelets count), and imaging exams 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. The case was assessed as BCCD level 4 for thrombosis/thromboembolism.
- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old male with medical history of COVID-19 positive 1 month 12 days ago, previous tobacco use and ongoing chronic obstructive pulmonary disease, who developed dyspnoea (blood oxygen saturation 88-93%) and deep vein thrombosis 21 and 29 days, respectively, after receiving VidPrevtyn Beta vaccine. Patient also developed pain in extremity, peripheral swelling, erythema and fatigue on an unknown day after vaccination. The patient's past vaccination included COVID-19 vaccine Moderna. Relevant laboratory test results included no evidence of low blood pressure, prostatic specific antigen 1.73 (no units reported), ultrasound doppler (right lower limb revealed a popliteal deep vein thrombosis). The patient was treated with apixaban for deep vein thrombosis and prednisolone for dyspnoea. The outcome was reported as recovering for dyspnoea, not recovered for the event peripheral swelling and unknown for all other events. Ongoing chronic obstructive pulmonary disease and prompt response to prednisolone administration may account for a different cause for the reported dyspnea. Further information regarding current condition at time of vaccination including concomitant medications, medical and drug history 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 in the pathogenesis of the reported deep vein thrombosis cannot be assessed. This case was assessed as a definitive case of thrombosis, according to BCCD level 1 for thrombosis/thromboembolism.
- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old male with reported medical history of COVID-19, aortic stenosis, periarthritis, ongoing hypertension and hypercholesterolaemia, who experienced fatigue (latency: 6 days), right arm paresis (monoparesis) (latency: 11 days), hypertension and pyrexia (latency: 14 days), and vaccination site rash 25 days after receiving VidPrevtyn Beta vaccine. Patient also experienced vaccination site movement impairment, vaccination site joint pain, insomnia, rash pruritic, hyperhidrosis, myalgia and malaise an unknown time after the vaccination. Concomitant medication included amlodipine for hypertension and rosuvastatin for hypercholesterolaemia. Relevant laboratory test results included blood culture (negative), blood tests (White Blood Count 14.5G/L, no neutrophilia), c-reactive protein (169mg/L), heart rate (tachycardia, 107 beats per minute) and limb X-ray (calcific tendinosis). Past vaccinations included COVID-19 vaccine Astra Zeneca. Outcome was reported as recovered for all events. Patient's history of periarthritis is a major confounding factor for the reported monoparesis. Further information on allergy history, past medications, precise localization and etiology of reported periartrithis, vaccination injection site, and 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 was assessed as BCCD level 4 for thrombosis/thromboembolism.

Additionally, one case report ([redacted]) from a literature article from [redacted] (Bryan P, Williams N, Haebich G. A case of suspected COVID-19 vaccine-induced antiphospholipid syndrome. British Journal of Dermatology 2023 ;188(4):iv18) reported subcutaneous thrombosis in the context of antiphospholipid syndrome in a 50-year-old patient about 2 weeks after receiving a second dose of COVID-19 vaccine from an unknown manufacturer.. Since this case occurred after primary vaccination, and the authors referred to a possible mechanism linked with mRNA platform, it is highly unlikely that this patient received Vidprevtyn Beta.

Based on the medical review of interval and cumulative data, no safety concern has been identified. In addition, no increased O/E ratio has been detected for the AESI of venous thromboembolism.

Rapporteur assessment comment:

The MAH added SMQ Embolic and thrombotic events for search of all potential venous thromboembolism events which revealed 18 reported cases during the covered period. Out of them, 4 cases concerned venous thromboembolism. Other cases are discussed in the section 2.3.9. (Stroke) of the AR.

3 cases were reported by the consumers and 1 case was reported by an HCP. In the HCP case, a patient with medical history of DVT experienced infectious pleural effusion, infection of lower respiratory tract, dyspnoea, pulmonary embolism and peripheral swelling. TTO was reported only for pleural effusion (4 days) and for lower respiratory tract (5 days). TTO of pulmonary embolism and peripheral swelling was not specified. The patient used anticoagulants in the past and it is not clear, when were stopped. Additionally, no information about laboratory results and results of other investigations was provided. The case lacks substantial information precluding in depth assessment.

The first consumer case concerns a patient who had a positive COVID-19 test approx. one month ago. COVID-19 disease is an alternative aetiology of DVT in this case. No information about concomitant medications, possible risk factors and laboratory results was provided. In the second consumer case, a patient reported pulmonary thrombosis and pulmonary embolism. Concomitant medications are suggestive for hypercholesterolaemia and hypertension in the medical history. No information about laboratory results and results of other investigations was provided. In the last case, a patient experienced monoparesis with latency of 11 days, but no other detail suggesting venous thromboembolism were provided. O/E ratio is not increased. Based on the available information, the causal relationship between venous thromboembolism and VidPrevtyn Beta cannot be established.

2.3.9. Stroke

9 new case reports and 2 follow-ups of potential Stroke were reported in the reporting period, 15 case reports have been reported cumulatively. Seven (7) of the 9 stroke cases reported during the reporting period (13 of the 15 cases reported cumulatively) have also been retrieved in the search for Venous thromboembolism (refer to section 18 Venous thromboembolism (including Pulmonary embolism and Deep vein thrombosis). All the cases were assessed against the BCCD for thrombosis/thromboembolism.

The 9 new case reports and 2 follow-ups are presented as follows:

- 2 case reports reported Hemorrhagic stroke (2 case reports cumulatively),

- 5 case reports (and 1 follow-up) reported Ischemic stroke (8 case reports cumulatively),

- 2 case reports (and 1 follow-up) reported a stroke where the type of stroke was not specified, and from the provided information it was not possible to identify it (5 case reports cumulatively).

To be noted that the 5 cases of unknown type stroke have been included in the O/E analysis for both stroke types, hemorrhagic and ischemic, as a conservative approach.

2.3.9.1. Haemorrhagic stroke

5 case reports of potential Hemorrhagic stroke were reported during the reporting period, 12 have been reported cumulatively. However, 10 of the 12 cumulative cases were also retrieved in the search strategy for Ischemic stroke. After medical review of the case reports, 5 of the 10 cases were considered as potential case reports of ischemic stroke (2 case reports reported during the reporting period), and for the remaining 5 case reports (2 case reports reported during the reporting period) the type of stroke could not be identified form available data. These case reports are presented in Section 19.3 Unknown type of stroke. In total, 2 case reports of potential Hemorrhagic stroke were considered during the reporting period and cumulatively and are presented below.

- Case [redacted] reported from an HCP via [redacted] involved a 78-year-old male with no reported medical history who developed hemorrhagic stroke 3 days after receiving VidPrevtyn Beta and was hospitalized. Reportedly, a CT of thorax discovered a bilateral pulmonary embolism 33 days after receiving the vaccination. The platelet count was not <150 G/L. Past vaccinations were not reported. Outcome was reported as recovering. Further information on medical history, past or concomitant medication, current condition at time of vaccination, clinical presentation of the reported event, results of imaging studies confirming the presence of the reported hemorrhagic stroke, laboratory tests results excluding alternative etiologies for the reported event, and in-hospital clinical management of patient, are needed to fully assess this case. Based upon the limited 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] reported from an HCP via MHRA, involved a 94-year-old female with reported medical history of sinus node dysfunction (dual chamber cardiac pacemaker inserted) and ongoing rheumatoid arthritis, hypothyroidism and hypertension, who developed pneumonia 14 days after receiving VidPrevtyn Beta. Patient also developed subdural haematoma and seizure 1 month following the vaccination and died 1 month 8 days after vaccination. Concomitant medications included folic acid, methotrexate, furosemide, levothyroxine, ferrous fumarate for iron deficiency anaemia, and omeprazole. Patient's past vaccinations included Comirnaty (5 vaccines). Relevant investigations included chest X-ray (evidence of bronchopneumonia and lung oedema), blood tests (raised inflammation markers) and computerised tomogram (acute right sided subdural haematoma). The patient was treated with sulfamethoxazole, trimethoprim and doxycycline for lower respiratory tract infection. No autopsy was done. The cause of death was reported as subdural haematoma, pneumonia and seizure. The seizure in this patient is most probably the result of the subdural haematoma. However, further information on clinical presentation of the reported events, laboratory investigations and imaging studies results excluding alternative etiologies for the reported events are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. The case was assessed as BCCD level 4 for generalized convulsions (reported seizure event, with no information about loss of consciousness).

Based on the cumulative medical review of the case report, no safety concern was identified. In addition, no increased O/E has been detected for hemorrhagic stroke.

Rapporteur assessment comment:

Discrepancy in number of stroke cases were observed in the previous PSUR. Therefore, the MAH provided an overview of stroke cases reported cumulatively. 16 cases were reported cumulatively and based on the medical review 2 cases were considered haemorrhagic stroke, 8 cases were considered ischaemic stroke and 5 cases were established as not specified type of stroke. The MAH specified that the medical review was performed to establish a type of stroke. The discrepancy in the previous PSUR was apparently caused by double-counting of some cases in the calculation of O/E ratio for haemorrhagic stroke as well as for ischaemic stroke.

2 cases of haemorrhagic stroke were reported by the HCPs during the covered period and cumulatively.

In the first case, a patient experienced haemorrhagic stroke with TTO 3 days and pulmonary embolism with TTO 33 days. Thrombocytopaenia was not observed. No details were provided, this case is unassessable. In the second case, which was of fatal outcome, a patient with cardiac pacemaker, hypertension, hypothyroidism and rheumatoid arthritis who used several medications including methotrexate experienced pneumonia and subdural haematoma. Thrombocytopaenia is a known ADR of methotrexate. It is not clear, if complete blood count was performed, only raised inflammation markers were described. O/E ratio is not increased. Based on the available information, the causal relationship between haemorrhagic stroke and VidPrevtyn Beta cannot be established.

2.3.9.2. Ischemic stroke

7 new cases and 1 follow-up of potential Ischemic stroke case reports were reported during the reporting period, 13 have been reported cumulatively. After medical review, for 2 of the 7 cases reported during the reporting period (5 of the 13 cumulative case reports), the type of stroke could not be identified and they are presented in Section describing unknown type of stroke.

In total, 5 new case reports and 1 follow-up of potential Ischemic stroke reported during the reporting period are presented below.

- Case [redacted] reported from a consumer via [redacted] involved a 77-year-old male, with past medical history including stroke (12 years ago), aortic regurgitation, type B aortic dissection, right sided weakness, use of 10 alcohol units per week and arterial disorder, who experienced transient ischemic attack (TIA), speech disorder and abnormal thinking one day after vaccination with VidPrevtyn Beta. At the time of the event, the patient had ongoing hypertension. Concomitant medications included bisoprolol, lansoprazole, finasteride, citalopram, losartan, atorvastatin, COD-liver oil, vitamins and losartan. Relevant laboratory test results included blood cholesterol 4.1 mmol/L, blood pressure 130/74 mmHg, glycosylated haemoglobin 46 mmol/L, heart rate 55 beats/min. ECG showed sinus bradycardia with first degree atrioventricular block. MRI head showed a large right parapharyngeal mass lesion measuring approximately 5.6 cm. This most likely represented an exophytic deep lobe right parotid salivary neoplasm. The differential diagnosis would have included a schwannoma arising from the mandibular division. Treatment for TIA included aspirin, clopidogrel and atorvastatin. The patient's past medical history of arterial disorders and stroke are confounding factors. Further information on allergy history, past medical history (with particular regard to cardiac history), previous laboratory investigations precluding 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 was assessed as BCCD level 3 for thrombosis/thromboembolism.
- Case [redacted] reported from an HCP via [redacted] involved a 78-year-old female with no reported medical history, who developed cerebral ischemia 1 month 3 days after the administration of

VidPrevtyn Beta vaccine and was hospitalized. Reportedly, the patient had right sided facial droop, heaviness to right side of the body and altered sensation to right arm. Relevant laboratory test results included blood cholesterol (result not provided), head computerised tomogram (no evidence of acute pathology), glycosylated haemoglobin (result not provided), head MRI (confirmed diagnosis of left sided acute infarct). Concomitant medications included plantago ovata, lansoprazole, and mirabegron. Outcome was reported as recovering. Further information on medical history, thrombosis risk factors and concurrent conditions precluding 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 was assessed against BCCD for thrombosis/thromboembolism as level 1.

- Case [redacted] reported from an HCP via [redacted] involved a male of unknown age with ongoing hypertension and atrial fibrillation who developed cerebrovascular accident 7 days after receiving VidPrevtyn Beta. Reportedly, he was admitted with left sided weakness, seizure and slurred speech. There was not any previous venous or arterial thrombosis. The patient had no confirmed or suspected autoimmune or inflammatory disease, including vasculitis and no history of current malignancy. The lowest platelet count after vaccine was 148 G/L. Patient had melaena while on apixaban but no source of bleeding found on flexible sigmoidoscopy and computerized tomography of abdomen and pelvis showed diffuse diverticulosis. The patient had no history of intracranial malignancy and intracranial infections, no recent surgical or medical interventions to the central nervous system (including lumbar puncture), no recent trauma or head injury. Other relevant laboratory test results included activated partial thromboplastin time (28.3s), head CT (ischemic stroke), MRI (ischemic stroke) and prothrombin time (12.7s). Concomitant medications included unspecified antihypertensive tablets and anticoagulants for atrial fibrillation. Past vaccinations were not reported. Outcome was reported as not recovered. Further information on atrial fibrillation time of onset and management, other thrombosis risk factors, 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. The case report was assessed as BCCD level 1 for thrombosis / thromboembolism.
- Case [redacted] reported from an HCP via [redacted] and involved a patient of an unknown age/gender with reported medical history of prostate cancer, transitional cell carcinoma, cognitive disorder and asthenia who developed cerebrovascular accident 8 days after receiving VidPrevtyn Beta vaccine. Patient was admitted with right facial droop and slurred speech and had poor swallowing. Patient had multi-embolic stroke on both hemispheres, more on the left. Normal sinus rhythm on ECG. Relevant laboratory test results included activated partial thromboplastin time (29.7s), platelet count (196 G/L), prothrombin time (11.7s) and MRI head (cerebrovascular accident). Patient was a non-smoker and needed assistance with personal activities of daily living. Past vaccinations were not reported. Outcome was reported as not recovered. Further information on patient's age, past and concomitant medications, current oncologic status at time of vaccination, previous vaccinations, and other thrombosis risk factors 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] reported from an HCP via MHRA involved a 90-year-old female with ongoing rheumatoid arthritis, malignant neoplasm, atrial fibrillation, hypertension and chronic kidney disease who experienced SARS-CoV-2 infection and cerebral infarction 10 days after receiving VidPrevtyn Beta vaccine and subsequently died. Reportedly, patient was admitted with right sided limb weakness, aphasia, aspiration, possibly new atrial fibrillation on ECG and was thrombolyzed. Concomitant medications included methotrexate for rheumatoid arthritis and omeprazole for gastroesophageal reflux disease. Patient's past vaccinations included 4 Comirnaty vaccines, 1 bivalent

Spikevax vaccine and Seqirus vaccines influenza. Relevant laboratory test results included head computerized tomogram (stroke- loss of the grey-white matter differentiation involving left insular and left frontal lobe, in keeping with areas of evolving left middle carotid artery territory infarction. Increased attenuation seen within M1 portion of left middle carotid artery in keeping with thrombus), SARS-CoV-2 test (positive). The patient was treated with apixaban for thrombosis. Autopsy information not reported. Patient had an ongoing malignant neoplasm and a SARS-CoV-2 infection, both of which are major confounding factors for the reported event. Further information regarding clinical picture and current health including status of atrial fibrillation, hypertension and malignant neoplasm at time of onset are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. The case was assessed against BCCD for thrombosis/thromboembolism as level 1. Refer also to Table 1 of fatal cases in Appendix 5.4.2.

- Follow-up on the case [redacted] reported in the previous PBRER was received in the reporting period. The case was reported from an HCP via [redacted] and involved a 78-year-old female patient, with ongoing TIA (1 month prior to vaccination) experienced stroke and dyspraxia one day after vaccination with VidPrevtyn Beta (her 5th dose). The patient's concurrent conditions included class III obesity, palpitations and hypertension. Patient's past vaccinations included 3 doses of Comirnaty, 1 dose of Bivalent Spikevax and 1 dose of Moderna vaccine. As per reporter, this case report was related to possible blood clots or low platelet counts and not related to possible myocarditis or pericarditis. Platelet count, D-dimer and anti-PF4 antibodies dosing results were not reported. Concomitant medications included atorvastatin for TIA, clopidogrel, diltiazem for palpitations, flucloxacillin for cellulitis, lansoprazole and ramipril for hypertension. Patient had neither any previous reactions to medications, especially heparin or anticoagulants, nor a history of, or current, malignancy. She had not confirmed or suspected autoimmune or inflammatory disease, including vasculitis. Relevant laboratory test results done before vaccination included blood culture positive for streptococcus dysgalactiae and computerised tomogram head normal. Three days after vaccination, patient's MRI head showed acute lacunar infarct. The patient had SARS-COV-2 test positive 1 day after vaccination. At the time of reporting, the outcome was not recovered. Further information on etiology of palpitations, family history, thrombosis risk factors and previous events, current ongoing treatments, laboratory results and examinations conducted 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 fully assessed in the occurrence of stroke in this patient with pre-existing conditions (TIA). Based on the additional information received in the follow-up, the BCCD assessment changed from level 4 to level 1 for thrombosis/thromboembolism.

Cumulatively, among the 8 potential cases of Ischemic stroke, 6 of them have been assessed as BCCD level 1 for thrombosis/thromboembolism, and 2 as level 3. Seven (7) of the 8 patients reported potential confounding factors/underlying diseases/alternative explanation for stroke such as hypertension, cancer, TIA/stroke and heart rhythm disorders. In addition, all patients were elderly (in 2 patients the exact age was unknown). One (1) of the 8 case reports had insufficient information on medical history or ongoing conditions for a proper assessment of the case. No specific pattern has been observed from these data.

Based on the cumulative medical review of the case report, no safety concern was identified. In addition, no increased O/E ratio has been detected for ischemic stroke (Refer to Appendix 6.3.2).

Rapporteur assessment comment:

5 cases of ischemic stroke were reported during the covered period and 8 cases were reported cumulatively. Regarding the cases reported during the period, 1 case was reported by a consumer and 4 cases were reported by the HCPs. In the consumer case, a patient with medical history of stroke (12 years ago), hypertension, which is currently balanced, experienced TIA one day after vaccination with VidPrevtyn Beta. MRI revealed parapharyngeal mass of diameter approx. 5,6 cm. The role of the mass in

occurrence of TIA was not discussed. The first HCP case lacks important information for the assessment, medical history was not provided as well as laboratory results and eventual risk factors for ischemic stroke. Stroke was confirmed on MRI. In the second HCP case a patient with atrial fibrillation and hypertension in medical history, which constitute the risk factors for ischaemic stroke, experienced cerebrovascular accident 7 days after administration of Vidprevtyn Beta. Ischaemic stroke was confirmed on CT scan. In the third case, an oncologic patient of unknown age experienced cerebrovascular accident 8 days following administration of VidPrevtyn Beta. Stroke was confirmed on MRI, however other eventual risk factors were not discussed. Several confounding factors are described in the last case, i.e. atrial fibrillation, hypertension, SARS-CoV-2 infection.

In addition, the MAH was requested to follow-up a case [redacted] which was described in the previous PSUR. A 78-year-old female 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 was not known. The details about type of stroke (lacunar infarct) and the laboratory result (positive SARS-CoV-2 test 1 day after vaccination) were completed.

O/E ratio is not increased. Based on the available information, the causal relationship between haemorrhagic stroke and VidPrevtyn Beta cannot be established.

2.3.9.3. Unknown type stroke

2 new case reports and 1 follow-up of potential Unknown type stroke were reported during the reporting period, 5 have been reported cumulatively. The cases reported in the reporting period (including the follow-up) are presented below.

- Case [redacted] reported from an HCP via [redacted] involved a 92-year-old female with no reported medical history who developed cerebrovascular accident 8 hours after receiving VidPrevtyn Beta and was hospitalized. Past vaccinations were not reported. Outcome was reported as not recovered. Further information regarding type of cerebrovascular accident (ischaemic or hemorrhagic), concurrent condition during vaccination, previous vaccinations and tolerance, medical and drug history, thrombosis or haemorrhage risk factors, laboratory investigations and imaging exams results excluding alternative etiologies for the reported event are needed to fullyassess 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 4 for thrombosis/thromboembolism.
- Case [redacted] reported from a consumer via [redacted] involved a 78-year-old male with reported medical history of COVID-19 positive, who experienced cerebrovascular accident 18 days after receiving VidPrevtyn Beta. The patient's past medical treatment included bisoprolol and amlodipine, but patient's blood pressure has been controlled to an average of 143/80 with a pulse of 60 prior to the stroke. The patient had a healthy lifestyle with golf and gym twice a week. Past vaccinations were not reported. The outcome was reported as recovered with sequelae. Although hypertension as a risk factor for stroke could be a confounding factor, further information on previous vaccination, medical history, clinical status before vaccination and previous laboratory investigations 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.
- Follow up of the case [redacted] presented in the previous period was received during the reporting period. The case was reported by an HCP and involved a patient of unknown age and gender, with no reported medical history, who experienced a stroke within minutes after vaccination with VidPrevtyn Beta. Upon follow up, no outcome was formally reported, however, it was reported

that events "were not vaccine-related as initially suspected". This new information has not impacted the previous assessment since insufficient information has been provided for a proper assessment of the case report and of the role of the vaccine. Further information on patient's age, gender, past medical history, allergy history, thrombosis risk factors, current medications, medical diagnosis including stroke type (ischaemic or haemorragic), condition at the time of reported event, laboratory and imaging investigations 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. The new information in the follow-up does not change the previous assessment of the case (BCCD level 4 for thrombosis/thromboembolism).

Based on the cumulative medical review of the case report, no safety concern was identified. As mentioned previously, the 5 cumulative case reports of unknown type stroke have been included in the O/E analysis of both, Ischemic stroke and Hemorrhagic stroke, as a conservative approach. No increased O/E ratio has been detected for any of the stroke types.

Rapporteur assessment comment:

2 case reports and 1 follow-up case of stroke of unknown origin were reported during the covered period. All cases lack substantial information precluding in-depth assessment. The MAH confirmed that all cases of unknown strokes were included in O/E analysis for haemorrhagic stroke as well as for ischaemic stroke.

2.3.10. Cerebral venous sinus thrombosis

No case report of potential Cerebral venous sinus thrombosis were reported during the reporting period, one case report with fatal outcome has been reported cumulatively.

Of note, despite follow-up of case report [redacted] to obtain as much as possible available information, no additional information was received.

Based on the cumulative medical review of the case report, no safety concern was identified. In addition, no significant O/E ratio increase has been detected for this AESI using a reporting rate of 100% or 50% (meaning that only 50% of the cases were reported).

O/E ratio and its 95% confidence interval for UK - DLP: 09 November 2023

RR 100%			UK				
Cerebral venous sinus thrombosis	Spain_BIFAP_PC	Doses	Primary Risk Window				
			Expected	Observed	OE	95% CI	95% CI
	IR per 100 000 person years		RW: 28 days	RW: 28 days		Lower bound	Higher bound
0-17	0.22	15	0	0	0	-	3688.879
18-29	0.3	180	0	0	0	-	3688.879
30-39	0.36	378	0	0	0	-	3688.879
40-49	0.25	912	0	0	0	-	3688.879
50-59	0.29	2768	0.001	0	0	-	3688.879
60-69	0.37	15966	0.005	0	0	-	737.776
70-79	0.16	893046	0.11	1	9.091	0.23	50.651
80+	0.32	1199195	0.294	0	0	-	12.547
ALL AGES	-	2112460	0.409	1	2.445	0.062	13.623

RR 50%			UK				
Cerebral venous sinus thrombosis	Spain_BIFAP_PC	Doses	Primary Risk Window				
			Expected	Observed	OE	95% CI	95% CI
	IR per 100 000 person years		RW: 28 days	RW: 28 days		Lower bound	Higher bound
0-17	0.22	15	0	0	0	-	3688.879
18-29	0.3	180	0	0	0	-	3688.879
30-39	0.36	378	0	0	0	-	3688.879
40-49	0.25	912	0	0	0	-	3688.879
50-59	0.29	2768	0.001	0	0	-	3688.879
60-69	0.37	15966	0.005	0	0	-	737.776
70-79	0.16	893046	0.11	1.5	13.636	0.981	58.33
80+	0.32	1199195	0.294	0	0	-	12.547
ALL AGES	-	2112460	0.409	1.5	3.667	0.264	15.688

One case report ([redacted]) from a literature article from [redacted](Danish F, Rabani AE, Subhani F, Yasmin S, Koul SS, Amer M. IVIG for vaccine-induced immune thrombotic thrombocytopenia (VITT). European Stroke Journal. 2023;8(2):568) reported potential cerebral venous thrombosis (CVT) and thrombosis with thrombocytopenia syndrome (TTS) in a patient of unknown age and gender on an unknown time after receiving a COVID-19 vaccine from an unknown manufacturer. The patient was treated with intravenous immunoglobulin for TTS. The outcome was unknown for CVT and not recovered for TTS. See also Section 21 Thrombosis with thrombocytopenia syndrome (TTS). However, this conference abstract was based on a systematic review of literature (secondary use of data). Although the references of original studies are not provided, based on the search frame I PubMed (from March 2020 to December 2022), it is highly unlikely that this patient could receive VidPrevtyn Beta.

Rapporteur assessment comment:

No case of cerebral sinus thrombosis was reported during the reporting period and 1 case ([redacted]) was reported cumulatively. In this case, a 78-year-old female experienced CVST 2 days after administration of VidPrevtyn Beta. In the medical history, there was COVID-19 approx. 3 months ago, use of aspirin and TIA approx. 2 years ago. No further information was obtained by the MAH despite of follow-up. O/E ratio is raised only due to this not well documented case.

2.3.11. Acute liver injury

One case report of potential Acute

liver injury has been reported during the reporting period and cumulatively.

- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old male with medical history of gout, Barrett's oesophagus, tendonitis, inflammatory bowel disease and ongoing type 2 diabetes mellitus and arthritis, experienced malaise 2 days after vaccination with VidPrevtyn Beta vaccine. His health deteriorated in the following days, he experienced hyperhidrosis and decreased appetite (latency: 3 days), liver injury (latency: 4 days), dizziness, disorientation, hypervolaemia (latency: 19 days), myocardial infarction (latency: 20 days), dyspnoea and asthenia an unknown time after vaccination. Relevant laboratory test results included echocardiogram (no results available), scan (shadow on liver, heart not working as it should, due to excess fluid built up and suspected mild heart attack due to fluid). Concomitant medications included pregabalin, metformin, linagliptin, lansoprazole, fexofenadine, atorvastatin, allopurinol and ferrous fumarate. The patient's past vaccinations included 4 SARSCoV-2 vaccine and COVID-19 Vaccine Moderna. Patient was treated with 2 saline drips and vitamin K injections for liver injury. The outcome was recovering for malaise, asthenia, dyspnoea, hypervolaemia, myocardial infarction; recovered for hyperhidrosis, decreased appetite; not recovered for the event liver damage, and unknown for dizziness and disorientation. Patient's ongoing condition of type 2 diabetes mellitus might be a contributing factor. Further information on current condition at time of vaccination, and laboratory investigations results (especially liver function tests and cardiac enzymes level) 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. See also Section 14 Coronary artery disease (including Myocardial infarction) of Appendix 5.4.1.

Based on medical review of the data, no safety concern has been identified. In addition, no increased O/E ratio has been detected for this AESI.

Rapporteur assessment comment: *1 consumer case of liver injury was reported during the covered period and cumulatively. The lack of information precludes any in-depth assessment.* *O/E ratio is not increased. Based on the available information, the causal relationship between liver injury and VidPrevtyn Beta cannot be established.*

2.3.12. Acute kidney injury (including glomerulonephritis)

2 case reports of potential Acute kidney injury (including glomerulonephritis) were reported in the period and cumulatively.

- Case [redacted] reported from an HCP via [redacted] involved a male of unknown age with medical history of COVID-19 who experienced upper abdominal pain on the same day of VidPrevtyn Beta administration. The patient was in bed for a week then collapsed and was admitted to hospital for another week with fatigue, dyspnea, syncope, dizziness, cough, orthostatic hypotension after an unknown latency post-vaccination. He was diagnosed with uncontrolled atrial fibrillation and acute kidney injury. Concomitant medications included atenolol, aspirin and a statin. Corrective treatment was edoxaban and bisoprolol for atrial fibrillation. Outcome was reported as recovering for atrial fibrillation and unknown for the other events. As per reporter, this case report was not related to possible blood clots or low platelet counts and was related to possible myocarditis or pericarditis. Further information on patient's medical and drug history, concurrent conditions at the time of vaccination, allergy history, laboratory investigation and imaging exams 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.

- Case [redacted] reported from an HCP via [redacted], involved an 84-year-old male with no reported medical history who experienced minimal lesion glomerulonephritis 16 days after VidPrevtyn Beta (dose 5) and Spikevax (reported to be administered concomitantly) vaccinations. Patient also experienced pemphigoid and oedema peripheral an unknown time after vaccination. The patient's past vaccinations included Comirnaty (three doses) and COVID-19 vaccine Moderna. Concomitant medications included calcium carbonate, bumetanide, famotidine, and unspecified proton pump inhibitors. The patient was treated with prednisolone for minimal lesion glomerulonephritis. Outcome was reported as recovering for minimal lesion glomerulonephritis and unknown for others. Further information on patient's medical history, tolerance to previous vaccines, time to onset of reported pemphigoid, results of histopathologic exams of the skin and of the kidney and any other 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.

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

Rapporteur assessment comment:

2 cases of AKI were reported during the covered period and cumulatively. Both cases lack important information precluding in-depth assessment. In the HCP case, the symptoms of minimal change disease and medical history of the patient were not provided as well as laboratory results and results of other investigations.

O/E ratio is not increased. Based on the available information, the causal relationship between haemorrhagic stroke and VidPrevtyn Beta cannot be established.

2.3.13. Seizures

2 case reports of potential Seizures were reported during the reporting period, 7 case reports have been reported cumulatively. All these cases were reported as serious with no fatal outcome being reported. Five (5) of these cases were reported in the elderly population and the age group was unknown in the remaining 2 cases. All cases were reported through [redacted], 3 initially from consumers and 4 initially from HCPs. All these cases were assessed as per the BCCD for seizures (1 has been assessed as level 2 and 6 cases have been assessed as level 4 for generalized convulsions. Two case reports reported during the reporting period are presented below.

- Case [redacted] reported from a consumer via [redacted] involving an unknown age male, with ongoing well controlled background epilepsy, who experienced seizure few days after the administration of VidPrevtyn Beta. Past vaccinations were not reported. Outcome was reported as recovered. Patient's medical history of epilepsy is an alternative explanation. Further information on patient's age, occurrence of loss of consciousness during the reported event, past or concomitant medication, assumption of concomitant substances at risk for seizures induction, previous vaccinations and tolerance and laboratory investigation 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 MHRA, involved a 94-year-old female with reported medical history of sinus node dysfunction (dual chamber cardiac pacemaker inserted) and ongoing rheumatoid arthritis, hypothyroidism and hypertension, who developed pneumonia 14 days after receiving VidPrevtyn Beta vaccine. Patient also developed subdural haematoma and seizure 1 month

following the vaccination and died 1 month 8 days after vaccination. Concomitant medications included folic acid, methotrexate, furosemide, levothyroxine, ferrous fumarate for iron deficiency anaemia, and omeprazole. Patient's past vaccinations included Comirnaty (5 vaccines). Relevant investigations included chest X-ray (evidence of bronchopneumonia and lung oedema), blood tests (raised inflammation markers) and computerized tomogram (acute right sided subdural haematoma). The patient was treated with sulfamethoxazole, trimethoprim and doxycycline for lower respiratory tract infection. No autopsy was done. The cause of death was reported as subdural haematoma, pneumonia and seizure. The seizure in this patient is most probably the result of the subdural haematoma. However, further information on clinical presentation of the reported events, laboratory investigations and imaging studies results excluding alternative etiologies for the reported events are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. The case was assessed as BCCD level 4 for generalized. Refer also to Section 19 Hemorrhagic stroke and Table 1 of fatal cases in Appendix 5.4.2.

Of note, despite the follow-up of the case [redacted] reported in the previous PBRER, no new follow-up information has been received for this case report. Respiratory arrest and seizures occurred 10 minutes after vaccination with VidPrevtyn Beta, adrenaline was administrated for query of anaphylaxis and the patient was intubated and transferred to emergency. The case report was assessed as BCCD Level 4 for generalized convulsions. It was not retrieved in the line listing as a potential case of anaphylactic reactions as it did not fulfill the SMQ Anaphylactic reaction (algorithmic) criteria.

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:

2 cases of seizures were reported during the period (1 HCP case, 1 consumer case), 7 cases were reported cumulatively. All cases are serious. Seizures occurred in elderly in 5 cases. 3 cases were reported by the consumers and 4 cases by the HCPs.

In a consumer case reported during the current period, seizure occurred in a patient who suffered from epilepsy few days after administration of VidPrevtyn Beta. No details were provided. The HCP case was already discussed in the section 2.3.9.1 Haemorrhagic stroke. The patient also experienced pneumonia and subdural haematoma. Subdural haematoma was probably the cause of seizure. The patient used several medications including methotrexate which is known to cause thrombocytopaenia. It is not clear, if complete blood count was performed, only raised inflammation markers were described in the case.

The MAH tried to follow-up a case [redacted]) of respiratory arrest and seizures which was reported during the previous period, however no new information was retrieved.

O/E ratio is not increased. Based on the available information, the causal relationship between seizures and VidPrevtyn Beta cannot be established.

2.3.14. Dizziness

12 case reports were reported during the period (4 serious and 8 non-serious) and 1 follow-up ([redacted]) with no additional safety information. Fifty-two (52) case reports of dizziness were reported cumulatively (54 events).

As part of close monitoring of events requested by EMA Committee for Medicinal Products for Human Use Assessment Report (10 November 2022), a medical review of all post-marketing cases reporting dizziness is being conducted on an ongoing basis. To further characterize the occurrence and context of reported dizziness after the use of VidPrevtyn Beta, a detailed medical review of all reported dizziness case reports (Data Lock Point (DLP) 30 June 2023) was finalized in September 2023. This analysis included 50 of the 52 cumulative post-marketing cases reports. It is available in Appendix 6.3.3. The conclusion was in alignment with the previous analysis' conclusions presented in the previous PBRER and is the following:

Based on medical review of cases of dizziness reported after the use of VidPrevtyn Beta, the cumulative evidence is considered not evocative of a causal association between dizziness as an isolated event and VidPrevtyn Beta. The collected evidence is in favor of an association between dizziness and the vaccination act itself (with no regard to the injected product) as part of procedure-related psychogenic reactions. Nonetheless, "anxiety-related reactions" are already mentioned in section 4.4 §3 of the Summary of Product Characteristics of VidPrevtyn Beta. See also Sections 4 and 16.3.3 in the body of the document.

The PRAC Rapporteur agreed that the most often co-reported reactions can occur as the symptoms of the immunisation-stress related reaction already included in the product information of the vaccine. However, it was notified that co-reported symptoms except dyspnoea are also the expected reactogenicity reactions already listed for VidPrevtyn Beta. Delayed time to onset arguing against psychogenic reaction or other symptoms of reactogenicity were reported in 21/50 cases. In addition, it was noted that dizziness is a listed reaction for other COVID-19 vaccines including recombinant, adjuvanted vaccine Bimervax. Considering 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, in which 2 events of dizziness were observed, the PRAC Rapporteur proposed to include dizziness to the product information with frequency "rare".

As of PBRER DLP, 2 additional non-serious cases of dizziness ([redacted], [redacted]) have been reported after the DLP of the medical review of dizziness case reports, 30 June 2023; these new cases are not impacting the conclusions of the medical review since in both cases insufficient information was provided for a complete assessment. However, the PRAC Rapporteur request to include dizziness to the product information with frequency "rare" is ongoing.

The 2 additional case reports are presented below:

- Case [redacted] reported from a consumer via [redacted] involved a 48-year-old female with no reported medical history who experienced dizziness 1 day after administering VidPrevtyn Beta. Reportedly, the patient felt lightheaded when standing, ears feel like they have popped also go hot when lightheaded. The outcome was reported as not recovered.
- Case [redacted] reported from an HCP via [redacted] involved a patient of unknown age and gender with no reported medical history who experienced dizziness the same day post administering VidPrevtyn Beta. Reportedly, the patient felt woozy and flushed. The patient was given chlorphenamine and the outcome was reported as not recovering at the time of reporting.

Of note, despite the follow-up of the case report [redacted] presented in the previous PBRER to obtain as much as possible information for the possibility of a meaningful assessment, only one nonsignificant follow-up of this case report has been received with no new safety information and no change of the case causality assessment. Additionally, no follow-up of the case [redacted] of dizziness presented in the previous PBRER has been received.

Additionally, 2 case reports of dizziness were reported with a COVID-19 vaccine from an unknown manufacturer:

- Case [redacted] reported from a consumer via [redacted] involved a 41-year-old male who experienced dizziness as well as feeling jittery, feeling of body temperature change, hyperhidrosis, chills, pyrexia, lethargy, headache, chest discomfort, terminal insomnia, mobility decreased, fatigue, impaired work ability, and had therapeutic product effect incomplete on an unknown date after vaccination. The outcome was reported as not recovered.

- Case [redacted] reported from a consumer via [redacted] involved a 63-year-old male who experienced dizziness, as well as dysgeusia, parosmia, movement disorder, panic reaction, abnormal behaviour, illness, pain in extremity, vomiting, arthralgia, headache, back pain, injection site mass and influenza like illness on the same day of vaccination with an unknown COVID-19 vaccine and an influenza vaccine, and 4 days after starting teriparatide for osteoporosis. The outcome was reported as unknown. See also section 32 Anosmia and ageusia.

Rapporteur assessment comment:

2 cases of dizziness were reported during the period. In the cases, dizziness occurred at the day of vaccination and 1 day after vaccination resp., the outcome was reported as not recovered. The MAH also made the follow-ups of two cases reported during the previous period, however, no new important information was obtained. Dizziness is a listed ADR with frequency of rare.

2.3.15. Paraesthesia

One case report of potential paraesthesia has been reported during the reporting period and cumulatively.

- Case [redacted] reported from a consumer via [redacted] involved a 77-year-old male with ongoing hypertension and hypercholesterolaemia who experienced fatigue, paraesthesia, dry mouth, irregular heartbeat, dysphonia, disturbance in attention and anxiety within 24 hours of VidPrevtyn Beta vaccination. Concomitant medication included bendroflumethiazide and losartan for hypertension and simvastatin for hypercholesterolaemia. Past vaccinations were not reported. Outcome was reported as not recovered for all the events. Further information on patient's clinical condition at the time of vaccination, injection site and localization of paraesthesia, past medication, previous vaccinations and tolerance and laboratory investigation 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. See also Section 13 Arrhythmia.

No safety concern has been identified from these data.

Rapporteur assessment comment:

1 case of paraesthesia was reported during the period and cumulatively. In the case, paraesthesia occurred within 24 hours after vaccination. Several other adverse events were reported. The outcome was reported as not recovered at the time of reporting. No important safety information was identified.

2.3.16. Acute Respiratory Distress Syndrome

One case report and 1 follow-up of potential Acute Respiratory Distress Syndrome were reported during the reporting period. Cumulatively, 3 serious case reports have been identified (1 case of respiratory arrest ([redacted]) also reported hypersensitivity manifestations, 1 case of respiratory arrest

([redacted]) also reported seizures, and 1 case of respiratory failure ([redacted]) also reported pneumonia.

Case reports (including the follow-up) received during the reporting period are presented below:

- Case [redacted] reported from HCP via MHRA involved a 90-year-old male, with reported medical history of gravitational oedema, skin ulcer, osteoarthritis and chronic kidney disease, who died due to respiratory failure and pneumonia 25 days after receiving VidPrevtyn Beta. Patient also had urinary tract infection, incontinence, dysuria and confusional state 22 days after the vaccination and asthenia 26 days after the vaccination. Patient was treated with antibiotics for urinary tract infection and urine analysis was normal. Concomitant medications included codeine, omeprazole, and paracetamol. Patient's past vaccinations included 5 bivalent Comirnaty vaccines. Autopsy information was not reported. Further information on clinical presentation of the reported event, laboratory investigations (of note, results of SARS-CoV-2 test, if performed) and imaging studies results, and autopsy exam 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.
- Follow-up of the case report [redacted] reported from an HCP via [redacted] involved a 93- year-old female with medical history of left ventricular dysfunction, fall, acute myocardial infarction and syncope, who experienced back pain, eye movement disorder, respiratory arrest and red face a couple of minutes after receiving VidPrevtyn Beta vaccine. She was laid down, feet were elevated, and she recovered 10 minutes later. Relevant test results included: systolic blood pressure measurement (180 mmHg), heart rate (90 beats/min), oxygen saturation (99 %) and SARS-CoV-2 test (negative). At the time of the event, the patient had ongoing shellfish allergy, hypertension and osteoarthritis. Concomitant medications included macrogol, potassium and sodium chloride, sodium bicarbonate, hydroxocobalamin, senna, loratadine, zopiclone, paracetamol, and lansoprazole. The patient's past vaccinations included Spikevax, Seqirus influenza vaccines, Comirnaty, and Astrazeneca COVID-19 vaccine (2 doses). Outcome was reported as recovered on the same day. Further information regarding tolerance of previous vaccinations 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 was assessed as BCCD level 3 for anaphylaxis.

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

Rapporteur assessment comment:

One fatal case of acute respiratory distress syndrome and one follow-up case were reported during the period. In the new case, a patient experienced urinary tract infection, pneumonia, and cardiac arrest. No details were provided. The MAH made the follow-ups of both cases reported during the previous period, however, no new important information was obtained.

O/E ratio is not increased. Based on the available information, the causal relationship between ARDS and VidPrevtyn Beta cannot be established.

2.3.17. Anosmia, ageusia

3 case reports of potential anosmia and ageusia were reported during the reporting period and 5 have been reported cumulatively. All case reports are presented below:

- Case [redacted] reported from a consumer via [redacted] involved a 79-year-old female with medical history of intestinal failure and immunodeficiency who experienced dysgeusia within

minutes of VidPrevtyn Beta vaccination and parosmia 2 days following the vaccination. Patient was receiving electroporation for ongoing vaginal cancer. Patient's past medical treatment included total parenteral nutrition and saline intravenously. Past vaccinations were not reported. Outcome was reported as recovered for dysgeusia on the same day and not recovered for parosmia. Further information regarding patient's current clinical conditions and concomitant medications 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 an HCP via [redacted] involved a 77-year-old patient of unknown gender with no reported medical history who experienced malaise on the same day of vaccination and dizziness, ageusia, fatigue and arthralgia 2 days after vaccination with VidPrevtyn Beta. Patient's past vaccinations were not reported. The outcome was reported as recovering for malaise, fatigue and arthralgia, and not recovered for dizziness and ageusia. Further information regarding patient's medical history, clinical 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] involved a 77-year-old male with no reported medical history, who experienced tinnitus, ocular hypertension, parosmia and cluster headache one day after vaccination with VidPrevtyn Beta. Patient's past vaccinations were not reported. At time of reporting, the outcome was recovering for cluster headache and not recovered for the rest of the events. Further information on patient's past medical history, concomitant medication, concurrent conditions excluding alternative aetiologies for the reported events 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 involved an 80-year-old male with a reported medical history of sepsis, high cholesterol and ongoing high blood pressure, who developed cough, intense oropharyngeal pain, feeding disorder, productive cough, asthenia, ageusia, anosmia and rhinorrhoea 1 month 6 days after receiving VidPrevtyn Beta. SARS-CoV-2 test was negative 15 days after vaccination. Concomitant medications included ramipril, atorvastatin, doxazosin. The patient's past vaccinations included Moderna and Pfizer COVID-19 vaccines. The patient was treated with paracetamol and cough pastilles. The outcome was reported as recovered for all events. Additional information regarding patient's treatment history, clinical condition at the time of vaccination, concomitant medications and laboratory tests result excluding other predisposing aetiologies would be needed for complete assessment of the case. Based upon the reported information, the role of the suspect vaccine cannot be assessed.
- Case [redacted] reported from a consumer involved a 75-year-old female with reported medical history of hysterectomy and ongoing high blood cholesterol, who developed productive cough 1 month 7 days after vaccination with VidPrevtyn Beta. The patient also experienced oropharingeal pain, feeding disorder, upper abdominal pain, abdominal discomfort, productive cough, asthenia, ageusia, anosmia, rhinorrea and aphonia an unknown time after vaccination with VidPrevtyn Beta. SARS-CoV-2 test was negative 20 days after the vaccination. Concomitant medications included clonidine and simvastatin. The patient's past vaccinations included Moderna and Pfizer COVID-19 vaccines (did have a sore arm after these injections). The patient was treated with paracetamol for all the events and cough pastilles for cough. The outcome was reported as recovering for all events. Additional information regarding patient's treatment history, clinical condition at the time of vaccination and laboratory tests results 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.

Cumulatively, 8 events of Anosmia/ageusia have been reported in 5 case reports (ageusia n=3, dysgeusia n=1, anosmia n=2 and parosmia n=2). Events were experienced mostly within 2 days after vaccination (n=4) to 1 month (n=2), unknown time to onset for 2 events. The outcome was reported as recovered for half of the events (n= 4), recovering for 2, and not recovered for 2 events. Important information about the patients' clinical status and investigations excluding or confirming other etiologies are missing for a complete assessment of the case reports.

One case ([redacted]) reported from a consumer via [redacted] involved a 63-year-old male who experienced dysgeusia and parosmia as well as dizziness, movement disorder, panic reaction, abnormal behaviour, illness, pain in extremity, vomiting, arthralgia, headache, back pain, injection site mass and influenza like illness on the same day of vaccination with a COVID-19 vaccine from an unknown manufacturer, and an influenza vaccine, and 4 days after starting teriparatide for osteoporosis.

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

Rapporteur assessment comment:

3 cases of anosmia and ageusia were reported during the covered period. 5 cases were reported cumulatively of which 4 cases were reported by the consumers and 1 case was reported by the HCP.

In 2 cases, productive cough, oropharyngeal pain, and rhinorrhoea also occurred at the time, when the patients experienced ageusia and anosmia. SARS-CoV-2 test was negative in one case and no details about investigations were provided in another case. Considering all symptoms, viral illness is an alternative explanation of anosmia and ageusia in these cases.

In the rest of cases, anosmia and ageusia occurred within 2 days after vaccination with VidPrevtyn Beta and was not recovered at the time of reporting except for one case in which outcome of dysgeusia was reported as recovered and outcome of parosmia as recovered. No details about concomitant medications and laboratory results were provided.

O/E ratio is not increased. Based on the available information, the causal relationship between anosmia and ageusia and VidPrevtyn Beta cannot be established.

2.3.18. Anaphylactic reactions

Utilizing the surveillance activities the MAH has determined that there was new relevant safety information that would have an impact on the understanding and characterization of the previously recognized potential risk of anaphylactic reactions. Please refer to SER in Appendix 5.3. (Signal evaluation is not reproduced in the AR)

On 14 May 2023, a safety signal "allergic including anaphylactic reactions" has been detected and the conclusion was the following:

- Based on medical review of cumulative data, the weighted cumulative evidence was considered sufficient to support a causal association between COVID-19 vaccine (recombinant, adjuvanted) and allergic including anaphylactic reactions. The RSI was updated to appropriately reflect the accumulating postmarketing safety data. The updated RSI was submitted (procedure EMEA/H/C/005754/II/0006) and approved to include anaphylactic reactions and allergic reactions (including rash, rash erythematous, urticaria, angioedema) as listed AEs for COVID-19 vaccine (recombinant, adjuvanted).

- As of PBRER DLP, three additional case reports and one follow-up of a previously reported case report of potential anaphylactic reactions, and five additional case reports of potential cases of angioedema were received after the DLP of the SER. The conclusion of the analysis remains unchanged.

Based on the MedDRA search criteria SMQ Anaphylactic reaction Algorithmic, 3 new case reports and 1 follow-up of a previously reported case report of potential Anaphylactic reactions were retrieved on the period, 8 case reports have been reported cumulatively with none met the BCCD level 1 or 2 of certainty for anaphylaxis.

The signal of allergic including anaphylactic reactions (presented in Late breaking information Section of the previous PBRER) was confirmed as an "identified" risk for VidPrevtyn Beta during the reporting period. It is further presented in Section 16.1.1. Signals categorized as potential or identified risk in the body of the document. The Safety Evaluation Report (SER) for this signal with the DLP of 17-May- 2023 is provided in Appendix 5.3. Case reports (including follow-ups) received after this DLP are presented below:

- Case [redacted] reported from a consumer involved a 76-year-old male, with ongoing hypertension and atrial fibrillation, who experienced myocardial ischaemia, circulatory collapse, dyspnea and had sudden death within 48 hours after receiving VidPrevtyn Beta. Patient had a medical history of angina. Concomitant medications included ramipril, edoxaban, diltiazem, atorvastatin and doxazosin. Post-mortem examination showed severe atherosclerosis of all three major coronary arteries cardiomegaly. There was a recognised risk of sudden cardiac death with this degree of ischaemic heart disease. Patient's past vaccinations include Comirnaty (4 doses) and Spikevax bivalent original/omicron vaccine. Further information on medical history, current condition, clinical presentation at the time of the reported event, previous laboratory investigations and autopsy results, 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. The case was assessed as BCCD level 5 for anaphylaxis.
- Case [redacted] reported from a consumer via [redacted] involved a 75-year-old male, with a medical history of immunodeficiency, nephrolithiasis and renal surgery 4 months ago, COVID-19 approximately 9 months ago, hernia repair and thyroid disorder treated conservatively, who experienced dyspnea, cardiac arrest and respiratory disorder 4 days after vaccination with VidPrevtyn Beta and was hospitalized. Five days after vaccination, patient experienced inflammatory marker increased, atrial fibrillation, lung consolidation, pneumonia and sepsis. Congestive cardiac failure was reported 24 days post vaccination. Patient also developed pleural effusion and left ventricular dysfunction an unknown time after vaccination. Relevant laboratory test results included echocardiogram that indicated atrial fibrillation and heart failure, ejection fraction was 35%. The patient was never diagnosed with atrial fibrillation previously. Patient was fit and strong with no respiratory problems. He never experienced any reaction to previous vaccinations for flu, COVID-19, pneumonia, or any other vaccination. His past medical treatment included simvastatin and fenofibrate. The patient was treated with apixaban, bisoprolol, eplerenone, furosemide, dapagliflozin, candesartan and digoxin. Outcome was reported as unknown for the event pleural effusion and left ventricular dysfunction, recovering for all others. No results of lab tests provided. Further information on concomitant medication and current condition precluding 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 per BCCD for anaphylaxis as not a case of anaphylaxis (level 5).

- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old male with medical history of COVID-19 positive 1 month 12 days prior, ex-tobacco user and ongoing chronic obstructive pulmonary disease (COPD), who developed dyspnoea (blood oxygen saturation 88-93%) and deep vein thrombosis respectively 21 and 29 days after receiving VidPrevtyn Beta vaccine. Patient also developed pain in extremity, peripheral swelling, erythema and fatigue an unknown latency after vaccination. The patient's past vaccination included COVID-19 vaccine Moderna. Relevant laboratory test results included no evidence of low blood pressure, prostatic specific antigen (1.73), ultrasound doppler (right lower limb revealed a popliteal deep vein thrombosis). The patient was treated with apixaban for deep vein thrombosis and prednisolone for dyspnea. Outcome was reported as recovering for dyspnea; not recovered for the event peripheral swelling and unknown for all other events. New follow-up information received allows to assess the reported case as a definitive case of thrombosis, according to BCCD. Ongoing COPD and prompt response to prednisolone administration may account for a different cause for the reported dyspnea. Further information regarding current condition at time of vaccination including concomitant medications, medical and drug history 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 in the pathogenesis of the reported deep vein thrombosis cannot be assessed. This case was assessed as BCCD for anaphylaxis as not a case of anaphylaxis (level 5).
- Follow-up of the case [redacted] received during the period that was presented in the SER was reported from an HCP via [redacted] and involved a 93-year-old female with medical history of left ventricular dysfunction, fall, acute myocardial infarction and syncope, who experienced back pain, eye movement disorder, respiratory arrest and red face a couple of minutes after receiving VidPrevtyn Beta. She was laid down, feet were elevated, and she recovered 10 minutes later. Relevant test results included: systolic blood pressure measurement (180 mmHg), heart rate (90 beats/min), oxygen saturation (99 %) and SARS-CoV-2 test (negative). At the time of the event, the patient had ongoing shellfish allergy, hypertension and osteoarthritis. Concomitant medications included macrogol, potassium and sodium chloride, sodium bicarbonate, hydroxocobalamin, senna, loratadine, zopiclone, paracetamol, and lansoprazole. The patient's past vaccinations included Spikevax, Seqirus influenza vaccines, Comirnaty and Astrazeneca COVID-19 vaccine (2 doses). The outcome was reported as recovered on the same day. Further information regarding tolerance of previous vaccinations 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 was assessed as BCCD level 3 for anaphylaxis. See Section 30 Acute respiratory distress syndrome.

The medical review of the new cases not included in the previous analysis of the case reports of anaphylactic reactions in the SER and of the new follow-up information, does not change the conclusion of the SER. No significant O/E ratio increase has been detected for this AESI using a reporting rate of 100%. However, a significant O/E ratio increase has been detected considering a reporting rate of 50% (meaning that only 50% of the cases were reported).

RR 100%	UK						
Anaphylaxis	UK_CPRD	Doses	Primary Risk Window				
			Expected	Observed**	OE	95% CI	95% CI
	IR per 100 000 person years		RW: 2 days	RW: 2 days		Lower bound	Higher bound
0-17	23.7	15	-	0	-	-	189502.563
18-29	19.29	180	-	0	-	-	19402.155
30-39	18.61	378	0	0	0	-	9576.714
40-49	18.07	912	0.001	0	0	-	4087.914
50-59	17.21	2768	0.003	0	0	-	1414.190
60-69	17.57	15966	0.015	0	0	-	240.152
70-79	13.13	893046	0.642	2	3.115	0.377	11.252
80+	8.19	1199195	0.538	2	3.719	0.450	13.434
ALL AGES	-	2112460	1	4	3.335	0.909	8.539

RR 50%	UK						
Anaphylaxis	UK_CPRD	Doses	Primary Risk Window				
			Expected	Observed**	OE	95% CI	95% CI
	IR per 100 000 person years		RW: 2 days	RW: 2 days		Lower bound	Higher bound
0-17	23.7	15	-	0	-	-	189502.563
18-29	19.29	180	-	0	-	-	19402.155
30-39	18.61	378	0	0	0	-	9576.714
40-49	18.07	912	0.001	0	0	-	4087.914
50-59	17.21	2768	0.003	0	0	-	1414.190
60-69	17.57	15966	0.015	0	0	-	240.152
70-79	13.13	893046	0.642	3	4.672	0.964	13.655
80+	8.19	1199195	0.538	3	5.578	1.150	16.302
ALL AGES	-	2112460	1	6	5.003	1.836	10.889

** Cases reported with TTO within selected RW and cases reported with missing TTO
For EEA/UK, 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

PRAC Rapporteur considered that case [redacted] should be assessed as level 2 certainty for anaphylaxis (PBRER Assessment Report). MAH is acknowledging the requested change in BCCD level evaluation to level 2. Of note, the case which was reported from a consumer via [redacted] involved a male of unknown age with no reported medical history who developed diarrhea on the day of vaccination with VidPrevtyn Beta. The patient also developed pruritus, pharyngeal swelling, vaccination site bruising, vaccination site warmth and lymphadenopathy on an unknown date after the vaccination. The patient's past vaccinations were not reported. The outcome was reported as not recovered for vaccination site bruising, vaccination site warmth, diarrhea, and unknown for pruritus, lymphadenopathy, and pharyngeal swelling. Based on BCCD for anaphylaxis by Gold MS et al, Nov 2022, this case was initially assessed as level 4 since it did not meet the criterion for rapid progression of the major or minor criteria (no information of signs progression, also unknown time to onset for pharyngeal swelling, two (2) signs for major criteria (swelling of the pharynx and diarrhea)). No new follow-up has been received for this case report.

Additionally, re-evaluation of all cases that reported 'Allergic and anaphylactic reactions' with an outcome as ongoing or not recovered done for case reports where further information was received, did not change the conclusion of the signal evaluation.

Based on the cumulative analysis of case reports of allergic including anaphylactic reactions during the previous reporting period, the signal of allergic including anaphylactic reactions has been confirmed as an identified risk during the current reporting period).

The updated RSI has been submitted to EMA and was approved on 21-Sep-2023 to include anaphylactic reactions and hypersensitivity (including rash, rash erythematous, urticaria, angioedema) as listed AEs in the RSI. See also Section 4 Changes to the Reference Safety Information in the body of the document.

Rapporteur assessment comment:

The causal relationship between allergic and anaphylactic reactions and VidPrevtyn Beta was

confirmed during the procedure EMEA/H/C/005754/II/0006. Anaphylactic reactions and Hypersensitivity (including rash, rash erythematous, urticaria, angioedema) were included to the PI with frequency of not known.

3 new cases were reported during the covered period. The MAH assessed the cases as BCC level 5 (not a case) which is endorsed. In the first case, a patient experienced dyspnoea and myocardial ischaemia within 48 hours after vaccination. In the second case, a patient experienced cardiac arrest, respiratory disorder, atrial fibrillation, pneumonia, and sepsis within 5 days after vaccination. In both cases, there is probable alternative aetiology of dyspnoea and cardiac disorders. In the last case a patient experienced dyspnoea 21 days and DVT 29 days after vaccination. TTO of dyspnoea is not consistent with TTO of anaphylaxis.

2.3.19. Swelling face/angioedema

5 case reports of potential Swelling face/angioedema has been reported during the reporting period (4 serious and 1 non-serious). Twenty (20) case reports have been reported cumulatively (10 serious and 10 non-serious).

Among the case reports reported during the reporting period, 2 of them have already been included in the analysis of the SER Allergic including anaphylactic reactions (Signal evaluation is not reproduced in the AR). The remaining 3 case reports are discussed below:

- Case [redacted] reported from a consumer via [redacted] involved a 75-year-old patient of unknown gender with medical history of COVID-19 positive, who experienced chronic urticaria, urticaria, tremor, headache and chills an unknown latency after receiving VidPrevtyn Beta. The patient had ongoing allergy to hazelnuts, peanuts, apples, peaches, lupin seed oil, septrin, negram, imodium and nitrofurantoin. Concomitant medications included esomeprazole, fexofenadine and iginic acid, aluminium hydroxide, calcium carbonate, magnesium trisilicate, sodium alginate, sodium bicarbonate. Outcome was reported as not recovered for chills and recovering for the other events. Further information on time to onset for events, concurrent conditions at the time of vaccination, duration of previous chronic urticaria, laboratory investigation, 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 was assessed as BCCD level 5 for anaphylaxis.
- Case [redacted] reported from a consumer via [redacted] involved a 75-year-old male with ongoing diabetes mellitus and hypertension, who experienced pruritus, rash pruritus, urticaria and rash 4 days after vaccination with VidPrevtyn Beta vaccine. Reportedly, the patient had itchy painful red spot on the right leg which gradually got bigger and darker and spots starting to appear over the entire body. The patient was treated with betamethasone valerate, fusidic acid, benzalkonium chloride, chlorhexidine hydrochloride, isopropyl myristate, paraffin, liquid and hydrocortisone cream 1%, still the itchy red painful spots continued to erupt and the whole body itched very badly especially at night. Then the patient was put on flucloxacillin for 7 days and told to continue with cetirizine 10mg. Concomitant medications included gliclazide for diabetes mellitus, lisinopril for blood pressure and cetirizine for seasonal allergy. Relevant laboratory investigation included blood immunoglobulin E (elevated above 400). Patient had other COVID vaccines (unspecified) and had no problem with them. Outcome was reported as not recovered. Further information on allergy history, clinical condition at the time of vaccination, 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.

- Case [redacted] reported from an HCP via [redacted] involved a 42-year-old female with no reported medical history and ongoing multiple allergies, who experienced an itchy rash across her chest spreading to her head and face within 4 minutes of administering VidPrevtyn Beta. Patient had no swelling of lips or throat. The patient had already taken oral antihistamine in the morning on the day of vaccination and again after the event. Patient's heart rate was 180 bpm which settled to 86 bpm within 10 minutes and blood pressure was measured as 165/80 on an unknown date. Outcome was reported as recovering. The patient's ongoing condition of multiple allergies could be a confounding factor. Further information regarding past medical history or family history, past medical treatment and concomitant medication are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

Based on medical review of cumulative data, a signal on Allergic including anaphylactic reactions has been validated and evaluated during the reporting period in the SER with DLP 17-May-2023 which is attached in Appendix 5.3 (SER is not reproduced in the AR). The new cases reported after the DLP of the SER do not change its conclusion.

The updated RSI has been submitted to EMA and was approved on 21-Sep-2023 to include anaphylactic reactions and hypersensitivity (including rash, rash erythematous, urticaria, angioedema) as listed AEs.

Rapporteur assessment comment: *The causal relationship between allergic and anaphylactic reactions and VidPrevtyn Beta was confirmed during the procedure EMEA/H/C/005754/II/0006 as is described above.* *3 cases were reported during the covered period however, angioedema is not reported in any case.*

2.3.20. Death (any cause)

A total of 24 case reports with fatal outcome have been received cumulatively (including two cases that reported sudden death), 11 new case reports and 4 follow-up case reports with fatal outcome were reported during the reporting period.

All cases are reported in elderly patients (unknown age in 4 patients), male female ratio (12:9) and 3 of unknown gender. For some of the patients, reported medical history indicated a possible explanation for the fatal outcome. Fatal outcome was mostly reported shortly after the vaccination from the same day to one day (n=7), 2-6 days (n=7), 9-20 days (n=5), after > 20 days (n=4) and unknown in the remaining case. All except one case report 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, the O/E analyses for death did not reveal an increased O/E ratio.

Case ID	Receipt date	Age	Sex	Latency	Batch	Short narratives/ Assessment
[redacted]	18-Apr-2023	78	Male	Same day	W2B042M	This case involves a 78-year-old male who experienced vomiting and aspiration pneumonia on the day of vaccination with VidPrevtyn Beta and then died in hospital 3 days after the vaccination. The morning of the vaccination the patient was fine. He had ongoing hypertension and severe dementia. Concomitant medications included amlodipine, lisinopril, omeprazole, and folic acid. Further information regarding previous vaccination tolerance, laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this case. No autopsy was conducted. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. **Follow-up information received on 14-Jun-2023: New event of pneumonia aspiration and cause of death added.** **Follow up information received on 02-Jul-23: Patient's age was updated from 28 years to 78 years.**
[redacted]	02-May-2023	86	Male	1 day	W2B042M	This case involves an 86-year-old male who died due to natural causes the day after receiving VidPrevtyn Beta. It was reported that the patient developed hypertension on an unknown date. The patient's medical history included breathlessness. Autopsy results revealed the cause of death was aortic aneurysm and hypertension. Further information on patient current condition (ongoing treatment of beclometasone, dipropionate, formoterol fumarate, lansoprazole, montelukast, salbutamol sulfate for breathlessness and sumatriptan) and medical history, previous laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this
[redacted]	02-May-2023	75	Male	4 days	W2B042M	This case involves a 75-year-old male who was found dead 4 days after receiving VidPrevtyn Beta. On an unknown date the patient developed hypertension. The patient's medical history included essential hypertension, breathlessness and chronic obstructive lung disease. Cause of death was reported to be aortic aneurysm and hypertension. Further information on allergy history, patient current 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. **Follow-up information was received on 14-Sep-2023: Autopsy information and cause of death added.**
[redacted]	09-May-2023	Unk	Unk	Same day	Not reported	This case involves an adult patient of unknown age and gender who died a few hours after the administration of VidPrevtyn Beta. No other information was provided. 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, 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. Upon a follow-up, it was reported that the death was not vaccine related as initially suspected. **Follow up information was received on 03-Jul-2023: death was not vaccine-related.**

[redacted]	12-Jun-2023	76	Male	48 hours	W2B061M	This case involves a 76-year-old male who experienced myocardial ischaemia, circulatory collapse, dyspnea and had a sudden death within 48 hours after receiving VidPrevtyn Beta. Patient had a medical history of angina and ongoing high blood pressure and irregular heartbeat. Concomitant medications included ramipril, edoxaban tosilate, diltiazem hydrochloride, atorvastatin and doxazosin. Post-mortem examination showed severe atherosclerosis of all three major coronary arteries, cardiomegaly. There was a recognised risk of sudden cardiac death with this degree of ischaemic heart disease. Patient's past vaccinations include Comirnaty (4 doses) and Spikevax bivalent original/omicron vaccine. Based upon the data reported, severe atherosclerosis of aorta and of all three coronary arteries could be the suspected etiology in the occurrence of ischaemic heart disease. **Follow up version received on 30-Aug-23: No new safety information received.**
[redacted]	13-Jun-2023	Unk	Female	39 days	W2B051M	This case involves an adult female of unknown age who experienced weight decreased (the same day), decreased appetite, asthenia, multiple organ dysfunction syndrome, sepsis (unknown latencies) and died 39 days after receiving VidPrevtyn Beta. Autopsy details were not reported. Further information on clear sequence of events, past medical history, concomitant medication, current condition and autopsy result 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. **Follow up information received on 14-Sep-2023 from physician: Information already present in the case (asthenia, multiple organ dysfunction syndrome and sepsis) were coded as new events in the database in this version.**
[redacted]	23-Jun-2023	Unk	Unk	15 days	W2B062M	This case involves a patient of unknown age and gender who died 15 days after receiving VidPrevtyn Beta. The patient felt lethargic and confused following vaccination, coughed out blood and felt dizzy. Further information on patient current condition, medical history, previous laboratory investigations, and autopsy 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.
[redacted]	25-Jun-2023	82	Female	22 days	W2B042M	This case involves an 82-year-old female who died 22 days after receiving VidPrevtyn Beta vaccine. Also, patient's past vaccination(s) included COVID-19 vaccines Astrazeneca and COVID-19 mRNA vaccine Biontech. The patient had ongoing type 2 diabetes mellitus, hypothyroidism, chronic obstructive pulmonary disease, atrial fibrillation and metastatic endometrial cancer. Concomitant medications included apixaban, bisoprolol, ferrous sulfate, furosemide, levothyroxine, megestrol, oxycodone, quinine sulfate, salbutamol and beclometasone/formoterol/glycopyrronium bromide. Further information regarding current condition, indication of reported concomitant medications and risk factors, laboratory investigation, examination results, and context for the reported event and autopsy report are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

[redacted]	26-Jun-2023	76	Male	2 days	W2B061M	This case involves a 76-year-old male patient who experienced myocardial ischaemia and was found dead in bed completely unresponsive, 2 days after receiving VidPrevtyn Beta (Booster dose 3). The patient had ongoing type 2 diabetes mellitus and hypertension. The postmortem computed tomography examination showed very severe coronary artery calcification indicative of established severe ischemic heart disease. Concomitant medications included pravastatin for cholesterol; perindopril for high blood pressure; and sertraline for depression. According to the autopsy report, death was due to natural causes, with medical history of diabetes mellitus type 2 (patient had from past 20 years) and hypertension being contributing factors. Based upon reported information, the role of the individual suspect vaccine can be excluded. **No additional safety information was received in a follow-up on 12-Sep-2023.**
[redacted]	29-Jun-2023	90	Male	25 days	W2B042M	This case involves a 90-year-old male who died due to respiratory failure and pneumonia 25 days after receiving VidPrevtyn Beta. The patient also had urinary tract infection, incontinence, dysuria and confusional state 22 days, and asthenia 26 days after the vaccination. He was treated with antibiotics for urinary tract infection and urine analysis was normal. The patient had a medical history of gravitational oedema, skin ulcer, osteoarthritis and chronic kidney disease. Concomitant medications included codeine for osteoarthritis; omeprazole for gastroesophageal reflux disease; and paracetamol. Patient's past vaccinations included 5 bivalent Comirnaty vaccines. Further information on clinical presentation of the reported event, laboratory investigations (of note, results of SARS-CoV- 2 test, if performed) and imaging studies results, and autopsy exam 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.
[redacted]	29-Jun-2023	90	Female	10 days	W2B042M	This case involves a 90-year-old female who experienced SARS-CoV-2 infection and cerebral infarction 10 days after receiving VidPrevtyn Beta and subsequently died. The patient had ongoing rheumatoid arthritis, malignant neoplasm, atrial fibrillation, hypertension and chronic kidney disease. Concomitant medications included methotrexate and omeprazole. Patient's past vaccinations included 4 Comirnaty vaccines, 1 bivalent Spikevax vaccine and Seqirus influenza vaccine. Relevant laboratory test results included: head computerized tomogram (thrombus within M1 portion of left middle carotid artery) and SARS-CoV-2 test (positive). The patient was trombolysed and then treated with apixaban. Patient's ongoing malignant neoplasm and SARS-CoV-2 infection are major confounding factors for the reported event. Further information regarding clinical picture and current health including status of atrial fibrillation, hypertension and malignant neoplasm at time of onset are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

[redacted]	29-Jun-2023	87	Male	9 days	W2B061M	This case involves an 87-year-old male who died due to aortic stenosis 9 days after receiving VidPrevtyn Beta. Reportedly, the patient had been diagnosed with critical aortic stenosis 4 months ago. Patient had ongoing hypertension and hypercholesterolemia. Concomitant medications included amlodipine, ramipril, and simvastatin. Patient's past vaccinations included COVID-19 vaccine AstraZeneca (2 vaccines), and Comirnaty (3 vaccines). Relevant investigations conducted: echocardiogram (no results available) 4 months prior to vaccination. No autopsy was done. The cause of death was reported as aortic stenosis. Further information on clinical presentation of the reported event, previous laboratory investigations and imaging studies results (in particular with regards to last echocardiogram conducted) 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. **Follow up information received on 15-Aug-2023: Cause of death added.**
[redacted]	29-Jun-2023	89	Male	37 days	W2B041M	This case involves an 89-year-old male who was diagnosed with liver metastases 31 days after receiving VidPrevtyn Beta. The patient became unwell with asthenia, weight loss, diarrhoea and hypotension on an unknown date after the vaccination and was admitted with worsening liver function tests. He rapidly deteriorated & died in hospital 37 days after the vaccination. The patient had a medical history of immunodeficiency and ongoing benign prostatic hyperplasia, left ventricular dysfunction, hypertension, myocardial infarction and chronic lymphocytic leukaemia. Concomitant medications included acalabrutinib, aspirin, atorvastatin, bisoprolol, losartan, finasteride, and tamsulosin. Patient's past vaccinations included Comirnaty (4 vaccines) and bivalent Comirnaty (1 vaccine). Relevant investigations conducted: blood test (results unknown), computerized tomogram (gross enlargement of the liver with multiple hypodense metastatic lesions), and ultrasound scan (results unknown). Autopsy was not done, and the cause of death was reported as metastases to liver, asthenia, abnormal loss of weight, diarrhoea, hypotension and neoplasm malignant. Patien's concurrent conditions of left ventricular dysfunction and chronic lymphocytic leukaemia are the most likely explanations for the reported event. Further information on laboratory tests and imaging studies dates and results excluding alternative etiologies 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. **Follow up information was received on 14-Sep-2023 from physician: No new significant safety information added.**

[redacted]	29-Jun-2023	94	Female	1 month 8 days	W2B041M	This case involves a 94-year-old female who developed pneumonia 14 days after receiving VidPrevtyn Beta. The patient also developed subdural haematoma and seizure 1 month following the vaccination and died 1 month 8 days after vaccination. She had a medical history of sinus node dysfunction (dual chamber cardiac pacemaker inserted), and ongoing rheumatoid arthritis, hypothyroidism and hypertension. Concomitant medications included folic acid, methotrexate, furosemide, levothyroxine, ferrous fumarate for iron deficiency anaemia, and omeprazole. Patient's past vaccinations included Comirnaty (5 vaccines). Relevant investigations included chest X-ray (bronchopneumonia, lung oedema), raised inflammation markers at blood tests, and computerized tomogram (subdural haematoma). The patient was treated with sulfamethoxazole, trimethoprim and doxycycline for lower respiratory tract infection. No autopsy was done. The cause of death was reported as subdural haematoma, pneumonia and seizure. The seizure in this patient is most probably the result of the subdural haematoma. However, further information on clinical presentation of the reported events, laboratory investigations and imaging studies results excluding alternative etiologies for the reported events are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. **Follow up information was received on 15-Aug-2023: New event seizure added.**
[redacted]	06-Jul-2023	78	Male	1 month 24 days	W2B052M	This case involves a 78-years-old male who experienced fatigue 1 day after receiving VidPrevtyn Beta, dyspnoea 13 days after the vaccination, and exacerbation of idiopathic pulmonary fibrosis 1 month and 24 days after vaccination. The patient also experienced decreased appetite and weight loss on an unknown date. It has been reported that patient experienced COVID-19, nonetheless, SARS-CoV-2 tests results were not provided. The patient died approximately 6 weeks after vaccination. Reportedly, the computerized tomography (CT) scan performed during the hospitalization showed a rapid deterioration of lung condition. Further information on medical history (especially previous COVID-19 episodes) and etiology of pulmonary fibrosis, current and previous SARS-CoV-2 PCR and serologic tests 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. **Follow up information was received on 14-Sep-2023: Patient age, medical and drug history details were added. Event onset date of two events (dyspnoea, idiopathic pulmonary fibrosis), laboratory details were added.**

Rapporteur assessment comment:

11 fatal cases and 4 follow-ups were reported during the covered period. 24 fatal cases were reported cumulatively. Regarding the cases reported during the current period, 12 cases were reported in elderly and 3 cases in patients of unknown age. The PRAC Rapp agrees with the MAH´s conclusion, that important information is lacking in vast majority of the cases e.g. medical history, concomitant medication, laboratory results, results of other investigations, which precludes in-depth assessment of the cases. In addition, O/E ratio is not increased. No significant safety finding was revealed.

2.3.21. COVID-19 cases

8 case reports (6 serious and 2 nonserious) of COVID-19 AESIs were reported during the reporting period, 16 cases have been reported cumulatively (8 serious and 8 non-serious). No safety concern nor specific pattern was identified from the medical review of the cases.

From the 16 cumulative cases reporting COVID-19 AESIs, 12 case reports (all assessed as BCCD level 5 for VAED) have been excluded as potential vaccine failure case reports as:

- Either time to onset was too short in 7 case reports (within 14 days after the VidPrevtyn Beta vaccination)

- within 7 days - in 4 case reports (1 serious and 3 non-serious)

- from 8-14 days - in 3 case reports (all serious)

- Or COVID-19 was reported before VidPrevtyn Beta vaccination - in 2 non-serious case reports
- Or time to onset was unknown - in 3 case reports (2 serious and 1 non-serious) which makes the assessment not possible.

The remaining 4 case reports were considered as potential case reports of vaccine failure:

- Time to onset 2-4 weeks in 2 case reports (1 serious and 1 non-serious)
- Time to onset within 2-4 months in 2 case reports (1 serious case and 1 non-serious).

Case reports received during the reporting period are presented below:

- Case [redacted] (serious) reported from an HCP via [redacted] involved a female patient of unknown age with no reported medical history who experienced SARS-CoV-2 infection (SARSCoV- 2 test positive) 16 days after VidPrevtyn Beta vaccination. Two months following the vaccination the patient developed acquired hypothyroidism and had ongoing fatigue 6 weeks post COVID infection. Patient's blood test showed low T4 and high TSH, with positive antibodies in the month of vaccination, and had the same results 2 months after vaccination. The outcome was reported as recovered for SARS-CoV-2 infection, not recovered for acquired hypothyroidism and was unknown for fatigue. Further information on patient's age, medical history, family history (especially regarding autoimmune diseases), past or concomitant medication, results of neck doppler ultrasonography if performed, any other laboratory test excluding alternative etiologies for the reported event and final diagnosis are needed to fully assess this case. Based upon the limited reported information, the role of the individual suspect vaccine cannot be assessed.
- Case [redacted] (serious) reported from a consumer via [redacted] involved an 80-year-old female with reported medical history of hypertonic bladder and ongoing osteoporosis and atrial fibrillation, who experienced tachycardia (reported heart rate of 175bpm) on

the same day she received VidPrevtyn Beta. The patient had low blood pressure, felt dizzy and had pain in left arm, shoulder, back, chest and stomach. Due to increase in pain, she was taken to the hospital on the next day. Patient also developed COVID-19 infection 1 month 2 days following the vaccine (SARS-CoV-2 test positive). Concomitant medication included edoxaban for atrial fibrillation. Flecainide and bisoprolol were added after the vaccination for treatment of atrial fibrillation. Past vaccinations were not reported. Patient took paracetamol for arm pain. Outcome was reported as recovered for all the events.

- Case [redacted] (non-serious) reported from a consumer involved a patient of unknown age and gender with no reported medical history who experienced COVID-19 (tested SARS-CoV-2 positive) on an unknown date after vaccination with VidPrevtyn Beta. It was not reported if the patient received a corrective treatment for the event. At time of reporting, the outcome was unknown for the event.
- Case [redacted] (non-serious) reported from a consumer via [redacted] involved a 77-year-old patient of unknown gender, already suspected to have COVID-19 before vaccination, who experienced malaise on the same day of vaccination with VidPrevtyn Beta. The patient had a feeding disorder 2 days after the vaccination, tested positive for COVID-19 positive 5 days after the vaccination, and developed cough, insomnia, feeling of cold, and chills on an unknown date after the vaccination. Patient's past vaccinations were not reported. Information on corrective treatment was not reported and the outcome was reported as not recovered.

Insufficient information was provided in both non-serious cases for a complete assessment. The second patient had suspected COVID-19 infection before vaccination. Also, both case reports were assessed as BCCD level 5 for VAED.

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

Additionally, one non-serious case ([redacted]) reported from a consumer involved a patient of unknown age and gender who experienced COVID-19, blood pressure increased and malaise on an unknown date after vaccination with a COVID-19 vaccine from an unknown manufacturer.

Rapporteur assessment comment:

The MAH provided a review of all COVID-19 cases. 16 cases (8 serious, 8 non-serious) were reported cumulatively of which 8 cases were reported during the covered period. The MAH excluded 12 cases because of too short TTO (within 14 days), COVID-19 before vaccination or unknown TTO. 4 cases were further assessed of which 3 cases were reported by the consumers and 1 case by the HCP. 2 cases were reported as serious. In the first case, a patient developed hypothyroidism 2 months after vaccination. In addition, the patient had a positive SARS-CoV-2 16 days after vaccination and persistent fatigue was reported 6 weeks after COVID-19. In the second case, a patient was hospitalized due to pain in the arm, shoulder, back, chest and stomach. In addition, the patient had a positive SARS-CoV-2 test approx. 1 month after vaccination. The remaining 2 cases fulfil the criteria for exclusion from the assessment of vaccination failure. In the first case, a patient experienced COVID-19 on unknown date after vaccination and in the second case COVID-19 was suspected already before vaccination and was confirmed 5 days after administration of vaccine. No significant safety findings were identified.

2.3.22. Vaccination failure

No case report of vaccination failure were retrieved using (N) Lack of efficacy/effect (SMQ). Based on the MedDRA search criteria as outlined Appendix 6.3.1 to retrieve all COVID-19 AESIs, all retrieved case reports of COVID-19 AESIs were also assessed for potential cases of vaccine failure according to time to onset, with at least the window of 14 days after vaccination and evaluated against the BCCD level of certainty for VAED (8). Refer also to Section 38 COVID-19 AESIs.

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

Rapporteur assessment comment:

The MAH's statement that no case report of vaccination failure was reported is not clear. Positive COVID-19 test was reported in 2 cases included in the assessment of COVID-19 cases more than 14 days after vaccination. Considering the mild symptoms of Omicron variant in majority of cases, it cannot be expected, that all COVID-19 cases will be confirmed with PCR tests. The MAH is requested to comment on. ***RSI***

2.3.23. Acute pancreatitis/autoimmune pancreatitis

1 case report of potential Acute pancreatitis/autoimmune pancreatitis has been reported during the reporting period or cumulatively.

- Case [redacted] reported from a consumer via [redacted] involved an 82-year-old female with a medical history of malignant neoplasm, leukemia or lymphoma (ongoing treatment with radiotherapy or chemotherapy) and rectal cancer some years ago, who experienced vomiting, chest discomfort and pancreatitis the day of vaccination with VidPrevtyn Beta. The patient experienced chest pain, pelvic pain, upper abdominal pain, infection and malaise 2 hours after vaccination. Patient was hospitalized. Relevant laboratory tests included blood test and X-ray (results not available). Past vaccinations were unspecified after which she had mild side effects (shivers and tiredness) and usually recovered within 24 to 36 hours. Patient was given an iron infusion and amoxicillin. Outcome was reported as recovering for vomiting, recovered for chest discomfort, recovered with sequelae for pancreatitis and unknown for others. Patient's ongoing malignancy and chemotherapy or radiotherapy treatment are confounding factors for the reported events. Further information on medical history, type of malignancy, concomitant medication, type of oncologic treatment, delay between reported events and last oncologic treatment, and current medical condition precluding 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.

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 this AESI.

Rapporteur assessment comment:

1 consumer case of pancreatitis was reported during the covered period and cumulatively. This case concerns a patient with ongoing malignant neoplasm on the not specified chemotherapy and radiotherapy who experienced vomiting, chest discomfort and pancreatitis at the day of vaccination. No information about concomitant medications and laboratory tests and other investigations was provided. The case lacks important details precluding further assessment. In addition, O/E ratio is not increased. No significant safety finding was revealed.

2.3.24. Immune-mediated/autoimmune AESIs/potential Immune-mediated diseases (pIMD), including Myasthenia gravis

13 case reports of Immune-mediated/autoimmune AESIs/pIMD were reported during the reporting period, 16 case reports have been reported cumulatively:

- 3 case reports of Rheumatoid arthritis (3 cumulatively)
- 1 case report of Thrombocytopenic purpura (1 cumulatively)
- 1 case report of Myocarditis (2 cumulatively)
- 1 case reports of Gout (2 cumulatively)
- 2 case reports of Polymyalgia rheumatica (2 cumulatively)
- 1 case report of Colitis ulcerative (1 cumulatively)
- 1 case report of Idiopathic pulmonary fibrosis (1 cumulatively)
- 1 case report of Glomerulonephritis minimal lesion (1 cumulatively)
- 1 case report of Erythema nodosum (1 cumulatively)
- 1 case report of Dermatitis bullous and Pemphigoid (1 cumulatively)

Additionally, 1 case report of vasculitis has been reported cumulatively (no case reports have been reported during the reporting period).

Case reports received during the reporting period are presented below:

- Three (3) case reports of Rheumatoid arthritis ([redacted], [redacted], [redacted]) (all reported during the reporting period) are presented in Section 7 Rheumatoid arthritis.
- Case report [redacted] of Thrombocytopenic purpura is presented in Section 9 (Idiopathic) thrombocytopenia including immune thrombocytopenia and thrombotic thrombocytopenic purpura.
- Case report of Myocarditis [redacted]) is presented in the body of the document, Section 16.3.1. New information on important potential risks of report body of this PBRER.
- Case report ([redacted]) from a consumer via [redacted] involved a 75-year-old male with reported medical history of suspected COVID-19 who experienced a gout flare two days after VidPrevtyn Beta vaccination. Concomitant medication included allopurinol for gout. Patient tested positive for SARS-CoV-2 on an unknown date. Patient already had a gout flare with a past administration of Moderna vaccine. Outcome was reported as recovering. Experience of a similar gout flare after a different COVID-19 vaccine previously received may account for a personal susceptibility rather than a specific vaccine's effect. Further information on patient's current condition during vaccination, lifestyle history, medical history and any other concomitant medications 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.

- Case report ([redacted]) from a consumer via [redacted] involved a 79-year-old male with ongoing suspected COVID-19 who experienced polymyalgia rheumatica the day of vaccination with VidPrevtyn Beta. The patient also experienced pain in extremity due to wrong technique in product usage process an unknown time after vaccination. Past vaccinations were not reported. Additional information on the outcome for event pain in extremity was added. Outcome was reported as not recovered for all events. Further information on patient's medical history, past or concomitant medication, concurrent illness at the time of vaccination, details about ongoing COVID-19 infection, details about reported error in administration technique, dates and results of laboratory investigation (in particular, complete blood count, c-reactive protein, rheumatoid factor and anti-citrullinated peptide), which sustained the diagnosis of polymyalgia rheumatica and excluded 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.

- Case report ([redacted]) from an HCP via [redacted] involved an 81-year-old female with ongoing Sjogren's syndrome who experienced polymyalgia rheumatica seven days after vaccination with VidPrevtyn Beta. Reportedly, the patient had raised inflammatory markers and proximal limb weakness. The patient demonstrated good response to steroids. Concomitant medications included metformin for type 2 diabetes mellitus, nitrofurantoin for urinary tract infection and omeprazole for reflux gastritis. The outcome was reported as recovering /resolving for the event. Although her ongoing Sjogren's syndrome might be a confounding factor for the event, further information regarding medical history, clinical condition at the time of vaccination and laboratory investigations report 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.

- Case report ([redacted]) from an HCP via [redacted] involved an 85-year-old female with medical history of Bell's palsy who experienced colitis ulcerative 2 days after receiving VidPrevtyn Beta vaccine and was hospitalized. Reportedly, patient had no previous symptoms or suggestive signs of colitis ulcerative. Past vaccinations were not reported. Outcome was reported as recovering. Further information on drug history, concomitant medication, current condition at the time of vaccination, laboratory investigations and imaging exams 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.

- Fatal case report ([redacted]) reported from a consumer via [redacted] involved a 78-year-old male with reported medical history of idiopathic pulmonary fibrosis with symptoms of some weight loss and fatigue (diagnosed approximately 1 year 5 months before) who experienced extreme fatigue one day after VidPrevtyn Beta vaccination followed by dyspnoea 13 days after vaccination. Patient's doctor prescribed an inhaler and antibiotics for this viral response to vaccine and advised X-ray and blood tests which were fine. Additionally, the patient also experienced decreased appetite and weight loss during this period. It has been reported that the patient experienced COVID-19 (latency unknown), nonetheless, SARS-Cov-2 tests results were not provided. One month later, the patient was hospitalized and his breathing continued to deteriorate. The computerised tomography scan found exacerbation of previous idiopathic pulmonary fibrosis and the patient died 1 month 24 days after the vaccination. There was no postmortem examination carried out. The certified cause of death was interstitial lung disease. The patient's past medical treatment included anti fibrotic drug nintedanib and COVID Pfizer vaccines from which patient had no adverse effects. Patient was well managed, and he was on no medication or oxygen prior to the vaccine. Further information on medical history (especially

previous COVID-19 episodes) and etiology of pulmonary fibrosis, current and previous SARS-CoV-2 PCR and serologic tests 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. The case was assessed as BCCD level 4 for VAED. See also Section 39 Vaccine failure and Table 1 of fatal cases in Appendix 5.4.2.

- Case report of Glomerulonephritis minimal lesion ([redacted]) is presented in Section 24 Acute kidney injury (including glomerulonephritis).
- Case report ([redacted]) from an HCP via [redacted] involved a 75-year-old female with no reported medical history who experienced erythema nodosum on left leg below 2 months and 24 days after administering VidPrevtyn Beta. At the time of the event, the patient had ongoing type 2 diabetes mellitus, hypertension and blood cholesterol increased. Concomitant medications included alendronic acid and vitamin D substances for osteoporosis, and levothyroxine for hypothyroidism. The outcome was reported as not recovered. Further information on patient's medical history, past medications, past vaccination history, laboratory investigations excluding alternative etiologies 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.
- Case report ([redacted]) from an HCP via [redacted] involved an 80-year-old female with reported medical history and multiple concomitant medications experienced rash on the back 8 days following VidPrevtyn Beta vaccine. Rash affected the back and top of shoulders. After 1 month 6 days, the rash spread to patient's face and lips, and she was hospitalized. After 2 months 14 days of vaccination, the rash became blistering with peeling skin on the back, arms, legs, face, hips and abdomen. The patient was diagnosed with dermatitis bullous and pemphigoid. Relevant investigations included bullous specific blood test positive and epidermal antibodies positive. Patient's medical history included cerebrovascular accident, asthenia, anxiety, depressed mood, Raynaud's phenomenon, ankle fracture, neuropathy peripheral, hordeolum, sleep apnoea syndrome, connective tissue disorder and appendectomy. At the time of the event, the patient had ongoing atrial fibrillation, rheumatoid arthritis and chronic obstructive pulmonary disease. Concomitant medications included a multivitamin/mulimineral, umeclidinium bromide/vilanterol trifenatate, bisoprolol, paracetamol, apixaban, baclofen, clobetasol, lansoprazole, fluoxetine, atorvastatin, laureth compounds, urea, salbutamol sulfate and calcium carbonate/colecalciferol. The patient was treated with fusidic acid, 3 courses of flucloxacillin, fucibet cream, hibiscrub wash, doxycycline and prednisolone. The outcome was reported as not recovered. High number of concomitant medications could be a confounding factor for the events. Further information regarding allergy history, previous vaccination history and tolerance are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

  Of note, a follow-up of the case report [redacted] concerning gout has been requested, however, no follow-up information has been received for this case report.

  Additionally, one case report ([redacted]) from a literature article from [redacted] (Bryan P, Williams N, Haebich G. A case of suspected COVID-19 vaccine-induced antiphospholipid syndrome. British Journal of Dermatology 2023 ;188(4):iv18) reported antiphospholipid syndrome with subcutaneous thrombosis in a 50-year-old patient about 2 weeks after receiving a second dose of COVID-19 vaccine from an unknown manufacturer. See also Section 18 Venous thromboembolism (including Pulmonary embolism and Deep vein thrombosis). Since this case occurred after primary vaccination, and the authors referred to a possible mechanism linked with mRNA platform, it is highly unlikely that this patient received Vidprevtyn Beta.

Based on medical review of cumulative data, no safety concern nor pattern on Immune-mediated/autoimmune AESIs/pIMD has been identified.

Rapporteur assessment comment:

13 cases concerning immune mediated AESI were reported during the covered period, 16 cases were reported cumulatively. The cases reporting rheumatoid arthritis, thrombocytopenic purpura, myocarditis, minimal change disease (glomerulonephritis minimal lesion) are discussed in the respective sections of the AR.

Regarding 2 cumulative cases of gout, the MAH was requested to follow-up the case [redacted] however, no additional information was obtained. 1 new consumer case of gout flare was received during the period. A patient already experienced a flare of gout after vaccination with Spikevax. No other details were provided.

2 cases of polymyalgia rheumatica were reported during the period. TTO was 0 days and 7 days resp. In both cases important details were not provided. In the first case, only diagnosis, TTO and outcome specified as not recovered were provided. In the second case, the laboratory results were described as inflammatory markers were increased and a symptom of limb weakness was reported. Outcome was specified as recovering. No details about results of ultrasonography, MRI or PET were reported in both cases. Diagnosis cannot be established only based on raised inflammatory markers because of their non-specificity and based on the symptom of limb weakness.

The case of exacerbation of idiopathic pulmonary fibrosis was already described among the fatal cases. A patient died 6 weeks after vaccination. According to the case, the patient also experienced COVID-19 however, not details were provided.

In addition, 2 not-well documented cases describing occurrence of erythema nodosum and dermatitis bullous and pemphigoid were reported.

No significant safety findings were identified.

2.3.25. Single organ cutaneous vasculitis

No case report of potential Single organ cutaneous vasculitis were reported during the reporting period, one case report has been reported cumulatively ([redacted]) and was assessed against the BCCD classification for Single Organ Cutaneous Vasculitis as level 5.

Of note, despite follow-up of the case report [redacted] no additional information has been received.

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:

During the current period, no case of single cutaneous vasculitis was reported. The MAH performed the follow-up of the case [redacted] as was requested during the previous PSUSA procedure, but no additional information was obtained.

2.3.26. Eye disorders

A total of 7 case reports were reported in the reporting period (5 serious and 2 non-serious cases), 23 case reports of Eye disorders were reported cumulatively, 14 serious and 9 non-serious cases.

Among these cases:

- 4 serious and 3 non-serious cases had other more likely explanations,

- 2 serious and 2 non-serious cases had confounding factors for eye disorders onset,

- 8 serious and 4 non-serious cases did not provide medical and drug history, thus being not assessable for confounding factors.

Case reports received during the reporting period are presented below:

- Non-serious case [redacted] reported from a consumer via [redacted] involved a patient of unknown age and gender, with medical history of blepharitis and malignant neoplasm who experienced rhinorrhoea 5 days after vaccination with VidPrevtyn Beta. Patient also experienced increased lacrimation and cough an unknown latency after vaccination. Patient had ongoing immunodeficiency. The patient's past medical treatment includes treatment for cancer (radiotherapy or chemotherapy). Past vaccinations were not reported. Concomitant medications included triptorelin, candesartan, rivaroxaban and unspecified treatments known to lower the immune response and increase the risk of infections. Outcome was reported as recovering for runny nose and unknown for other events. Patient's medical history of blepharitis could be an alternative explanation for event occurrence. Further information regarding latency, patient's clinical condition during vaccination, previous vaccination details, laboratory investigations 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] involved a 78-year-old female with medical history including inflammatory bowel disease and trabeculectomy 2.5 months before vaccination who experienced blurry vision the day of vaccination with VidPrevtyn Beta. Reportedly, the patient also experienced "15 watery loose stools during night after jab", stomach pain, asthenia, dizziness and eye pain. Concomitant medications included azathioprine. At the time of reporting, the outcome was recovering for ache and not recovered for the event blurry vision. The probably underlying glaucoma (trabeculectomy is a therapy for glaucoma) might be an alternative explanation, however, further information on status of the eyes, allergy history, previous laboratory investigations excluding alternative aetiologies for the reported event are needed to fully assess this case. Based upon the reported limited information, the role of the individual suspect vaccine cannot be assessed.

- Case [redacted] reported from an HCP via [redacted] involved an 83-year-old female who experienced microvascular cranial nerve palsy an unknown time after vaccination with VidPrevtyn Beta. As per reporter, this case report was not related to possible blood clots or low platelet counts or possible myocarditis or pericarditis. It was not reported if the patient received a corrective treatment for the event. At time of reporting, the outcome was unknown for the event. Based on the limited information provided in the case, causal role of the company suspect product cannot be assessed.

- Case [redacted] reported from a consumer via [redacted] involved an 85-year-old female with no medical history who experienced diplopia 3 days following the administration of

VidPrevtyn Beta. Patient's past vaccinations were not reported. Information on corrective treatment was not reported and the outcome was reported as recovered. Further information regarding previous vaccination/drugs, tolerance, all investigations excluding alternative aetiologies for the reported event are needed for a complete assessment of the case. Based upon the reported information, the individual role of the suspect vaccine cannot be assessed.

- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old female with no reported medical history who experienced pyrexia, diplopia, malaise and headache 1 day after vaccination with VidPrevtyn Beta. Patient's past vaccinations were not reported. Outcome was reported as recovering for pyrexia, recovered for diplopia, not recovered for others. Further information on patient's medical history, concurrent conditions at the time of vaccine, past or concomitant medication, tolerance to previous vaccinations, 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.
- Case [redacted] reported from a consumer via [redacted] involved a 76-year-old female with no reported medical history who experienced myalgia six days after VidPrevtyn Beta vaccination (5th dose). The patient also experienced blurred vision, bone pain and headache an unknown date after the vaccination. Concomitant medication included vitamin B12. Outcome was reported as not recovered for myalgia and unknown for rest of the events. Further information on medical or allergy history 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.
- Non-serious case [redacted] reported from an HCP via [redacted] involved a female of unknown age with reported medical history of mitral valve disease, ongoing osteopenia, chronic kidney disease and atrial fibrillation who experienced fatigue 3 days after VidPrevtyn Beta vaccine. Patient also experienced dyspnoea 2 months 3 days after, international normalised ratio (INR) increased, and vision blurred 2 months 17 days following the vaccination. Concomitant medications included candesartan, digoxin and warfarin. Outcome was reported as recovering for the event fatigue, unknown for INR increased, not recovered for dyspnea and vision blurred. Patient's concurrent conditions of chronic kidney disease and atrial fibrillation are contributing factors, however further information on patient's clinical condition at the time of vaccination, previous vaccination history and any laboratory investigations excluding alternative etiologies 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.

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

Of note, case report [redacted] of retinal haemorrhage experienced on the same day of vaccination with VidPrevtyn Beta reported in the previous PBRER with very limited information has been followed up; however, no new information has been received for this case report.

Rapporteur assessment comment:

7 cases of Eye disorders (5 serious, 2 non-serious) were reported during the covered period. 5 cases were reported by the consumers and 2 cases by the HCPs. Following ADRs were reported: blurred vision – 3 cases, diplopia - 2 cases, increased lacrimation – 1 case, microvascular nerve palsy – 1 case. The results of eye examination and laboratory results were not provided in the cases. TTO,

information about concomitant medications and outcome (2 case – recovered, 2 cases not recovered) were provided in 4 cases. In addition, the MAH performed the follow-up of the case [redacted]) describing retinal haemorrhage as was requested in the previous PSUSA procedure, but no new information was obtained.

The MAH concluded that no safety concern nor specific pattern is identified. It is endorsed.

2.4. Characterisation of risks

2.4.1. New information on important potential risks

Myocarditis/Pericarditis

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

O/E ratio and its 95% confidence interval for UK - DLP: 09 November 2023

RR 100% Myocarditis/Pericarditis	UK						
	UK_CPRD	Doses	Primary Risk Window				
			Expected	Observed**	OE	95% CI	95% CI
	IR per 100 000 person years		RW: 28 days	RW: 28 days		Lower bound	Higher bound
0-17	2.9	15	0	0	0	-	3688.879
18-29	13.5	180	0.002	0	0	-	1844.44
30-39	14.57	378	0.004	0	0	-	922.22
40-49	15.91	912	0.011	0	0	-	335.353
50-59	16.78	2768	0.036	0	0	-	102.469
60-69	16.05	15966	0.196	0	0	-	18.821
70-79	15.82	893046	10.83	1	0.092	0.002	0.514
80+	9.96	1199195	9.156	1	0.109	0.003	0.609
ALL AGES	-	2112460	20.236	2	0.099	0.012	0.357

RR 50% Myocarditis/Pericarditis	UK						
	UK_CPRD	Doses	Primary Risk Window				
			Expected	Observed**	OE	95% CI	95% CI
	IR per 100 000 person years		RW: 28 days	RW: 28 days		Lower bound	Higher bound
0-17	2.9	15	0	0	0	-	3688.879
18-29	13.5	180	0.002	0	0	-	1844.44
30-39	14.57	378	0.004	0	0	-	922.22
40-49	15.91	912	0.011	0	0	-	335.353
50-59	16.78	2768	0.036	0	0	-	102.469
60-69	16.05	15966	0.196	0	0	-	18.821
70-79	15.82	893046	10.83	1.5	0.139	0.01	0.592
80+	9.96	1199195	9.156	1.5	0.164	0.012	0.701
ALL AGES	-	2112460	20.236	3	0.148	0.031	0.433

Rapporteur assessment comment:

The MAH's conclusion is endorsed. For further information please see the section 2.3.7. of the AR.

Vaccine Associated Enhanced Disease including Vaccine Associated Enhanced Respiratory Disease

The MAH has determined that there was new relevant safety information that would have an impact on the understanding and characterization of the previously recognized potential risk of VAED including VAERD. Details regarding the new relevant safety information are included below:

- Source of new information: Cases retrieved for the reference interval from PSPV Safety database.
- Background relevant to the evaluation: For more details on this risk, see also Section 16.4.
- Methods of evaluation including data sources, search criteria, and analytical approaches: The PSPV safety database was searched for the following SMQ "(N) COVID-19 (SMQ)". Case reports have been assessed against the Brighton Collaboration Case Definition (BCCD) level of certainty.
- Results: From the review of PSPV Safety database, 16 cases were retrieved from post-marketing surveillance, none meeting BCCD (the two serious cases with compatible time to onset were not assessed as not VAED/VAERD).

During the reporting interval, the MAH received updated information to analyze the risk of VAED including VAERD. Based on information received during the reporting interval, the risk of VAED including VAERD is now removed from the list of safety concerns of the EU-RMP version 2.0. No impact is deemed necessary on labelling.

The topic of VAED including VAERD, was initially considered as an important potential risk in RMP at the initial conditional MA for COVID-19 vaccine (recombinant, adjuvanted) in the EU (10 November 2022) and in alignment with all COVID-19 vaccines.

The potential for increased disease severity in naive vaccines upon exposure to wild-type virus, a phenomenon known as VAED including VAERD, was raised as a theoretical safety concern with COVID-19 vaccines early in the pandemic. At that time, long-term safety and efficacy data were insufficient to definitively rule out VAED including VAERD as a safety concern.

The VAED including VAERD risk, as defined by the BCCD, is not applicable to booster vaccination as it only concerns SARS-CoV-2 seronegative individuals or those with an unknown serostatus and no prior COVID-19 infection. Since COVID-19 vaccine (recombinant, adjuvanted) is administered as a booster vaccination, this risk is not applicable.

Furthermore, there is currently no widely accepted case definition for VAED including VAERD. A publication by the BC provides some guidance for assessment of potential VAED including VAERD in COVID-19 and suggests that VAED including VAERD may be identified first as a vaccine failure (ie, VAED requires exposure to and infection by SARS-CoV-2 in a person who has been fully immunized). The authors acknowledge that there is presently no pathognomonic set of clinical findings to characterize VAED. In addition, case classifications that can be readily applied to individual-level data from spontaneous reporting are not defined. The BC working group states that a definitive case of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED. Probable cases must show an increase in severity or rates of atypical findings when compared to a non-vaccinated control group, however this criterion must be considered at a population or group level rather than an individual level. Given that there have been numerous epidemiologic studies evaluating effectiveness of mRNA vaccines in millions of vaccinees and that there have not been findings showing an increased risk of COVID-19 disease in vaccinees (or a subgroup of vaccinees) compared to those not vaccinated, real

world evidence does not show occurrence of VAED. Moreover, there is an absence of medical literature supporting the existence of VAED due to vaccines against COVID-19.

There is no reasonable expectation that the existing or future feasible PV activities could further characterize the safety profile of the product with respect to VAED and especially with COVID-19 vaccine (recombinant, adjuvanted) being administered as a booster only.

Accumulated evidence with COVID-19 vaccine (recombinant, adjuvanted) supported by evidence accumulated with other COVID-19 vaccines of different platforms does not suggest that this theoretical risk is still of relevance for COVID-19 vaccine (recombinant, adjuvanted) especially in the context of booster vaccination:

- No evidence of increase in COVID-19 severity was observed in VAT00008 clinical study when comparing the placebo and the vaccine groups (primary series). In addition, participants of ongoing clinical studies were followed up on any COVID-19 outcome (active and passive surveillances), without any safety concerns identified. Even with the emergence of multiple new variants/serotypes of SARS-CoV-2, with their potential to provoke sub-neutralizing antibodies in individuals who have encountered similar (but poorly cross reactive) epitopes, as was the case for SARS-CoV-2 variant Omicron, no enhancement of disease has been reported.
- More than two million doses of COVID-19 vaccine (recombinant, adjuvanted) have been administered since initial approval of the vaccine in November 2022 up to RMP DLP without any safety concern identified. This is supported by the absence of any VAED including VAERD safety concerns identified from other COVID-19 vaccines despite widespread use of COVID-19 vaccines administered since the first emergency use authorization (EUA) granted in December 2021 (mRNA vaccines). This is likely in this extensive exposure that VAED would have been observed and reported if this theoretical risk was confirmed. Effectiveness data generated from UK Health Security Authority showed effectiveness of COVID-19 vaccine (recombinant, adjuvanted) against hospitalization.
- Animal models of SARS-CoV-2 infection have not shown evidence of VAED disease after immunization. This (19), (20) is supported by available data for other COVID-19 vaccines from different platforms, including COVID-19 vaccine (recombinant, adjuvanted) platform.

Conclusion: The MAH considers that there is no convincing evidence to support the hypothesis that VAED including VAERD exists. There is sufficient justification for removing VAED including VAERD as an important potential risk from the EU-RMP for COVID-19 vaccine (recombinant, adjuvanted) being administered as a booster and proposes to continue monitoring occurrence and severity of COVID-19 disease in vaccinated individuals through routine surveillance of vaccination failures/lack of efficacy and ongoing post-authorization safety studies (PASS) as applicable. Any change in the available evidence (risk re-evaluation as per incidence and severity) would lead to a re-evaluation of this statement.

2.4.2. Update on missing information

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 and while breast-feeding were reported.

However, one case reported vaccine exposure during pregnancy after vaccination with a COVID-19 vaccine of an unknown manufacturer with no ADRs. No safety concerns have been identified from these data.

Use in immunocompromised subjects

No significant information about the use in immunocompromised subjects was identified.

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 in frail subjects with unstable health conditions and co-morbidities was identified.

Use in subjects with autoimmune or inflammatory disorders

No significant information about the use in subjects 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 on long-term safety.

Rapporteur assessment comment:

The MAH proposed to remove VAED/VAERD from the list of safety concerns for purposes of PSUR.

The PRAC Rapp agrees that many uncertainties are linked with VAED/VAERD including clear case definition and identification. However, considering these uncertainties and the level of experience with VidPrevtyn Beta, the PRAC Rapp is of opinion that VAED/VAERD should not be removed from the list of safety concerns for purposes of PSUR at the time (RMP is not assessed during the PSUSA procedure).

The safety concerns remain unchanged.

3. Benefit evaluation

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 assessment.

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.

During the covered period, the product information was updated to include anaphylactic reactions and hypersensitivity (including rash, rash erythematous, urticaria, angioedema).

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 VidPrevtny Beta remains unchanged.

The MAH requested to withdraw the marketing authorisation with a withdrawal effective date on 18 March 2024. The withdrawal decision is not based on the grounds provided in Articles 116 and 117 (i.e., not driven by quality, safety, efficacy or benefit/risk concerns). The European Commission decision to withdraw the Marketing Authorization of VidPrevtyn Beta has been adopted on 11 March 2024.

The MAH should provide addendum including all relevant information covering the period from 10 November 2023 to 18 March 2024 as previously agreed. **RSI**

5. Rapporteur Request for supplementary information

1. The MAH is requested to clarify the statement that no case report of vaccination failure was reported although positive COVID-19 test more than 14 days after vaccination was reported in 2 cases included in the assessment of COVID-19 cases.
2. The MAH should provide addendum including all relevant information covering the period from 10 November 2023 to 18 March 2024 as previously agreed.

6. MAH responses to Request for supplementary information

1. The MAH is requested to clarify the statement that no case report of vaccination failure was reported although positive COVID-19 test more than 14 days after vaccination was reported in 2 cases included in the assessment of COVID-19 cases.

MAH's response:

The MAH acknowledges Rapporteur Request for Supplementary Information and would like to clarify that no case report of potential vaccination failure was retrieved when using search criteria "MedDRA SMQ (N) Lack of efficacy/effect". However, using search criteria "MedDRA SMQ COVID-19", 16 case reports of potential vaccination failure were retrieved cumulatively and presented under Section 38 COVID-19 AESIs.

It is also acknowledged that considering the mild symptoms of Omicron variant in majority of cases, it cannot be expected that all COVID-19 cases will be confirmed with PCR tests. Indeed, the strategy employed to retrieve potential vaccination failure case reports utilized "MedDRA SMQ COVID-19" which is encompassing not only COVID-19 test positive MedDRA PTs but also COVID-19 or SARS-CoV-2 related MedDRA PTs (without COVID-19 tests being specified). In addition, analysis was conducted based on time to onset of symptoms rather than on the presence of reported COVID-19 test.

As mentioned in VidPrevtyn Beta Reference Safety Information, "As with any vaccine, vaccination with VidPrevtyn Beta may not protect all vaccine recipients".

No safety concern nor specific pattern was identified from the medical review of spontaneous case reports of potential vaccine failure in a context of more than 2.1 million VidPrevtyn Beta doses administered cumulatively up to PBRER Data Lock Point 09 November 2023.

Rapporteur assessment comment:

The MAH adequately explained the previous statement. No case report of vaccination failure was retrieved using the MedDRA SMQ search criteria "Lack of efficacy/effect", however 16 case reports were retrieved cumulatively using the search criteria for "COVID-19". Cases of vaccination failure including occurrence of COVID-19 with the relevant TTO are therefore presented and evaluated in section 2.3.21 of this assessment report. No significant safety findings were identified.

2. The MAH should provide addendum including all relevant information covering the period from 10 November 2023 to 18 March 2024 as previously agreed.

MAH's response:

The PSUR Addendum with all relevant information covering the period from 10 November 2023 to 18 March 2024 is included in this submission.

Executive summary

This Addendum to Periodic Benefit Risk Evaluation Report for Recombinant Prefusion Spike Delta TM Protein (severe acute respiratory syndrome-coronavirus-2 strain) vaccine, hereafter referred to as "COVID-19 vaccine (recombinant, adjuvanted)", was prepared to complement the latest submitted Periodic Benefit Risk Evaluation Report with a data lock point of 09 November 2023.

This addendum report summarizes the cumulative safety information for COVID-19 vaccine (recombinant, adjuvanted) received by Sanofi's Patient Safety & Pharmacovigilance department from spontaneous sources, from 10 November 2023 through 18 March 2024, which is the effective date of COVID-19 vaccine (recombinant, adjuvanted) withdrawal.

A global safety data exchange agreement is in place between Sanofi and GlaxoSmithKline Biologicals SA for multiple territories.

The first marketing authorization for COVID-19 vaccine (recombinant, adjuvanted) was obtained in the European Union on 10 November 2022. During the period covered by this addendum report, at the Sanofi's request, the European central marketing authorization withdrawal has been adopted by European Commission with an effective date on 18 March 2024. The withdrawal decision is not driven by quality, safety, efficacy, or benefit-risk concerns.

Based upon available data, 7057 doses of COVID-19 vaccine (recombinant, adjuvanted) were administered worldwide from marketing experience during the current review period, with a total of 2 151 791 doses administered cumulatively to 18 March 2024.

The European Union Summary of Product Characteristics for COVID-19 vaccine (recombinant, adjuvanted), version 2 dated 21 September 2023 was the reference safety information valid at the beginning of the Addendum to Periodic Benefit Risk Evaluation Report period. During the review period, the following changes were made to the European Union Summary of Product Characteristics:

• Section 4.8 - Undesirable effect: Including additional safety data based on the safety reports from studies VAT00008 and VAT00002 Cohort 2 further to the extension of the safety database over 2000 and 3000 participants with six weeks safety follow-up.

• Section 4.8 - Addition of dizziness as an adverse reaction with frequency rare as per the pharmacovigilance risk assessment committee recommendation received on 30 November 2023, and the adoption of the periodic safety update report opinion by Committee for Medicinal Products for Human Use on 14 December 2023.

• Section 5.1 - Pharmacodynamic Properties: Change of the anatomical therapeutic code and the name of the pharmacotherapeutic group.

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

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), as a booster dose for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus-2 Strain in adults who have previously received a messenger ribonucleic acid or adenoviral vector COVID-19 vaccine (recombinant, adjuvanted) remained positive in the approved conditions of use.

There were no validated signals that were ongoing or closed for COVID-19 vaccine (recombinant, adjuvanted) during the reporting period. No signal was identified during the reporting period.

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

During the reporting period of this addendum to PBRER, 34 case reports were spontaneously reported (21 serious and 13 non-serious). Safety topics were monitored during the reporting period to address EMA's request based on the Core-Risk Management Plan (RMP) guidance (2), Responses to Rapporteurs final list of questions on RMP dated 23 June 2022 (Reference submission: EMEA/H/C/005754/0000), dated 15 August 2022 (Reference submission: EMEA/H/C/005754/0000), EMA Committee for CHMP assessment report dated 10 November 2022, Medicines and Healthcare products Regulatory Agency (MHRA) request dated 20 December 2022, and EMA PRAC Assessment Report dated 30 November 2023 (procedure number-EMEA/H/C/PSUSA/00011035/202305).

The safety topics are presented in the order of list of adverse events of special interests (AESIs) in Annex 7.2 of EU-RMP (refer to medical dictionary for regulatory activities [MedDRA] search strategy outlined in Appendix 6.3.1 of PBRER DLP 09 November 2023).

Utilizing the search strategy as described in Appendix 6.3.1 of PBRER DLP 09 November 2023, the MAH did not identify any new information that would impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

The detailed analyses are included in Appendix 2. *The following cases of safety topics under monitoring were reported and presented in the Addendum (Appendix 2):*

Acute aseptic arthritis

Based on the MedDRA search strategy on Acute aseptic arthritis outlined in Appendix 6.4.1 of PBRER DLP 09 November 2023, one case report of Polyarthritis has been reported during the reporting period and three case reports have been reported cumulatively. The case reported during the reporting period is presented below:

• Case report [redacted] reported from a healthcare professional via Health Authorities involved a 90-year-old male with no reported medical history who experienced polyarthritis seven days after receiving VidPrevtyn Beta. Reportedly, patient had arthralgia in the wrists, shoulder gridle and the hands appeared swollen. Biology showed an inflammatory syndrome with C-reactive protein (CRP) increased to 92.5. Patient was prescribed immunological check-up which is still pending. Patient's past vaccinations included Comirnaty (four doses) and his past medical history did not include any rheumatic history neither personal nor family. Patient had a medical history of alcohol use (one drink on weekends). Patient was prescribed diclofenac sodium and was initially taking paracetamol. Outcome was reported as not recovered. Further information regarding clinical status of the patient and concurrent conditions at the time of vaccination, concomitant medication and other laboratory investigations, including pending results of the immunological check-up are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

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

Arrythmia

Based on the MedDRA search strategy outlined in Appendix 6.4.1 of PBRER DLP 09 November 2023, one case report of potential Arrythmia has been reported during the reporting period and 13 case reports have been reported cumulatively. The case reported during the reporting period is presented below:

• Case report [redacted] reported from a healthcare professional via [redacted] involved a 62-year-old female with reported medical history of mast cell activation syndrome, food intolerance and hypersensitivity who experienced myalgia, cardiac discomfort, palpitations, contact dermatitis, dyspnea, brain fog, radiculopathy, visual acuity reduced, food intolerance, ligamentitis, allergy to metals, eczema, photophobia, tachycardia, alopecia, visual impairment, heart rate increased, extrasystoles, gingival recession, gastrointestinal disorder, lung disorder, rash, fatigue and malaise on unknown time after receiving VidPrevtyn Beta. Patient's previous vaccinations include Shingrix, Influenza virus and COVID-19 mRNA vaccine (three doses) from unknown manufacturer. Concomitant medications included amlodipine, candesartan for hypertension; diazepam for hypermobility syndrome; cromoglicate sodium, chlorphenamine maleate for food intolerance and cetirizine. Outcome was reported as recovering for fatigue; not recovered for visual acuity reduced, food intolerance, lung disorder; unknown for ligamentitis, allergy to metals, eczema, photophobia, tachycardia, alopecia and recovered for rest of the events. Further information regarding time to onset for events, patient's concurrent conditions at the time of vaccination, 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.

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

Venous thromboembolism (including Pulmonary embolism and Deep vein thrombosis)

Based on the MedDRA search strategy outlined in Appendix 6.4.1 of PBRER DLP 09 November 2023, two case reports of potential venous thromboembolism have been reported in the reporting period, 25 case reports of different types of thromboembolic AESIs (including stroke) have been reported cumulatively. Case reports have been assessed against the BCCD for thrombosis/thromboembolism.

The following case reports have been reported during the reporting period and cumulatively:

• Thrombosis (two case reports on the period, five case reports cumulatively),

• Deep vein thrombosis (two case reports cumulatively),

• Pulmonary thrombosis (one case report cumulatively),

• Monoparesis (one case report cumulatively),

• Pulmonary embolism (two case reports cumulatively),

• Cerebral venous sinus thrombosis (one case report cumulatively)

• Cases of different stroke types (13 case reports cumulatively):

- Cerebrovascular accident (10 case reports cumulatively)

- Cerebral ischemia (one case report cumulatively)

- Hemorrhagic stroke (one case report cumulatively)

- Cerebral infarction (one case report cumulatively).

The cases reported during the reporting period are presented below:

• Case report [redacted] reported from a consumer via [redacted] involved a 75-year-old male with reported medical history of COVID-19 positive, asthma and photosensitivity reaction on prednisolone who experienced rash three days after receiving VidPrevtyn Beta. Twenty days following the vaccination, patient was suspected deep vein thrombosis (thrombosis). At the time of reporting, patient had ongoing systemic lupus erythematosus (SLE) and poor peripheral circulation. The patient's past vaccinations included Comirnaty (two doses), Comirnaty Omicron XBB.1.5 and Spikevax Omicron XBB.1.5. Patient had a family history of heart attack (brother and sister collapsed and died from heart attacks). The patient took an anticoagulant to disperse the blood clot after the vaccination. The patient was treated with blood thinners for thrombosis, antibiotics (including clarithromycin) and steroid/antibiotic cream for the rash. Outcome was reported as not recovered for rash and recovered for thrombosis. Further information regarding localization of the rash, laboratory investigations excluding alternative etiologies for the reported event are needed to fully assess this case. Patient's concurrent condition of SLE and poor blood circulation cannot be underestimated either. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed. The case was assessed as BCCD level 3 for thrombosis/thromboembolism.

• Case report [redacted] reported from a consumer via [redacted] involved an unknown age female with reported medical history of suspected COVID-19, migraine, hypertension and Raynaud's phenomenon who experienced thrombosis (latency three days) and COVID-19 (SARS-CoV-2 test positive) two months one day after receiving VidPrevtyn Beta. Reportedly, patient also developed varicose veins, brain fog and difficulty with coordination unknown duration after vaccination. Ultrasound doppler revealed presence of thrombosed area in superficial right saphenous vein. Patient's past vaccinations include Pfizer BioNtech COVID-19 vaccine (developed marked menstrual bleeding, clotting for over two weeks, with severe abdominal cramping and slightly enlarged heart), AstraZeneca COVID-19 vaccine (developed chills and body aches). Patient recovered from COVID-19 infection and recovered with sequelae from thrombosis. Further information on patient age, risks factors and condition, concomitant medications and tolerance 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. The case was assessed as BCCD level 1 for thrombosis/thromboembolism.

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

Stroke

Based on the MedDRA search strategy outlined in Appendix 6.4.1 of PBRER DLP 09 November 2023, one new case report and one follow-up of potential Stroke have been reported in the reporting period, 16 case reports have been reported cumulatively. The one new case report and one follow-up are presented as follows:

• One case report reported Hemorrhagic stroke (three case reports cumulatively),

• No case report of Ischemic stroke on the period (eight case reports cumulatively),

• One follow-up reported a Stroke where the type of stroke was not specified, and from the provided information it was not possible to identify it (five case reports cumulatively).

Hemorrhagic stroke

Based on the MedDRA search strategy outlined in Appendix 6.4.1 of PBRER DLP 09 November 2023, one new case report and one follow up to previously reported case of potential Hemorrhagic stroke were reported during the reporting period, three have been reported cumulatively. One follow-up case report was reported during the reporting period, as the type of stroke could not be identified form available data. The case report is presented below and follow up case is presented under section Unknown type of stroke.

• Case report [redacted] reported from a consumer via [redacted] involved an 83-year-old male with reported medical history of myocardial infarction and knee arthroplasty who experienced subdural hematoma, balance disorder, coordination abnormal, depressed level of consciousness, dyskinesia, urinary tract infection and fatigue two days after receiving VidPrevtyn Beta. Concomitant medications included aspirin, bisoprolol, ramipril and simvastatin for myocardial infarction; influenza vaccine for immunization; paracetamol for arthritis. Patient's computerized tomogram results were not reported. Outcome was reported as recovering for subdural hematoma, not recovered for fatigue, unknown for rest of the events. Further information regarding any underlying diseases that could lead to subdural hematoma, concurrent conditions, previous vaccination and tolerance, 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.

Based on the medical review of the case reports, no safety concern was identified.

Unknown type stroke

One follow-up of potential unknown type Stroke and no new case reports were reported during the reporting period, five have been reported cumulatively. The follow-up case reported during the reporting period is presented below:

• Case report [redacted] reported from a consumer via [redacted] involved a 78-year-old male with reported medical history of COVID-19 positive, ex-tobacco user who experienced cerebrovascular accident 18 days after receiving VidPrevtyn Beta. The patient's concomitant medications included bisoprolol, amlodipine and atorvastatin, but patient's blood pressure has been controlled to an average of 143/80 with a pulse of 60 prior to the stroke. Patient had no previous problems with blood clotting, or irregular heart rhythm and not had a clot in leg, lung, brain or coronary arteries. The patient received bisoprolol, amlodipine, clopidogrel, atorvastatin, rosuvastatin as corrective treatment for the stroke. The outcome was reported as recovered with sequelae. Although hypertension as a risk factor for stroke could be a confounding factor, further information on previous vaccination, medical history, clinical status before vaccination and previous laboratory investigations 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. The case was assessed as BCCD level 4 for thrombosis/thromboembolism.

Based on the medical review of the case reports, no safety concern was identified.

Dizziness

Based on the MedDRA search strategy outlined in Appendix 6.4.1 of PBRER DLP 09 November 2023, three new case reports have been reported during the period (one serious and two non-serious) and one follow-up ([redacted]) with no additional safety information. Fifty-five (55) case reports of dizziness have been reported cumulatively (57 events).

Cases reported in the reporting period are presented below:

• Case report [redacted] reported from a consumer via [redacted] involved a 79-year-old female with no reported medical history who experienced severe dizziness on walking one day after receiving VidPrevtyn Beta. Outcome was reported as recovered. Further information regarding concurrent condition during 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.

• Case report [redacted] reported from a consumer involved an elderly female of unknown age with no reported medical history who experienced dizziness three weeks after receiving VidPrevtyn Beta. Outcome was reported as unknown. Further information regarding concurrent condition during 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.

• Case report [redacted] reported from a healthcare professional via [redacted] involved a 77-year-old female, with ongoing multiple allergies who experienced pain in extremity, confusional state, vision blurred, muscular weakness and myalgia one day after vaccination with VidPrevtyn Beta. Additionally, eight days after vaccination, the patient experienced dizziness. Patient was admitted to hospital and underwent CT scan/MRI to investigate the possibility of blood clots, had physiotherapy for leg weakness and joint pain and was still experiencing some confusion 'brain fog'. At time of reporting, the patient's vision had recovered and other events were recovering. Further information regarding patient's medical history, previous vaccination and tolerance, concomitant medication and allergic history are needed to fully assess this case.

Based on the medical review of the case reports, no safety concern has been identified. A detailed medical review of all reported dizziness case reports with DLP 30 June 2023 was finalized in September 2023. This analysis included 50 of the 52 cumulative post-marketing cases reports and is available in Appendix 5.4.3 of PBRER DLP 09 November 2023. Current analysis is in alignment with the detailed medical review. Following PRAC request, Sanofi has submitted to European Medicine Agency on 29 November 2023 an update of section 4.8 of the Summary of Product Characteristics (and Product Information Leaflet) to add dizziness as an adverse reaction, with frequency rare. The approval was granted during this addendum to the PBRER, on 14 December 2023.

Anaphylactic reactions

Based on the MedDRA search criteria SMQ Anaphylactic reaction Algorithmic, four new cases and one follow-up of a previously reported case report of potential Anaphylactic reactions have been reported on the period, 12 case reports have been reported cumulatively with 2 meeting the BCCD level 1 of certainty for anaphylaxis (4). Case reports (including follow-ups) received during the review period are presented below:

• Case report [redacted] reported from a healthcare professional via [redacted] involved a 21-year-old female with reported medical history of B-cell lymphoma and anaphylactic reaction after previous Pfizer and AstraZeneca COVID-19 vaccines as well as rash after Novavax vaccine, who experienced anaphylaxis on the same day after receiving VidPrevtyn Beta. Reportedly, the patient was feeling itchy with generalized rash, hoarseness and ongoing upper body skin rash with noisy breathing, no lip swelling. At the time of reporting, patient had ongoing drug hypersensitivity (rituximab and etoposide). Concomitant medications included folic acid. The patient was treated with chlorphenamine, epinephrine and hydrocortisone for anaphylactic reaction and the outcome was reported as recovered on the next day. History of previous similar reactions after other COVID-19 vaccinations as well as plausible time to onset are in favor of the role of the vaccine in the occurrence of anaphylactic reaction. The case was assessed as BCCD level 1 for anaphylaxis.

• Case report [redacted] reported from a consumer via [redacted] involved an 88-year-old male with no reported medical history who experienced eye swelling, lip swelling, swollen tongue and itchy upper limbs on an unknown time to onset after administering VidPrevtyn Beta. At the time of the event, the patient had ongoing drug hypersensitivity to penicillin and the current reaction is similar to previous penicillin reaction for which patient stayed in hospital. Concomitant medications included Spikevax Omicron XBB.1.5, CHADOX1 NCOV-19, COVID-19 vaccine AstraZeneca and Comirnaty for immunization. The patient took antihistamines but were totally ineffective and the outcome was reported as not recovered. Patient's ongoing condition of drug hypersensitivity might be an alternative explanation. Further information on patient's medical history, clinical condition at the time of vaccination, past or concomitant medication, tolerance to previous vaccinations excluding alternative etiologies 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. The case was assessed as BCCD level 1 for anaphylaxis.

• Case report [redacted] ([redacted]) reported from a healthcare professional via [redacted] involved a 53-year-old female with reported medical history of anaphylactic reaction after previous Comirnaty/Pfizer COVID-19 vaccine and acute allergic reaction with Astra Zeneca/Vaxzevria COVID-19 vaccine experienced throat irritation and anaphylactic reaction 8 minutes after administering VidPrevtyn Beta. The reaction worsened over the next 20 minutes to acute full-blown anaphylaxis (coughing, chest tightness, tingling tongue, wheezy and throat closing). Concomitant medications included chlorpheniramine and regular steroid treatment. The patient was treated with four doses of adrenaline and the outcome was reported as recovering. History of previous similar reactions after other COVID-19 vaccinations as well as plausible time to onset are in favor of the role of the vaccine in the occurrence of anaphylactic reaction. The case was assessed as BCCD level 4 for anaphylaxis.

• Case report [redacted] ([redacted]): detailed in Section 13 Arrhythmia. The case was assessed as BCCD level 5 for anaphylaxis.

• Case report [redacted] ([redacted]) reported from a consumer involved a 76-year-old male, with ongoing hypertension and atrial fibrillation who experienced myocardial ischaemia, circulatory collapse, dyspnea and had sudden death within 48 hours (about two days) after receiving VidPrevtyn Beta. The patient had a medical history of angina. Concomitant medications included ramipril, edoxaban, diltiazem, atorvastatin and doxazosin. Post-mortem examination showed severe atherosclerosis of all three major coronary arteries cardiomegaly. There was a recognized risk of sudden cardiac death with this degree of ischaemic heart disease. Patient's past vaccinations include Comirnaty (four doses) and Spikevax bivalent original/omicron vaccine. Autoptic examination revealed severe atherosclerosis of aorta and of all three coronary arteries and did neither reveal any feature of myocarditis nor pericarditis nor cerebrovascular accident. Based upon the data reported, severe atherosclerosis of aorta and of all three coronary arteries could be suspected etiology in the occurrence of ischaemic heart disease. The case was assessed as BCCD level 5 for anaphylaxis.

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

Swelling face/angioedema

Based on MedDRA search strategy SMQ Angioedema_narrow, one non serious case report of potential Swelling face/angioedema has been reported during the reporting period and 21 case reports have been reported cumulatively (10 serious and 11 non-serious). Case reported during the reporting period is presented below:

• Case report [redacted] ([redacted]) reported from a consumer via [redacted] involved an 88-year-old male with no reported medical history who experienced eye swelling, lip swelling, swollen tongue and itchy upper limbs on unknown time to onset after administering VidPrevtyn Beta. At the time of the event, the patient had ongoing drug hypersensitivity to penicillin and current reaction is similar to previous penicillin reaction for which patient stayed in hospital. Concomitant medications included Spikevax Omicron XBB.1.5, CHADOX1 NCOV-19, COVID-19 vaccine Astrazeneca and Comirnaty for immunization. The patient took antihistamines but were totally ineffective and the outcome was reported as not recovered. Patient's ongoing condition of drug hypersensitivity might be an alternative explanation. Further information on patient's medical history, clinical condition at the time of vaccination, past or concomitant medication, tolerance to previous vaccinations excluding alternative etiologies 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.

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

COVID-19 AESIs

Based on the MedDRA search strategy outlined in Appendix 6.4.1 of PBRER DLP 09 November 2023, one new serious case report and one new non-serious case report of COVID-19 AESIs have been reported during the reporting period, 18 cases have been reported cumulatively (nine serious and nine non-serious). Case reported during the reporting period are case report [redacted] ([redacted]: detailed in Section 18 Venous thromboembolism (including Pulmonary embolism and Deep vein thrombosis) and case report [redacted] ([redacted]: detailed in Section 48 Eye disorders.

No safety concern nor specific pattern was identified from the medical review of the cases. See also

All other Immune-mediated/autoimmune AESIs/potential Immune-mediated diseases (pIMD), including Myasthenia gravis

Based on the MedDRA search strategy outlined in Appendix 6.4.1 of PBRER DLP 09 November 2023, one case report of Immune-mediated/autoimmune AESIs/pIMD has been reported during the reporting period, 16 case reports have been reported cumulatively:

- No case report of Rheumatoid arthritis (three cumulatively)
- No case report of Thrombocytopenic purpura (one cumulatively)
- No case report of Myocarditis (two cumulatively)
- No case report of Gout (two cumulatively)
- No case report of Polymyalgia rheumatica (two cumulatively)
- No case report of Colitis ulcerative (one cumulatively)
- No case report of Idiopathic pulmonary fibrosis (one cumulatively)
- No case report of Glomerulonephritis minimal lesion (one cumulatively)
- No case report of Erythema nodosum (one cumulatively)
- One case report of Pemphigoid (two cumulatively)

Additionally, one case report of Vasculitis has been reported cumulatively (no case report has been reported during the reporting period).

- Case report [redacted] ([redacted]) reported from a consumer via [redacted] involved a 77-year-old male who collapsed and experienced unconsciousness, syncope, loss of consciousness, respiratory rate increased, cold sweat and erythema 17 hours after Vidprevtyn Beta vaccination (second dose received after six months). The patient's past medical history included immunodeficiency, back pain, vasectomy, haemorrhoids, temporomandibular joint syndrome, psoriasis, neurodermatitis, nail avulsion, sciatica, gastric ulcer, endoscopy upper gastrointestinal tract, fall, inguinal hernia, cataract. Patient's past medications/ vaccinations includes anaesthetic, two doses of COVID-19 mRNA vaccines (lethargy and pain in extremity the day of vaccination respectively and also experienced headache one day after second dose); two doses of tozinameran (pruritus allover seven days after 1st dose vaccination and pemphigoid nine months 25 days after the vaccination) and one dose of elasomeran. Concomitant medications included ongoing steroid therapy, calcium carbonate/colecalciferol, doxycycline, folic acid, methotrexate, omeprazole, prednisolone for pemphigoid and clobetasol propionate for pruritus. Laboratory test results including blood pressure, body temperature, electrocardiogram, heart rate and oxygen saturation, were normal on an unknown date. The outcomes at the time of reporting were recovered for lethargy, pain in extremity, not recovered for headache, recovering for pruritus and bullous pemphigoid and unknown for respiratory rate increased, cold sweat, syncope, loss of consciousness and erythema. Further information on diagnosis, allergy history, previous laboratory investigations excluding alternative etiologies for the

reported events are needed to fully assess this case. Based upon the reported, the role of the individual suspect vaccine cannot be assessed.

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

Eye disorders

Based on the MedDRA search strategy outlined in Appendix 6.4.1 of PBRER DLP 09 November 2023, a total of four case reports have been reported in the reporting period (one serious and three non-serious cases), 27 case reports of Eye disorders have been reported cumulatively.

Case reports received during the reporting period are presented below:

• Case report [redacted]: detailed in Section 33 Anaphylactic reactions.

• Case report [redacted]: detailed in Section 13 Arrhythmia.

• Case report [redacted] reported from a consumer involved an unknown age male patient, with ongoing cancer who experienced chronic obstructive pulmonary disease with symptoms of dyspnoea and wheezing, lacrimation increased, neck pain and developed post-acute COVID-19 syndrome on an unknown time to onset after vaccination with VidPrevtyn Beta. The MRI scan showed a trapped nerve, but it was suspected that the inflammation may have exaggerated the findings. The pulmonary function test results indicated evidence of chronic obstructive pulmonary disease. At time of reporting, the outcome was unknown for the events.

Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

• Case report [redacted] reported from a healthcare professional via [redacted] involving a 77-year-old female, with ongoing multiple allergies who experienced pain in extremity, confusional state, vision blurred, muscular weakness and myalgia one day after vaccination with VidPrevtyn Beta. Additionally, eight days after vaccination, the patient experienced dizziness. Patient was admitted to hospital and underwent CT scan/MRI to investigate the possibility of blood clots, had physiotherapy for leg weakness and joint pain and was still experiencing some confusion 'brain fog'. At time of reporting, the patient's vision had recovered and other events were recovering. Further information regarding patient's medical history, previous vaccination, concomitant medication and tolerance and allergic history are needed to fully assess this case. Based upon the reported information, the role of the individual suspect vaccine cannot be assessed.

Based on the medical review of the case reports, no safety concern nor specific pattern has been identified.

Rapporteur assessment comment:

With respect to the marketing authorization withdrawal with an effective date on 18 March 2024, the MAH submitted an Addendum to supplement currently evaluated PSUR with DLP 09 November 2023. The Addendum covers the remaining marketing authorization period, i.e. from 10 November 2023 through 18 March 2024. According to the MAH, the withdrawal decision is not driven by quality, safety, efficacy, or benefit-risk concerns.

During this period, 7057 doses of Vidprevtyn Beta were administered worldwide, with a total of 2 151 791 doses administered cumulatively (to 18 March 2024).

34 spontaneous cases were reported during the covered period including 21 serious and 13 non-serious cases. ***The analysis provided by the MAH includes and evaluates information on 16 new cases that belong to the monitored categories of AESI, and other safety topics:*** *Acute aseptic arthritis (1), Arrythmia (1), Venous thromboembolism (2), Haemorrhagic stroke (1), Dizziness (3), Anaphylactic reactions (4), Swelling face/angioedema (1), Pemphigoid (1), Eye disorders (4), COVID-19 AESIs (2).*

Most reported cases lack substantial information, e.g. TTO for events, patient's concurrent conditions at the time of vaccination and medical history, concomitant medication or laboratory investigations, precluding a proper assessment. Also, some risk factors have been identified that complicate causality assessment, i.e. hypertension and anaphylactic reaction for arrhythmia; poor peripheral circulation, systemic lupus erythematosus, hypertension, varicose veins, and COVID-19 for DVT; antithrombotic treatment for haemorrhagic stroke; ongoing drug hypersensitivity to penicillin and current similar reaction to previous penicillin reaction for which patient stayed in hospital (for swelling face/angioedema after Vidprevtyn Beta).

The MAH identified 4 new cases of anaphylactic reaction, one of them includes 21yo female with the history of previous anaphylactic reaction after previous COVID-19 vaccination with Comirnaty and Vaxzevria, with the history of rash after vaccination with Nuvaxovid as well as drug hypersensitivity (rituximab, etoposide). The anaphylactic reaction has been observed on the same day after receiving Vidprevtyn Beta. The MAH assessed the case as of BCC level 1 which is endorsed. In addition, the causality is probable. The second case includes 53yo female with reported history of similar reactions after Comirnaty and Vaxzevria who experienced anaphylactic reaction including throat irritation 8 minutes after administration of Vidprevtyn Beta. Other symptoms as throat closing, wheezing, tingling tongue, chest tightness and cough occurred within 20 minutes after vaccination. The PRAC Rapp assess this case as of BCC level 3 and as probably related. In the other two cases unknown time to onset have been reported precluding in depth assessment.

Of note, anaphylactic reactions and dizziness are already listed ADRs of VidPrevtyn Beta. Based on the available information, the causal relationship between the rest of safety topics and VidPrevtyn Beta cannot be established at the moment.

Please see section 2.3. for previous assessment of risk and safety topics under monitoring.

***Moreover, five follow-up reports were received during this period and classified under following safety issues:** Unknown type stroke (1), Dizziness (1), Anaphylactic reactions (1), Death cases (2). However, no new important information was obtained from those follow-ups.*

***No case report of the following safety topics was reported during the period covered by the Addendum:** Guillain-Barré syndrome, Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multisystem inflammatory syndrome, Kawasaki disease, Sub-acute thyroiditis/auto-immune thyroiditis, Bell's Palsy, Rheumatoid arthritis, Type 1 diabetes mellitus, (Idiopathic) thrombocytopenia including immune thrombocytopenia and thrombotic thrombocytopenic purpura, Microangiopathy and thrombotic microangiopathy, Heart failure, Stress cardiomyopathy, Coronary artery disease (including Myocardial infarction), Myocarditis/Pericarditis, Single organ cutaneous vasculitis, Disseminated intravascular coagulation, Ischemic stroke, Cerebral venous sinus thrombosis, Thrombosis with thrombocytopenia syndrome, Thrombotic thrombocytopenic purpura, Acute liver injury, Acute kidney injury (including glomerulonephritis), Seizures (including general convulsions and all other seizure presentations), Neurological AESIs (Neuropathies/Polyneuropathies, Demyelinating disorders including Multiple Sclerosis and Optic neuritis), Meningoencephalitis/encephalitis, Paraesthesia, Acute respiratory distress syndrome, Dermatological AESIs (including Chilblains, Erythema Multiforme, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis), Anosmia and ageusia, Sudden death, Gout, Polymyalgia rheumatica, Colitis ulcerative, Idiopathic pulmonary fibrosis, Erythema nodosum, Musculoskeletal AESIs (including Rhabdomyolysis and Fibromyalgia), Appendicitis, Gastro-intestinal disorders, Heavy menstrual bleeding, Postural-orthostatic tachycardia syndrome, Pregnancy related AESIs.*

No signal was identified, validated, ongoing or closed for Vidprevtyn Beta during the reporting period.

Overall, no new safety findings that would impact the safety profile of Vidprevtyn Beta were identified.

7. Comments from Member States

Member State comment – MS1

We fully endorse the PRAC Rapp assessment and have no further comments.

Lead Member State assessment comments:
The endorsement of MS1 is greatly appreciated.

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-May-2023 to 09-Nov-2023

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

Report reference: VV-PV-0532989
Name: Anne-Laure Chabanon, Pharm D, Ph D
Function: Global Safety Officer
By delegation from the Sanofi QPPV
Signature: Signature on file

Date: 10-Jan-2024

Total number of pages: 83 (+Appendices)

EXECUTIVE SUMMARY

This Periodic Benefit Risk Evaluation Report for Recombinant Prefusion Spike Delta TM 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 Sanofi's Patient Safety and Pharmacovigilance department from worldwide sources, from 10 May 2023 through 09 November 2023.

The COVID-19 vaccine (recombinant, adjuvanted) belongs to the pharmacotherapeutic group "Vaccine, other viral vaccines"; 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. The preferred site is the deltoid muscle of the upper arm.

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.

The use of this vaccine should be in accordance with official recommendations.

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.

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

The safety and efficacy of COVID-19 vaccine (recombinant, adjuvanted) in children and adolescents less than 18 years of have not been established. No data are available.

A global safety data exchange agreement is in place between Sanofi Patient Safety and Pharmacovigilance and GlaxoSmithKline Biologicals SA for multiple territories.

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, no marketing authorization for COVID-19 vaccine (recombinant, adjuvanted) was granted.

The cumulative exposure to COVID-19 vaccine (recombinant, adjuvanted), in interventional clinical trials sponsored by the Marketing Authorization Holder is estimated to be 22 303 participants.

Based upon available data, 507 775 doses of COVID-19 vaccine (recombinant, adjuvanted) were administered worldwide in the marketing experience for the current review period, with a total of 2 144 734[1] doses administered cumulatively to date.

The European Union Summary of Product Characteristics for COVID-19 vaccine (recombinant, adjuvanted), version 01 dated 10 November 2022 was the reference safety information valid at the beginning of the Periodic Benefit Risk Evaluation Report period.

The reference safety information was revised on 21 September 2023 and the following amendments were made:

- Summary of Product Characteristics - Section 4.8 - Undesirable effects: Addition of "Anaphylactic reactions. Hypersensitivity (including rash, rash erythematous, urticaria, angioedema)" with frequency "Not known".

[1] On 30-Nov-2023, a new update from the Department for Business, Energy and Industrial Strategy from United Kingdom government was available notifying 6240 doses have been administered in the United Kingdom during the Fall campaign during the reporting interval. In total, 2 118 700 doses have been administered up to 09-Nov-2023 in the United Kingdom.

- Product Information Leaflet - Section 4 - Possible side effects: Addition of "Allergic reactions such as rash or hives or swelling of the face. Severe allergic reactions (anaphylaxis)" with frequency "Not known (cannot be estimated from available data)".

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

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), as a booster dose for active immunization to prevent Coronavirus Disease-2019 caused by severe acute respiratory syndrome coronavirus-2 Strain in adults who have previously received an messenger Ribonucleic Acid or adenoviral vector COVID-19 vaccine (recombinant, adjuvanted) remains positive in the currently approved conditions of use.

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ABBREVIATIONS

Ab:	Antibody
ADR:	Adverse Drug Reaction
AE:	Adverse Event
AESI:	Adverse Events of Special Interest
APHP:	Assistance Publique Hopitaux Paris
AS03:	Adjuvant System 03
BC:	Brighton Collaboration
BCCD:	Brighton Collaboration Case Definition
BiV:	Bivalent
BMI:	Body Mass Index
CDC:	Centers for Disease Control and Prevention
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CLI:	COVID-19-Like Illness
COPD:	Chronic Obstructive Pulmonary Disease
CoV-2:	Coronavirus-2
CoV-2 preS dTM:	Coronavirus-2 Prefusion Spike Delta TM
COVID-19:	Coronavirus Disease-2019
CTAP:	Coronavirus Treatment Acceleration Program
CVD:	Cardiovascular Disorders
C-VIPER:	Coronavirus Disease-2019 Vaccine International Pregnancy Exposure Registry
D:	Day
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
EC:	European Commission
ECDC:	European Centre for Disease Prevention and Control
ECMO:	Extracorporeal Membrane Oxygenation
EEA:	European Economic Area
ESC:	Externally Sponsored Collaborative
EU:	European Union
EUA:	Emergency Use Authorization
EUL:	Emergency Use Listing
FDA:	Food and Drug Administration
GMT:	Geometric Mean Titer
GMTR:	Geometric Mean Titer Ratio

GSK:	GlaxoSmithKline
GVP:	Good Pharmacovigilance Practices
HIV:	Human Immunodeficiency Virus
HLT:	High Level Term
IBD:	International Birth Date
ICH:	International Conference on Harmonisation
ID:	Identification
IMV:	Invasive Mechanical Ventilation
IND:	Investigational New Drug
IRR:	Incidence Reporting 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
mFAS-PD2:	Modified Full Analysis Set Post Dose 2
MHRA:	Medicines and Healthcare Products Regulatory Agency
mRNA:	Messenger Ribonucleic Acid
MV:	Monovalent
NHP:	Non-Human Primates
NIAID:	National Institute of Allergy and Infectious Diseases
O/E:	Observed Versus Expected
PASS:	Post-Authorization Safety Study
PBRER:	Periodic Benefit Risk Evaluation Report
PD2:	Post Dose 2
pIMD:	Potential Immune-Mediated Disease
PSPV:	Patient Safety and Pharmacovigilance
PSUR:	Periodic Safety Update Report
PsVN:	Pseudovirus Neutralization
PT:	Preferred Term
PV:	Pharmacovigilance
RBD:	Receptor Binding Domain
RMM:	Risk Minimization Measure
RMP:	Risk Management Plan
RPS:	Recombinant Perfusion Spike
S:	Spike
SAE:	Serious Adverse Event
SARS:	Severe Acute Respiratory Syndrome
SDEA:	Safety Data Exchange Agreement
SMQ:	Standardized MedDRA Query
suPAR:	Soluble Urokinase Plasminogen Activator Receptor

UAE:	United Arab Emirates
UK:	United Kingdom
UN:	United Nations
UNK MFR:	Unknown Manufacturer
US:	United States
VBM:	Variants Being Monitored
VE:	Vaccine Efficacy
VOC:	Variants of Concern

1 INTRODUCTION

This Periodic Benefit Risk Evaluation Report (PBRER) for Recombinant Prefusion Spike (RPS) Delta TM 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 (PSUR) (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 Patient Safety and Pharmacovigilance (PSPV) department from worldwide sources, from 10 May 2023 through 09 November 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 vaccines"; 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). The 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. The preferred site is the deltoid muscle of the upper arm.

It is indicated 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 use of this vaccine should be in accordance with official recommendations.

It is administered IM as a single dose of 0.5 mL at least four months after a previous COVID-19 vaccine. The 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.

The safety and efficacy of COVID-19 vaccine (recombinant, adjuvanted) in children and adolescents less than 18 years of have not been established. No data are available.

A global safety data exchange agreement (SDEA) is in place between Sanofi PSPV and GlaxoSmithKline (GSK) Biologicals SA for multiple territories.

COVID-19 vaccine (recombinant, adjuvanted) is not available as fixed dose combination/fixed ratio combination. During the reporting interval, this is the only PBRER prepared by the MAH for this product.

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 (IBD). 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, no MA for COVID-19 vaccine (recombinant, adjuvanted) was granted.

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 and is administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

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, 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 SmPC for COVID-19 vaccine (recombinant, adjuvanted), version 01 dated 10 November 2022 was the RSI valid at the beginning of the PBRER period.

The RSI was revised on 21 September 2023 and the following amendments were made:

- Summary of Product Characteristics – Section 4.8 - Undesirable effects: Addition of "Anaphylactic reactions. Hypersensitivity (including rash, rash erythematous, urticaria, angioedema)" with frequency "Not known".
- Product Information Leaflet – Section 4 - Possible side effects: Addition of "Allergic reactions such as rash or hives or swelling of the face. Severe allergic reactions (anaphylaxis)" with frequency "Not known (cannot be estimated from available data)"

Of note, Sanofi has submitted to EMA on 28 September 2023 an update of section 4.8 of the SmPC to include additional safety data based on the safety reports from studies VAT00008 and VAT00002 Cohort 2 further to the extension of the safety database over 2000 and 3000 participants with six weeks safety follow-up. The procedure started on 16 October 2023 with an expected EMA Committee for Medicinal Products for Human Use (CHMP) opinion on the 14 December 2023.

The current RSI at the data lock point (DLP) is the EU SmPC dated 21 September 2023 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 22 303 participants. Actual exposure data from completed or open-label clinical trials 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 (MV) and bivalent (BiV).

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	1359
SARS-CoV-2 preS dTM Monovalent B.1.351	10 953
SARS-CoV-2 preS dTM Bivalent D614+B.1.351	1295
Placebo	1062
Two injections	
SARS-CoV-2 preS dTM Monovalent D614	12 300
SARS-CoV-2 preS dTM Bivalent D614+B.1.351	6060
Placebo/Placebo	10 784
Three injections	
SARS-CoV-2 preS dTM Monovalent D614	137
Total	
SARS-CoV-2 preS dTM Monovalent and Bivalent	**22 303**
Placebo	**4843**

Data as of 09-Nov-2023 from studies: VAT00001 (completed), VAT00002 (ongoing), and VAT00008 (ongoing).
VAT00002 and VAT00008 participants may choose to receive one booster injection after a primary series vaccination.
A subset of participants in VAT00002 received the D614 formulation as both primary series vaccination and booster injection.
VAT00008 placebo participants may choose to receive a primary series vaccination (if unvaccinated) or one booster injection (if vaccinated) after meeting specific criteria. Therefore, participants in VAT00008 who received placebo in the first stage and received the vaccine during the crossover/booster phase are now counted in the vaccine row.
Participants who received more than one treatment are counted in each of the treatments, as received injections.
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; preS dTM: Prefusion Spike Recombinant Protein.

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

Exposure from the cumulative experience is available from 10 November 2022 through 09 November 2023.

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/EEA 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 EU country and age group as of 09 November 2023 are presented in Table 2 (last update of EU tracker was on 05 October 2023).

Table 2 - Number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in EU by country and age group through 09 November 2023

Country	EUROPE								Total
	Unknown	0-17	18-24	25-49	50-59	60-69	70-79	80+	
AUSTRIA	0	2	12	104	67	67	64	35	351
FRANCE	6881	0	0	0	0	0	0	0	6881
ITALY	53	0	3	48	20	51	23	14	212
PORTUGAL	6	0	1	21	14	17	15	3	77
SLOVENIA	0	0	0	0	1	0	0	0	1
Total	6940	2	16	173	102	135	102	52	7522

EU: European Union

Of note, open access data on the Public Health France website (1) are available: the cumulative number of doses administered during the 2023 French fall vaccination campaign categorized by COVID-19

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

vaccine type indicate 18 512 of COVID-19 vaccine (recombinant, adjuvanted) administered in France as per week 45.

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 available. The number of doses of COVID-19 vaccine (recombinant, adjuvanted) administered in England per age group as of 09 November 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 09 November 2023

Country	UK									Total
	Unknown	0-17	18-29	30-39	40-49	50-59	60-69	70-79	80+	
England	9	15	180	378	912	2 768	15 966	893 042	1 199 190	2 112 460[a]

a On 30-Nov-2023, a new update from the Department for Business, Energy & Industrial Strategy from UK government was available notifying 6240 doses have been administered in the UK during the Fall campaign during the reporting interval. In total, 2 118 700 doses have been administered up to 09-Nov-2023 in the UK.

UK: United Kingdom

Based upon available data, 507 775 doses of COVID-19 vaccine (recombinant, adjuvanted) were administered worldwide for the current review period, with a total of 2 144 734[3] doses administered cumulatively.

The interval and cumulative patient exposure are presented above; therefore, Appendix 5.2.2 and Appendix 5.2.3 are not applicable.

5.2.2 Post-approval use in special populations

The MAH does not have access to cumulative post-marketing 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 2 108 198 doses administered 60 years and older (Department for Business, Energy & Industrial Strategy from the UK government).

[3] On 30-Nov-2023, a new update from the Department for Business, Energy and Industrial Strategy from UK government was available notifying 6240 doses have been administered in the United Kingdom during the Fall campaign during the reporting interval. In total, 2 118 700 doses have been administered up to 09-Nov-2023 in the UK.

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

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

Use in subjects with autoimmune or inflammatory disorders is a missing information and is planned to be studied in the scope of non-interventional study VAT00007 (not yet initiated). Please refer to Section 16 for further information.

Use in elderly: In the UK, country where most doses were administered, the indication is targeting the population aged 75-year-old and above. Thus, most of the post-marketing 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 profile presented in this PBRER can be considered as reflecting the safety profile 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 26.1 was used for the coding of adverse events (AEs) and adverse drug reactions (ADRs) and for analyses based on Standardized MedDRA Query (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 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 1073 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 ADRs from spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, and Regulatory Authorities.
- Serious adverse reactions from non-interventional studies and
- Solicited reports of serious adverse reactions.[4]

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 for regulatory reporting purposes.

A total of 1980 cumulative adverse reactions have been reported, 754 of which were reported during the present reporting period for COVID-19 vaccine (recombinant, adjuvanted) (see Appendix 2.2.1).

A total of 128 cumulative adverse reactions have been reported, 109 of which were reported during reporting period for an unknown manufacturer (UNK MFR) (see Appendix 2.2.2).

[4] 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 period of this PBRER, one clinical trial (VAT00001) where COVID-19 vaccine (recombinant, adjuvanted) was the investigational product under study or development has been completed. As of the DLP, a total of two clinical trials are ongoing: VAT00002 and VAT00008.

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

VAT00001 study was completed during the reporting period. The final data confirmed the interim data showing that a two-injection schedule of vaccination was necessary to induce neutralizing antibodies (Ab) and that the low-dose adjuvanted vaccine induced higher titers of neutralizing Abs compared to high-dose unadjuvanted protein-alone vaccine demonstrating the benefit of the adjuvant. In addition, the CoV2 preS dTM antigen adjuvanted with AS03 induced higher titers of neutralizing Abs compared to both the AF03 adjuvanted group and compared to the unadjuvanted groups with a two-injection schedule. However, even in the best performing vaccine group (two-injection schedule of high-dose + AS03), seroconversion rates at Day 36 [D] were below 90% in all adults with lower rates in older adults (82.4% in 50 years and older, 57.1% in 60 years and older). These results indicated the need for further optimization of the antigen formulation and dose, with doses higher than the effective high dose of 2.6 µg used in this study. Due to confounding effects, there was limited ability to meaningfully conclude on the durability of neutralizing Ab responses for longer term timepoints.

7.1.2 Safety findings

All vaccinations in the VAT00001 study occurred prior to the review period. The safety follow-up period of the study was completed prior to the review period. There were no clinically important emerging safety findings in this study completed during the reporting interval.

7.2 ONGOING CLINICAL TRIALS

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 (2).

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) (3).

- 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 5µg 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 Adverse Events of Special Interest (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 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, 5 µg (D614 component) + 5 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 BiV vaccine. Thus, by design, the inclusion of the B.1.351 antigen with the D614 antigen in the BiV 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 AESI) (4).

No safety concern was raised from the VAT00008 study for the MV or BiV vaccine formulations.

There was no new clinically important information arising from studies ongoing during the reporting interval and during the interval between the overlapping DSUR DLP (28 August 2023) and the PBRER DLP (09 November 2023)

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. Registration for the C-VIPER registry is currently open in several countries except in France.

As of the DLP, no participants vaccinated with COVID-19 vaccine (recombinant, adjuvanted) vaccine have been enrolled in VAT00012.

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, two investigator-sponsored studies (VAT00013 and VAT00029, both sponsored by Assistance Publique Hopitaux 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 subunit 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.

An ancillary study of VAT00013 study has been launched to evaluate the immune response of a second booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine in comparison to mRNA Pfizer/BioNTech prototype vaccine in elderly participants (≥ 60 years of age) who received three doses of vaccination with mRNA vaccines.

VAT00029: This investigator-sponsored study is a randomized, single blinded-multicenter clinical trial to assess the immunogenicity and safety following a booster dose of the Sanofi-GSK Monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine compared to a BiV mRNA vaccine (Comirnaty Original/Omicron BA.4-5, BioNTech-Pfizer) in adults previously vaccinated with at least three doses of COVID-19 mRNA vaccine.

VAT00026: This phase II study 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 and during the interval between the overlapping DSUR DLP (28 August 2023) and the PBRER DLP (09 November 2023).

9.2 MEDICATION ERRORS

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

Events are coded in the PSPV 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 ARs 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.

During the reporting period, a total of 10 cases have been reported with medication error. All PTs within the Medication error SMQ reported with COVID-19 vaccine (recombinant, adjuvanted) by High Level Term (HLT) and PT are presented in Table 4.

The reported PTs within the Medication error SMQ reported with UNK MFR by HLT and PT are presented in Table 5.

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 with COVID-19 vaccine (recombinant, adjuvanted)

Medication Error description	PT for Medication Error	Count of events of Medication Error
Children of 5 and 11 years-old received the vaccine.	*Product administered to patient of inappropriate age*	2
A child and an elderly patient received COVID-19 vaccine (recombinant, adjuvanted) instead of Pfizer vaccine against COVID-19.	*Wrong product administered*	2
Medication error reported by a consumer: for him, this reaction "occurred as a result of a mistake made in the administration of the vaccine since when the vaccination was administered it was painful, compared to the first 5 COVID-19 vaccinations".	*Medication error*	1
Patient mistakenly received COVID-19 vaccine (recombinant, adjuvanted) vaccine as primary dose.	*Product use in unapproved indication*	1

Medication Error description	PT for Medication Error	Count of events of Medication Error
Incorrect placement of COVID-19 vaccination (confirmed by rheumatologist).	*Wrong technique in product usage process*	1
Vaccine administered the month of the expiry date or just after.	*Expired product administered*	1
Patient received his COVID-19 vaccine (recombinant, adjuvanted) less than four months after his previous COVID-19 vaccine dose.	*Inappropriate schedule of product administration*	1
Pharmacist ordered COVID-19 vaccine (recombinant, adjuvanted) doses in Oct-2023, those patient received expired the same month.	*Product dispensing error*	1
Patient received lower volume than recommended.	*Incorrect dose administered*	1

PT: Preferred Term; COVID-19: Coronavirus Disease-2019

Table 5 - Most frequently reported medication errors reported during the interval with UNK MFR

Medication Error description	PT for Medication Error	Count of events of Medication Error
According to "documentation", two vaccines were administered to the elderly patients: COVID-19 vaccine (recombinant, adjuvanted) and Efluelda®. The patient thinks it is a documentation error because patient only has one arm available for vaccination (patient has a plaster on a vaccination site).	*Transcription medication error*	1

PT: Preferred Term; COVID-19: Coronavirus Disease-2019; UNK MFR: Unknown Manufacturer

Out of the 10 cases of medication errors reported during the review period, three (one serious and two non-serious) were reported with AEs (30 %) and seven cases had no reported AEs (70 %). The three cases associated with AEs are described for the assessment of interval medication error cases reporting AEs (Table 6).

Table 6 - Interval medication error cases reporting adverse events

Case ID Seriousness	Medication Error PT	PT(s) of reported AE(s)	Suspected vaccine	Comment
[redacted] / Serious	Wrong technique in product usage process	*Polymyalgia rheumatica* *Pain in extremity*	COVID-19 vaccine (recombinant, adjuvanted)	Case reported by a consumer. A 79-year-old patient reported pain in extremity and wrong technique in product usage process the day of vaccination with COVID-19 Vaccine (dose 5).

Case ID Seriousness	Medication Error PT	PT(s) of reported AE(s)	Suspected vaccine	Comment
				Severe left upper arm pain was due to incorrect placement of COVID-19 vaccination (confirmed by rheumatologist). The patient also experienced polymyalgia rheumatica on the same day. Hospital report states that polymyalgia was possibly triggered by the COVID-19 vaccine. As per reporter this reaction occurred was not a result of a mistake made in the administration of the vaccine. At time of reporting, the outcome was not recovered for the events polymyalgia and pain in extremity.
[redacted] Non-Serious	Medication error	*Erythema* *Somnolence* *Injection site mass* *Arthralgia* *Injection site pain* *Asthenia*	COVID-19 vaccine (recombinant, adjuvanted)	Case reported by a consumer. An 82-year-old patient with ongoing arthritis, experienced redness, sleepiness, injection site mass, injection site pain, feeling of total lack of energy and reported medication error the day of vaccination (6th dose). Patient also reported pain in hip, five days after vaccination. As per reporter "this reaction occurred as a result of a mistake made in the administration of the vaccine since when the vaccination was administered it was painful, compared to the first five COVID-19 vaccinations." At time of reporting, the outcome was not recovered/ not resolved for all events. *MAH comment: Although the pain during vaccination might have been linked with a vaccination technique, there is no evidence to conclude on any error and any link between the applied vaccination technique and the symptoms reported except for Injection site pain.*
[redacted] Non-Serious	Wrong product administered	Rhinorrhoea, Pain, Pyrexia	COVID-19 vaccine (recombinant, adjuvanted)	Case reported by a physician, who is also the patient. The patient of unknown age experienced fever, runny nose and body aches an unknown date after vaccination. At time of event, patient had prostate cancer, Parkinson's disease, bone marrow dysplasia, polyneuropathy, diabetes mellitus, Myelodysplastic syndrome and sleep apnea syndrome (device assisted). The patient already had symptoms (fatigue, dizziness) before vaccination. The patient was supposed to receive Pfizer COVID-19 vaccine but the day of vaccination, the pharmacy called him back and told him that there was an error, and he would receive VidPrevtyn Beta®.

Case ID Seriousness	Medication Error PT	PT(s) of reported AE(s)	Suspected vaccine	Comment
				Patient does not think symptoms are related to the vaccine but to repeated infections that te patient gets very regularly because of his sleep apnea device. At time of reporting, the outcome was unknown for the event.

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

There were no relevant safety findings on patterns of medication errors and potential medication errors identified which would require specific risk minimization measures (RMMs) 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.

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 AESI 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 studies

After MAH's proposal in the last PBRER to implement a focused strategy for literature screening, PRAC agreed to focus the scientific literature search strategy on the vaccines of the same or similar platform.

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

Class-related articles for other protein-based and protein nanoparticle vaccines:

Altman N, Berning AA, Mann SC, Quaife RA, Gill E, Auerbach SR, et al. Vaccination-Associated Myocarditis and Myocardial Injury. Circulation Research. 2023 May 12;132(10):1338–57. (5)

The article discussed SARS-CoV-2 vaccine–associated myocarditis of various platforms, including protein-based vaccine (NVX-CoV2373 – adjuvanted recombinant spike protein vaccine, NUVAXOVID®). Five (5) cases of temporally related myocardial injury that clinically could have been myocarditis, plus one case of pericarditis were reported in Phase 3 clinical trials with Nuvaxovid within ten days of vaccine receipt, versus one case of possible myocarditis in the placebo arm that occurred 72 days post-vaccination. It was reported that the risk of myocarditis after the Nuvaxovid and mRNA vaccines may be similar, and that mRNA-induced immune activation as a major mechanism of vaccine-associated myocarditis is therefore not supported.

MAH comment: From the data provided in the article, it seems that mRNA-induced immune activation may not be the only mechanism of vaccine-associated myocarditis. Genetic variation in ACE2 leading to differences in S protein binding affinity may explain a similar degree of infrequent myocarditis case reports between mRNA and recombinant protein-based vaccines.

Wilkinson B, Patel KS, Smith K, Walker R, Wang C, Greene AM, et al. A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for the NOVAVAX® COVID-19 Vaccine (NVX-CoV2373), a recombinant spike protein vaccine with Matrix-M adjuvant to prevent disease caused by SARS-CoV-2 viruses. Vaccine. 2023 Oct 26;41(45):6762–73. (6)

The authors presented NOVAVAX COVID-19 Vaccine (NVX-CoV2373, Nuvaxovid), a recombinant spike protein vaccine with Matrix-M adjuvant, in the Brighton Collaboration (BC) standardized template with key considerations for a benefit/risk assessment to prevent disease caused by SARS-CoV-2 viruses. Clinical data in over 31 000 adult and adolescent participants administered Nuvaxovid has demonstrated that in primary two-dose vaccination there was a well-tolerated response to Nuvaxovid and high vaccine

efficacy against mild, moderate or severe COVID-19. Similarly, for the booster vaccination (six months after primary vaccination), there was a high vaccine efficacy (substantial increases in humoral antibodies against both the prototype strain and all evaluated variants, similar to or higher than the antibody levels observed in phase 3 studies), and a well-tolerated safety profile in both primary and booster vaccination.

In regard to the AESI of Myocarditis/pericarditis, two events of myocarditis in the Nuvaxovid group, and one event in the placebo group were reported in the pre-crossover period (risk difference of zero (95% CI, 0.02–0.02). In the post-crossover from placebo to active vaccine, two events of pericarditis and one event of myocarditis were reported for Nuvaxovid, and one event of myocarditis for placebo (risk difference of 0 (95% CI, 0.02–0.05) for myocarditis and 0.02 (95% CI, 0.00–0.08) for pericarditis). However, myocarditis/pericarditis was classified as an important identified risk for Nuvaxovid, based on reports received in the post-authorization setting.

MAH comment: Myocarditis/pericarditis is considered an important potential risk for COVID-19 vaccine (recombinant, adjuvanted) and is closely monitored through both routine and additional pharmacovigilance (PV) *activities.*

Song JY, Choi WS, Heo JY, Kim EJ, Lee JS, Jung DS, et al. Immunogenicity and safety of SARS-CoV-2 recombinant protein nanoparticle vaccine GBP510 adjuvanted with AS03: interim results of a randomised, active-controlled, observer-blinded, phase 3 trial. EClinicalMedicine. 2023 Oct 1;64:102140. (7)

The authors presented the interim results of a phase three multinational study for GBP510 (SKYCOVIONE®) vaccine adjuvanted with AS03 (GBP510/AS03) compared with ChAdOx1-S in healthy adults aged ≥18 years, up to six months after the second dose. GBP510 is a recombinant protein vaccine consisting of self-assembling, two-component nanoparticles displaying SARS-CoV-2 spike receptor-binding domains (receptor binding domain [RBDs] adjuvanted with AS03. A total of 4036 participants were randomized to receive two-doses of GBP510/AS03 (n = 3039) or ChAdOx1-S (n = 997). In the safety analysis, the proportion of participants with AEs after any vaccination was higher with GBP510/AS03 versus ChAdOx1-S for solicited local AEs (56.7% versus 49.2%) but was similar for solicited systemic AEs (51.2% versus 53.5%) and unsolicited AEs (13.3% versus 14.6%) up to 28 days after the second vaccination. A total of six cases reporting AESIs were reported, three in the GBP510/AS03 group (acute kidney injury, rapidly progressive glomerulonephritis, and cutaneous vasculitis) and three in the ChAdOx1 S group (acute pancreatitis, anaphylactic reaction, and psoriasis). No safety concerns were identified during follow-up for six months after the second vaccination. Additionally, five pregnancies were reported in the GBP510/AS03 group and two in the ChAdOx1-S group; all individuals gave birth without any abnormal outcomes or SAEs.

MAH comment: The interim findings of this study suggested that GBP510/AS03 met the superiority criterion for neutralizing antibodies and non-inferiority criterion for seroconversion rate compared with ChAdOx1-S and showed a clinically acceptable safety profile.

Sanofi-Sponsored studies published during the reporting interval:

Of note, the following two articles were published during the reporting period, presenting the results of the Sanofi sponsored studies with two different SARS-CoV-2 recombinant protein vaccines with AS03 adjuvant (see also Section 17.2):

de Bruyn G, Wang J, Purvis A, Ruiz MS, Adhikarla H, Alvi S, et al; VAT00002 booster cohorts study team. 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: a phase 3, parallel-group study. EClinicalMedicine. 2023 Jul 22;62:102109. (8)

MAH Comment: This publication refers to the Sanofi sponsored phase III study VAT00002 (Supplemental Cohorts). It presents the interim analyses up to 14 days post-last vaccination for immunogenicity and over a median duration of five months for safety. 549-RSP-COVID-19_NS / 561-RSP-COVID-19-bi vaccine boosters demonstrated acceptable safety and elicited robust neutralizing antibodies against multiple variants, regardless of priming vaccine.

Dayan GH, Rouphael N, Walsh SR, Chen A, Grunenberg N, Allen M, et al. Efficacy of a monovalent (D614) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant in adults: a phase 3, multi-country study. eClinicalMedicine. 2023 Oct 1;64:102168. (9)

MAH comment: This publication refers to the Sanofi sponsored phase III study parallel, international randomized, double-blind, placebo-controlled study for the prototype MV (D614) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant. The vaccine was well-tolerated with an acceptable safety profile and some level of protection against the Delta strain in participants regardless of prior infection, comparable to vaccine efficacy with other D614-based COVID-19 vaccines.

12 OTHER PERIODIC REPORTS

COVID-19 vaccine (recombinant, adjuvanted) is not available as fixed dose combination/fixed ratio combination. During the reporting interval this is the only PBRER prepared by the MAH for this product.

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

The following significant changes were proposed to the RSI after the DLP of the report following final PRAC updated assessment report dated 30 November 2023 to include "dizziness" to the Adverse Reactions section of the EU SmPC and PIL with frequency "rare". The approval of the EU SmPC and PIL including this update was granted on 14 December 2023.

15 OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

A tabulation of signals that were ongoing at the DLP or closed during the reporting interval is presented in Appendix 3.

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

- Patient Safety and 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 database
- Regulatory Authority websites

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

- Safety queries and requests from Regulatory Authorities
- Clinical trials and other studies in human (individual study data and integrated study data), Independent Data Monitoring Committee reports
- Non-clinical safety information (eg, toxicology, safety pharmacology, pharmacokinetic 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 PSPV 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 Product complaint database such as event counts and frequency or proportion thresholds, sorting, and cross-tabulations, based on thresholds, evaluation algorithms and medical judgment.

Allergic including anaphylactic reactions signal, presented in the Late breaking information section of the previous PBRER, was reviewed after DLP of the previous PBRER and has been confirmed as an identified risk (refer to Appendix 5.3). It has also been added into the RSI (refer to Section 4). This topic remains under surveillance via routine PV.

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

The following safety topics were monitored during the reporting period to address EMA's request based on the Core-Risk Management Plan (RMP) guidance (10), Responses to Rapporteurs Final List of Questions on RMP dated 23 June 2022 (Reference submission: EMEA/H/C/005754/0000), dated 15 August 2022 (Reference submission: EMEA/H/C/005754/0000), EMA Committee for CHMP Assessment Report dated 10 November 2022, Medicines and Healthcare products Regulatory Agency (MHRA) request dated 20 December 2022, and EMA PRAC Assessment Report dated 30 November 2023 (procedure number- EMEA/H/C/PSUSA/00011035/202305).

The safety topics are presented in the order of list of AESIs in Annex 7.2 of EU-RMP (Refer to MedDRA search strategy outlined in Appendix 6.3.1). The conclusions of the safety topics analyses are provided below, and the detailed analyses are included in Appendix 5.4.1.

Utilizing the search strategy as described in Appendix 6.3.1, the MAH did not identify any new information that would impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile. In addition, observed versus expected (O/E) analysis when conducted did not detect any O/E ratio for any safety topic (see Appendix 6.3.2).

15.1.1 Guillain- Barré syndrome

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.2 Acute Disseminated Encephalomyelitis

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

Please refer to Section 15.1.43 Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multisystem inflammatory syndrome, Acute pancreatitis/autoimmune pancreatitis, Kawasaki disease, Sub-acute thyroiditis/auto-immune thyroiditis.

15.1.3 Transverse Myelitis

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

Please refer to Section 15.1.43 Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multisystem inflammatory syndrome, Acute pancreatitis/autoimmune pancreatitis, Kawasaki disease, Sub-acute thyroiditis/auto-immune thyroiditis.

15.1.4 Bell's Palsy

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.5 Narcolepsy

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

Please refer to Section 15.1.43 Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multisystem inflammatory syndrome, Acute pancreatitis/autoimmune pancreatitis, Kawasaki disease, Sub-acute thyroiditis/auto-immune thyroiditis.

15.1.6 Acute aseptic arthritis

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Acute aseptic arthritis. Refer to Appendix 6.3.2.

15.1.7 Rheumatoid arthritis

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Rheumatoid arthritis. Refer to Appendix 6.3.2.

15.1.8 Type 1 diabetes mellitus

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.9 (Idiopathic) thrombocytopenia including immune thrombocytopenia and thrombotic thrombocytopenic purpura

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.10 Microangiopathy and thrombotic microangiopathy

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.11 Heart failure

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Heart failure. Refer to Appendix 6.3.2.

15.1.12 Stress cardiomyopathy

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.13 Arrhythmia

During the reporting period the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Arrhythmia. Refer to Appendix 6.3.2.

15.1.14 Coronary artery disease (including myocardial infarction)

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for coronary artery disease (including myocardial infarction). Refer to Appendix 6.3.2.

15.1.15 Myocarditis/Pericarditis

Myocarditis/pericarditis is considered an important potential risk. Please refer to Section 16, Section 16.3.1.1 and Appendix 5.4.1 for further details.

In addition, no increased O/E ratio has been detected for Myocarditis/Pericarditis. Refer to Appendix 6.3.2.

15.1.16 Single organ cutaneous vasculitis

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Single organ cutaneous vasculitis. Refer to Appendix 6.3.2.

15.1.17 Disseminated intravascular coagulation

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.18 Venous thromboembolism (including Pulmonary embolism and Deep vein thrombosis)

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Venous thrombo-embolism. Refer to Appendix 6.3.2.

15.1.19 Stroke

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.19.1 Hemorrhagic stroke

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E has been detected for Hemorrhagic stroke. Refer to Appendix 6.3.2.

15.1.19.2 Ischemic stroke

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Ischemic stroke. Refer to Appendix 6.3.2.

15.1.20 Cerebral venous sinus thrombosis

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for cerebral venous sinus thrombosis. Refer to Appendix 6.3.2.

15.1.21 Thrombosis with thrombocytopenia syndrome (TTS)

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.22 Thrombotic thrombocytopenic purpura

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

Please refer to Section 15.1.9 (Idiopathic) thrombocytopenia including immune thrombocytopenia and thrombotic thrombocytopenic purpura and Section 15.1.44 All other Immune-mediated/autoimmune AESIs/potential Immune-mediated diseases (pIMD), including Myasthenia gravis.

15.1.23 Acute liver injury

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Acute liver injury. Refer to Appendix 6.3.2.

15.1.24 Acute kidney injury (including glomerulonephritis)

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Acute kidney injury. Refer to Appendix 6.3.2.

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

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Seizures (including general convulsions and all other seizure presentations). Refer to Appendix 6.3.2.

15.1.26 Neurological AESIs (Neuropathies/Polyneuropathies, Demyelinating disorders including Multiple Sclerosis and Optic neuritis)

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.27 Meningoencephalitis/encephalitis

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.28 Dizziness

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

A detailed medical review of all reported dizziness case reports with DLP 30 June 2023 was finalized in September 2023. This analysis included 50 of the 52 cumulative post-marketing cases reports. It is available in Appendix 5.4.3. Current analysis is in alignment with the detailed medical review.

Following PRAC request, Sanofi has submitted to European Medicine Agency on 29 November 2023 an update of section 4.8 of the Summary of Product Characteristics (and Product Information Leaflet) to add dizziness as an adverse reaction, with frequency rare. The approval was granted on 14 December 2023.

15.1.29 Paresthesia

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.30 Acute Respiratory Distress Syndrome

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Acute Respiratory Distress Syndrome. Refer to Appendix 6.3.2.

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

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.32 Anosmia and ageusia

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Anosmia and ageusia. Refer to Appendix 6.3.2.

15.1.33 Anaphylactic reactions

During the reporting period, Anaphylactic reactions has been reclassified as an identified risk.

No significant O/E ratio increase has been detected for Anaphylactic reactions using a reporting rate of 100%; however, a significant O/E ratio increase has been detected considering a reporting rate of 50% (meaning that only 50% of the cases were reported). Refer to Appendix 6.3.2 and Section 16.2.1 Signals categorized as potential or identified risk and Section 4 Changes to the RSI.

15.1.34 Swelling face/angioedema

During the reporting period, allergic reactions, including swelling face/angioedema have been classified as identified risk. Refer to Section 16.2.1 Signals categorized as potential or identified risk and Section 4 Changes to the RSI.

15.1.35 Multisystem inflammatory syndrome

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

Please refer to Section 15.1.43 Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multisystem inflammatory syndrome, Acute pancreatitis/autoimmune pancreatitis, Kawasaki disease, Sub-acute thyroiditis/auto-immune thyroiditis.

15.1.36 Death (any causes)

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

As in all PBRERs and although there was no signal, all cases with a fatal outcome were reviewed during the period. The results of this analysis are provided in Appendix 5.4.1 and Appendix 5.4.2.

In addition, no significant O/E ratio increase has been detected for death. Refer to Appendix 6.3.2.

15.1.37 Sudden death

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile. Refer to Appendix 5.4.2.

15.1.38 COVID-19 AESIs

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.39 Vaccine failure

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.40 Sub-acute thyroiditis/auto-immune thyroiditis

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

Please refer to Section 15.1.43 Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multisystem inflammatory syndrome, Acute pancreatitis/autoimmune pancreatitis, Kawasaki disease, Sub-acute thyroiditis/auto-immune thyroiditis.

15.1.41 Acute pancreatitis/autoimmune pancreatitis

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

In addition, no increased O/E ratio has been detected for Acute pancreatitis/autoimmune pancreatitis. Refer to Appendix 6.3.2.

Please refer to Section 15.1.43 Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multisystem inflammatory syndrome, Acute pancreatitis/autoimmune pancreatitis, Kawasaki disease, Sub-acute thyroiditis/auto-immune thyroiditis.

15.1.42 Kawasaki disease

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

Please refer to Section 15.1.43 Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multisystem inflammatory syndrome, Acute pancreatitis/autoimmune pancreatitis, Kawasaki disease, Sub-acute thyroiditis/auto-immune thyroiditis.

15.1.43 Specific Immune-mediated/autoimmune AESIs: Acute Disseminated Encephalomyelitis, Transverse myelitis, Narcolepsy, Multisystem inflammatory syndrome, Acute pancreatitis/autoimmune pancreatitis, Kawasaki disease, Sub-acute thyroiditis/auto-immune thyroiditis

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.44 All other Immune-mediated/autoimmune AESIs/potential Immune-mediated diseases (pIMD), including Myasthenia gravis

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.45 Musculoskeletal AESIs (including Rhabdomyolysis and Fibromyalgia)

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.46 Appendicitis

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.47 Gastro-intestinal disorders

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.48 Eye disorders

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.49 Heavy menstrual bleeding

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.50 Post-orthostatic tachycardia syndrome

During the reporting period, the MAH has not identified any new safety information on the monitored event that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile.

15.1.51 Pregnancy related AESIs

There was no reported use in pregnancy during the reporting period or cumulatively. Use in pregnancy is also a missing information for COVID-19 vaccine (recombinant, adjuvanted) (see Section 16.3.5).

New relevant efficacy and/or effectiveness or vaccine failure findings from published clinical studies performed in authorized indications made available during the reporting interval are further discussed in Section 17.2.

15.1.52 Use in elderly population

During the reporting period, the MAH has not identified any new safety information on the monitored events that would have an impact on the COVID-19 vaccine (recombinant, adjuvanted) safety profile. Please refer to Section 5.2.2.

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 RMP. 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 Practice 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 7.

Table 7 - 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	Using 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 Interaction 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

Closed signals that are categorized as identified risks not categorized as important

Allergic including anaphylactic reactions:

There was one signal that was categorized as identified risk (non-important) for COVID-19 vaccine (recombinant, adjuvanted) during the reporting interval. This signal of "Allergic including anaphylactic reaction" was mentioned in Section 14 Late-breaking information of the previous PBRER DLP 09 May 2023 and the conclusion, classification and full safety analysis reported were already submitted to EMA on 03 August 2023 through a Type II variation. The updated RSI was submitted (procedure EMEA/H/C/005754/II/0006) and approved to include anaphylactic reactions and allergic reactions (including rash, rash erythematous, urticaria, angioedema) as listed AEs for COVID-19 vaccine (recombinant, adjuvanted).

Based on medical review of cases of allergic including anaphylactic reactions reported after the use of COVID-19 vaccine (recombinant, adjuvanted), the cumulative weight of evidence is sufficient to support a causal association between allergic including anaphylactic reactions and COVID-19 vaccine (recombinant, adjuvanted). A labeling change evaluation was deemed necessary to include anaphylactic as listed adverse events for COVID-19 vaccine (recombinant, adjuvanted) and was performed through an RSI update. Overall, the benefit-risk ratio of the COVID-19 vaccine (recombinant, adjuvanted) remains favorable in its approved indication under the current recommended conditions of use. Please refer to SER in Appendix 5.3.

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.

16.3 EVALUATION OF RISKS AND NEW INFORMATION

16.3.1 New information on important potential risks

16.3.1.1 Myocarditis/Pericarditis

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 risk of myocarditis and pericarditis. Refer also to Appendix 5.4.1. In addition, no increased O/E ratio has been detected for myocarditis/pericarditis. Refer to Appendix 6.3.2.

16.3.1.2 Vaccine Associated Enhanced Disease including Vaccine Associated Enhanced Respiratory Disease

Utilizing the surveillance activities defined in Section 15, the MAH has determined that there was new relevant safety information that would have an impact on the understanding and characterization of the previously recognized potential risk of VAED including VAERD. Details regarding the new relevant safety information are included below:

- Source of new information: Cases retrieved for the reference interval from PSPV Safety database.
- Background relevant to the evaluation: For more details on this risk, see also Section 16.4.
- Methods of evaluation including data sources, search criteria, and analytical approaches: The PSPV safety database was searched for the following SMQ *"(N) COVID-19 (SMQ)*". Case reports have been assessed against the Brighton Collaboration Case Definition (BCCD) level of certainty (11).
- Results: From the review of PSPV Safety database, 16 cases were retrieved from post-marketing surveillance, none meeting BCCD (the two serious cases with compatible time to onset were not assessed as not VAED/VAERD).

During the reporting interval, the MAH received updated information to analyze the risk of VAED including VAERD (refer to Section 16.4). Based on information received during the reporting interval, the risk of VAED including VAERD is now removed from the list of safety concerns of the EU-RMP version 2.0. No impact is deemed necessary on labelling.

The topic of VAED including VAERD, was initially considered as an important potential risk in RMP at the initial conditional MA for COVID-19 vaccine (recombinant, adjuvanted) in the EU (10 November 2022) and in alignment with all COVID-19 vaccines (12).

The potential for increased disease severity in naive vaccines upon exposure to wild-type virus, a phenomenon known as VAED including VAERD, was raised as a theoretical safety concern with

COVID-19 vaccines early in the pandemic. At that time (11), (13), (14), (15), (16), long-term safety and efficacy data were insufficient to definitively rule out VAED including VAERD as a safety concern.

The VAED including VAERD risk, as defined by the BCCD, is not applicable to booster vaccination as it only concerns SARS-CoV-2 seronegative individuals or those with an unknown serostatus and no prior COVID-19 infection. Since COVID-19 vaccine (recombinant, adjuvanted) is administered as a booster vaccination, this risk is not applicable (11).

Furthermore, there is currently no widely accepted case definition for VAED including VAERD. A publication by the BC provides some guidance for assessment of potential VAED including VAERD in COVID-19 (11) and suggests that VAED including VAERD may be identified first as a vaccine failure (ie, VAED requires exposure to and infection by SARS-CoV-2 in a person who has been fully immunized). The authors acknowledge that there is presently no pathognomonic set of clinical findings to characterize VAED. In addition, case classifications that can be readily applied to individual-level data from spontaneous reporting are not defined. The BC working group states that a definitive case of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED. Probable cases must show an increase in severity or rates of atypical findings when compared to a non-vaccinated control group, however this criterion must be considered at a population or group level rather than an individual level. Given that there have been numerous epidemiologic studies evaluating effectiveness of mRNA vaccines in millions of vaccinees and that there have not been findings showing an increased risk of COVID-19 disease in vaccinees (or a subgroup of vaccinees) compared to those not vaccinated, real world evidence does not show occurrence of VAED. Moreover, there is an absence of medical literature supporting the existence of VAED due to vaccines against COVID-19.

There is no reasonable expectation that the existing or future feasible PV activities could further characterize the safety profile of the product with respect to VAED and especially with COVID-19 vaccine (recombinant, adjuvanted) being administered as a booster only.

Accumulated evidence with COVID-19 vaccine (recombinant, adjuvanted) supported by evidence accumulated with other COVID-19 vaccines of different platforms does not suggest that this theoretical risk is still of relevance for COVID-19 vaccine (recombinant, adjuvanted) especially in the context of booster vaccination:

- No evidence of increase in COVID-19 severity was observed in VAT00008 clinical study when comparing the placebo and the vaccine groups (primary series). In addition, participants of ongoing clinical studies were followed up on any COVID-19 outcome (active and passive surveillances), without any safety concerns identified. Even with the emergence of multiple new variants/serotypes of SARS-CoV-2, with their potential to provoke sub-neutralizing antibodies in individuals who have encountered similar (but poorly cross reactive) epitopes, as was the case for SARS-CoV-2 variant Omicron, no enhancement of disease has been reported.
- More than two million doses of COVID-19 vaccine (recombinant, adjuvanted) have been administered since initial approval of the vaccine in November 2022 up to RMP DLP without

any safety concern identified. This is supported by the absence of any VAED including VAERD safety concerns identified from other COVID-19 vaccines despite widespread use of COVID-19 vaccines administered since the first emergency use authorization (EUA) granted in December 2021 (mRNA vaccines) (17), (18), This is likely in this extensive exposure that VAED would have been observed and reported if this theoretical risk was confirmed. Effectiveness data generated from UK Health Security Authority showed effectiveness of COVID-19 vaccine (recombinant, adjuvanted) against hospitalization.

- Animal models of SARS-CoV-2 infection have not shown evidence of VAED disease after immunization. This (19), (20) is supported by available data for other COVID-19 vaccines from different platforms, including COVID-19 vaccine (recombinant, adjuvanted) platform (17), (18).

Conclusion: The MAH considers that there is no convincing evidence to support the hypothesis that VAED including VAERD exists. There is sufficient justification for removing VAED including VAERD as an important potential risk from the EU-RMP for COVID-19 vaccine (recombinant, adjuvanted) being administered as a booster and proposes to continue monitoring occurrence and severity of COVID-19 disease in vaccinated individuals through routine surveillance of vaccination failures/lack of efficacy and ongoing post-authorization safety studies (PASS) as applicable. Any change in the available evidence (risk re-evaluation as per incidence and severity) would lead to a re-evaluation of this statement.

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 determined that there was new relevant safety information that would have an impact on the understanding and characterization of the previously recognized potential risk of anaphylactic reactions. Please refer to Appendix 5.4.1.

On 14 May 2023, a safety signal "allergic including anaphylactic reactions" has been detected and the conclusion was the following (please refer to Section 4 and 16.2):

- Based on medical review of cumulative data, the weighted cumulative evidence was considered sufficient to support a causal association between COVID-19 vaccine (recombinant, adjuvanted) and allergic including anaphylactic reactions. The RSI was updated to appropriately reflect the accumulating postmarketing safety data. The updated RSI submitted (procedure EMEA/H/C/005754/II/0006) was approved to include anaphylactic reactions and hypersensitivity reactions (including rash, rash erythematous, urticaria, angioedema) as listed AEs for COVID-19 vaccine (recombinant, adjuvanted).

No significant O/E ratio increase has been detected for this AESI using a reporting rate of 100%. However, a significant O/E ratio increase has been detected considering a reporting rate of 50% (meaning that only 50% of the cases were reported) (Refer to Appendix 6.3.2).

16.3.4 New information on other identified 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 identified risk(s) not categorized as important or warrants further discussion in the PBRER.

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 and while breast-feeding were reported.

However, one case reported vaccine exposure during pregnancy after vaccination with a COVID-19 vaccine of an UNK MFR with no ADRs. No safety concerns have been identified from these data. See also Appendix 5.4.1.

Use in immunocompromised subjects

No significant information about the use in immunocompromised subjects was identified.

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 in frail subjects with unstable health conditions and co-morbidities was identified.

Use in subjects with autoimmune or inflammatory disorders

No significant information about the use in subjects 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 on long-term safety.

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.

The risks of VAED including VAERD is being removed from the list of safety concerns. The non-important potential risk "Anaphylactic reactions" was re-classified as non-important identified risk for the PBRER.

A summary of the safety concerns for product COVID-19 vaccine (recombinant, adjuvanted) identified at the end of the reporting interval is presented in Table 8.

Table 8 - Summary of safety concerns at the end of the reporting interval

Important identified risks	None
Important potential risks	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

16.4.1 Important identified and potential risks

Table 9 - 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

Potential risk	Myocarditis and pericarditis
	acute respiratory syndrome coronavirus has been associated with myocarditis as well, and multiple cases have been described since the outbreak of the COVID-19 pandemic (21). The majority of patients are young, healthy males (22). 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 (23). Several mechanisms have been hypothesised to account for COVID-19 mRNA vaccine associated myocarditis including autoimmunity triggered by molecular mimicry (22), (23), immune-mediated pathology (24), pro-inflammatory cascade (25).
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 (26). 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 (27), (28). 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 (24). 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 COVID-19 vaccine (recombinant, adjuvanted) (29). 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. 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 COVID-19 vaccine (recombinant, adjuvanted). However, based on potential risk from other COVID-19 vaccines, participants of ongoing clinical studies with COVID-19 vaccine (recombinant, adjuvanted) 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. Postmarketing data available with COVID-19 vaccine (recombinant, adjuvanted) as of the PBRER DLP did not raise any safety concerns. 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 one-four cases per 100 000 vaccinated persons (21). 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 (27), (28).
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk.
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 (30).
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 (24). Balanced with the risk of death and illness (including myocarditis) seen with COVID-19 itself, the impact on the risk-benefit balance of the vaccine is considered as minimal (21).

IRR: Incidence Reporting Ratio; COVID-19: Coronavirus Disease-2019; CoV-2 preS dTM: CoV-2 prefusion Spike delta TM; mRNA: Messenger Ribonucleic Acid; PBRER: Periodic Benefit Risk Evaluation Report; DLP: Data Lock Point; AS: Adjuvant Stimulated

16.4.2 Missing information

Table 10 - 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 COVID-19 vaccine (recombinant, adjuvanted) in pregnancy and while breast-feeding is considered as missing information until sufficient evidence is available.

Missing Information	Use in pregnancy and while breast-feeding
	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 (31). 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 (VAT00002 and VAT00008) and due to exclusion criteria, only limited number of pregnancy exposures were reported. No safety concern was identified. No exposure in pregnant and while breast-feeding women has been reported from post-marketing data available with COVID-19 vaccine (recombinant, adjuvanted) as of the PBRER DLP.
Anticipated risk/consequence of the missing information	It is not yet known whether COVID-19 vaccine (recombinant, adjuvanted) could cause any fetal harm when administered to a pregnant woman or if any detrimental effects could occur when administered in breast-feeding women. 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 (32). Preliminary findings in pregnant persons who received mRNA COVID-19 vaccines did not show 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 (33). No safety concern has been identified as of PBRER DLP.

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 11 - Missing information: Use in immunocompromised subjects

Missing Information	Use in immunocompromised subjects
Evidence source(s) and strength of evidence	The safety profile of COVID-19 vaccine (recombinant, adjuvanted) 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. 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 12 - 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 COVID-19 vaccine (recombinant, adjuvanted) in frail patients is not yet known even though elderly population and individuals with co-morbidities (30) or high-risk conditions were represented in Clinical Studies: Individuals with co-morbidities (30) 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 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. 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 13 - 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 COVID-19 vaccine (recombinant, adjuvanted) 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. No safety concern has been identified as of PBRER DLP.

Missing Information	Use in subjects with autoimmune or inflammatory disorders
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.

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: 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 COVID-19 vaccine (recombinant, adjuvanted) 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	It is not yet known if COVID-19 vaccine (recombinant, adjuvanted) interacts with other vaccines with regards to safety or immunogenicity.

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 15 - 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 COVID-19 vaccine (recombinant, adjuvanted). 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 COVID-19 vaccine (recombinant, adjuvanted) is progressively accruing without any safety concerns observed 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 MINIMISATION

No effectiveness evaluation is established for COVID-19 vaccine (recombinant, adjuvanted), since there are no RMMs 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[5].

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[6].

Globally, till 09 November 2023, there have been 772 166 517 confirmed cases of COVID-19, including 6 981 263 deaths, reported to WHO (34). Although all regions have reported substantive numbers of cases, the greatest cumulative numbers of confirmed cases to date have been in Europe (>277 million cases), the Western Pacific (>207 million cases) and the Americas (>193 million cases) (34).

Key risk factors for severe COVID-19 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[7]. Older age (particularly ≥65 years) is a recognized risk factor for more severe COVID-19 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 (35).

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

Omicron variant 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

[5] EU-Risk Management Plan for VidPrevtyn® Beta (COV2 PRES DTM-AS03 [B.1.351]); version 1.0, dated 10 Nov 2022.
[6] EU-Risk Management Plan for VidPrevtyn® Beta (COV2 PRES DTM-AS03 [B.1.351]); version 1.0, dated 10 Nov 2022.
[7] EU-Risk Management Plan for VidPrevtyn® Beta (COV2 PRES DTM-AS03 [B.1.351]); version 1.0, dated 10 Nov 2022.

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 (36).

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 (PsVN). 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[8] (37), (38).

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

The 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 (US). Per-protocol analysis population included 615 participants who received CoV2 preS dTM-AS03 (B.1.351 strain) vaccine four to ten months after receiving primary vaccination with two-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, five 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], 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[9].

17.2 NEWLY IDENTIFIED INFORMATION ON EFFICACY AND EFFECTIVENESS

One clinical report from a study (VAT00001) conducted by the MAH with COVID-19 vaccine (recombinant, adjuvanted) in approved indications, and including relevant efficacy data was made available during the reporting interval and is summarized in Section 7.1.1.

[8] Sanofi. 2.5 Clinical Overview – Addendum (COVID-19): VAT00013. [VV-CLIN-0638481]
[9] Sanofi. Brief Interim Clinical Study Report: VAT00002; version 1.0.

Of note the following studies were published during the reporting period identified and are described hereafter:

Dayan GH, Rouphael N, Walsh SR, Chen A, Grunenberg N, Allen M, et al. Efficacy of a monovalent (D614) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant in adults: a phase 3, multi-country study. EClinicalMedicine. 2023;64:102168. (9)

Background: The literature on first generation COVID-19 vaccines show they were less effective against new SARS-CoV-2 variants of concern (VOC) including Omicron (BA.1, BA.2, BA.4 and BA.5 subvariants). New vaccines developed against variant strains may provide cross-protection against emerging variants when used as boosters and facilitate vaccination across a range of countries, healthcare settings and populations. However, there are no data on such vaccines when used as a primary series.

Methods: A global Phase 3, multi-stage efficacy study (NCT04904549) among adults (≥18 years) was conducted in 53 research centers in eight countries (US, Honduras, Japan, Colombia, Kenya, India, Ghana, Nepal). Participants were randomized 1:1 to receive two intramuscular injections of a MV SARS-CoV-2 recombinant protein vaccine with AS03-adjuvant (10 µg of the spike (S) protein from the ancestral D614 strain) or placebo on D 01 and D 22. The primary efficacy endpoint was prevention of virologically confirmed SARS-CoV-2 infection with symptoms of COVID-19-like illness (CLI) ≥14 days after the second injection (post-dose 2 [PD2]) in participants who were SARS-CoV-2 naive on D01 + D22. Safety and reactogenicity were also evaluated.

Findings: Between May 26 and November 72 021, 10 114 participants received ≥1 study injection, and 9441 participants received both injections. 2108 (20.8%) participants were SARS-CoV-2 naive at D 01 and D 22. The primary endpoint was analyzed in a subset of the full analysis set (the modified full analysis set PD2 [mFAS-PD2], excluding participants who did not complete the vaccination schedule or received vaccination despite meeting one of the contraindication criteria, had onset of symptomatic COVID-19 between the first injection and before 14-days after the second injection, or participants who discontinued before 14 days after the second injection [n = 9377; vaccine, n = 4702; placebo, n = 4675]). Data were available for 2051 SARS-CoV-2 naive and 7159 non-naive participants. At the cut-off date (28 January 2022), symptomatic COVID-19 was reported in 169 naive participants (vaccine, n = 81; placebo, n = 88) ≥14 days PD2, with a VE of 15.3% (95% CI, −15.8; 38.2). The VE regardless of D01/D22 serostatus was 32.9% (95% CI, 15.3; 47.0) and VE in non-naive participants was 52.7% (95% CI, 31.2; 67.9). Viral genome sequencing was performed up to the data cut-off point and identified the infecting strain in 99/169 adjudicated cases in the PD2 naive population (Delta [25], Omicron [72], other variants [3], one participant had infection with both Delta and Omicron variants and has been included in the totals for both Delta and Omicron). The vaccine was well-tolerated with an acceptable safety profile.

Interpretation: In the context of changing circulating viral variants, it is challenging to induce protection in naive individuals with a two-dose priming schedule based on the parental D614 strain. However,

while the primary endpoint of this trial was not met, the results show that a MV D614 vaccine can still be of value in individuals previously exposed to SARS-CoV-2.

Bruyn GD, Wang J, Purvis A, Ruiz MS, 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: a phase 3, parallel-group study. EClinicalMedicine. 2023 Jul 22;62:102109. (3)

Background: In a parallel-group, international, phase 3 study (ClinicalTrials.gov NCT04762680), the authors evaluated prototype (D614) and Beta (B.1.351) variant recombinant spike protein booster vaccines with AS03-adjuvant (CoV2 preS dTM-AS03).

Methods: Adults, previously primed with mRNA (BNT162b2, mRNA-1273), adenovirus-vectored (Ad26.CoV2.S, ChAdOx1nCoV-19) or protein (CoV2 preS dTM-AS03 [MV D614; MV (D614)]) vaccines were enrolled between 29 July 2021 and 22 February 2022. Participants were stratified by age (18–55 and ≥ 56 years) and received one of the following CoV2 preS dTM-AS03 booster formulations: MV (D614) (n = 1285), MV (B.1.351) (n = 707) or BiV D614 + B.1.351 (BiV; n = 625). Unvaccinated adults who tested negative on a SARS-CoV-2 rapid diagnostic test (control group, n = 479) received two primary doses, 21-days apart, of MV(D614). Anti-D614G and anti-B.1.351 antibodies were evaluated using validated PsVN assay 14 days post-booster (day [D]15) in 18–55-year-old BNT162b2-primed participants and compared with those pre-booster (D1) and on D36 in 18–55-year-old controls (primary immunogenicity endpoints). The PsVN titers to Omicron BA.1, BA.2 and BA.4/5 subvariants were also evaluated. Safety was evaluated over a 12-month follow-up period. Planned interim analyses are presented up to 14 days post-last vaccination for immunogenicity and over a median duration of 5 months for safety.

Findings: All three boosters elicited robust anti-D614G or-B.1.351 PsVN responses for mRNA, adenovirus-vectored and protein vaccine-primed groups. Among BNT162b2-primed adults (18–55 years), geometric means of the individual post-booster versus pre-booster titer ratio (95% confidence interval [CI]) were: for MV (D614), 23.37 (18.58–29.38) (anti-D614G); for MV (B.1.351), 35.41 (26.71–46.95) (anti-B.1.351); and for BiV, 14.39 (11.39–18.28) (anti-D614G) and 34.18 (25.84–45.22 (anti-B.1.351). GMT ratios (98.3% CI) versus post-primary vaccination GMTs in controls, were: for MV(D614) booster, 2.16 (1.69; 2.75) [anti-D614G]; for MV (B.1.351), 1.96 (1.54; 2.50) [anti-B.1.351]; and for BiV, 2.34 (1.84; 2.96) [anti-D614G] and 1.39 (1.09; 1.77) [anti-B.1.351]. All booster formulations elicited cross-neutralizing antibodies against Omicron BA.2 (across priming vaccine subgroups), Omicron BA.1 (BNT162b2-primed participants) and Omicron BA.4/5 (BNT162b2-primed participants and MV D614-primed participants). Similar patterns in antibody responses were observed for participants aged ≥ 56 years. Reactogenicity tended to be transient and mild-to-moderate severity in all booster groups. No safety concerns were identified.

Interpretation: CoV2 preS dTM-AS03 boosters demonstrated acceptable safety and elicited robust neutralizing antibodies against multiple variants, regardless of priming vaccine.

Kirsebom FCM, Andrews N, Stowe J, Dabrera G, Ramsay M, Bernal JL. Effectiveness of the adjuvanted Sanofi/GSK (VidPrevtyn Beta) and Pfizer-BioNTech (Comirnaty Original/Omicron BA.4-5) bivalent vaccines against hospitalisation amongst adults aged 75 years and older in England, estimated using a test-negative case control study design. medRxiv. 2023 Sep, 29. DOI: 10.1101/2023.09.28.23296290. (39)

Background: In England, the Joint Committee for Vaccination and Immunization recommended a spring 2023 booster program for all adults aged 75 years and older and the immunosuppressed. The vaccines advised were the Sanofi/GSK AS03-adjuvanted MV beta variant (VidPrevtyn Beta) booster vaccine and the Pfizer-BioNTech mRNA (Comirnaty Original/Omicron BA.4-5) BiV vaccine. This is the first time an adjuvanted COVID-19 vaccine has been administered as part of a UK COVID-19 vaccination program. In clinical trials, the antibody levels generated by the Sanofi/GSK vaccine were comparable to levels generated by COVID-19 mRNA vaccines but to date there are no real-world data on the effectiveness or duration of protection of this vaccine.

Methods: The authors used a test-negative case-control study design to estimate the incremental vaccine effectiveness of the Sanofi/GSK and Pfizer BiV BA.4-5 boosters against hospitalization amongst those aged 75 years and older in England. The study period for tests contributing to all analyses was from 3 April 2022 to 27 August 2023. Vaccine effectiveness was estimated relative to those who had received at least two doses prior to their spring booster, with their last dose being an autumn 2022 booster given at least three months prior.

Findings: Overall, there were 14 174 eligible tests from hospitalized individuals aged 75 years and older, with 3005 being cases and 11 169 being controls. Effectiveness against hospitalization was highest in the period nine to 13 days post vaccination for both manufacturers at about 50%; 43.6% (95% C.I; 20.1 to 60.2%) and 56.4% (95% C.I; 25.8 to 74.4%) for Sanofi/GSK and Pfizer BA.4-5, respectively. There was some evidence of waning with a reduction to about 30% for both manufacturers five-nine weeks post vaccination.

Interpretation: Together, these results provide reassuring evidence that both the adjuvanted Sanofi/GSK and Pfizer BA.4-5 booster vaccines provided a good boost to protection against hospitalization amongst adults aged 75 years and older. The finding that the adjuvanted vaccine targeting the now distant Beta strain had similar effectiveness to the mRNA vaccine targeting more closely matched Omicron sub-lineages BA.4-5 during a period of Omicron circulation may reflect improved protection due to the adjuvant in the Sanofi/GSK product.

Branche A, Rouphael N, Diemert D, Falsey A, Losada C, Baden LR, et al. Bivalent and Monovalent SARS-CoV-2 Variant Vaccine Boosters Improve coverage of the known Antigenic Landscape: Results of the COVID-19 Variant Immunologic Landscape (COVAIL®) Trial. Res Sq [Preprint]. 2023 May 5:rs.3.rs-2653179. Update in: Nat Med. 2023 Sep;29(9):2334-2346. (40)

Vaccine protection against COVID-19 wanes over time and has been impacted by the emergence of new variants with increasing escape of neutralization. The COVID-19 Variant Immunologic Landscape

(COVAIL) randomized clinical trial (clinicaltrials.gov NCT 05289037) compares the breadth, magnitude and durability of antibody responses induced by a second COVID-19 vaccine boost with mRNA (Moderna mRNA-1273 and Pfizer-BioNTech BNT 162b2), or adjuvanted recombinant protein (Sanofi CoV2 preS DTM-AS03) MV or BiV vaccine candidates targeting ancestral and variant SARS-CoV-2 spike antigens (Beta, Delta and Omicron BA.1). The authors found that boosting with a variant strain is not associated with loss in neutralization against the ancestral strain. However, while variant vaccines compared to the prototype/wildtype vaccines demonstrated higher neutralizing activity against Omicron BA.1 and BA.4/5 subvariants for up to three months after vaccination, neutralizing activity was lower for more recent Omicron subvariants. The study, incorporating both antigenic distances and serologic landscapes, can provide a framework for objectively guiding decisions for future vaccine updates.

Launay O, Gupta R, Machabert T, Konate E, Rousseau A, Claire V, et al. Beta-variant recombinant SARS CoV-2 vaccine induces durable cross-reactive antibodies against Omicron variants. Research Square. 2023 Jan 30. (41)

The authors previously reported the safety and immunogenicity data from a randomized trial comparing the MV recombinant protein Beta-variant (MVB.1.351) and MV ancestral protein (MVD614) booster vaccines with AS03 adjuvant (Sanofi/GSK) to mRNA BNT162b2 vaccine (Pfizer-BioNTech). First booster of the vaccines was administered in adult participants previously primed with two doses of BNT162b2. A subset of these participants with available blood samples collected at Day 0 (D0), at 28 days (D28), and three months (M3) post-booster were contacted for additional testing (195/208 participants). The persistence of cross-neutralizing antibodies, including against Omicron BA.1 and BA.4/5, up to three months after boosting was evaluated using a validated pseudovirus neutralization assay. The data showed that the MVB.1.351 vaccine induced higher and durable cross-neutralizing antibodies against Omicron subvariants up to three months after boosting compared to a MV ancestral and the mRNA BNT162b2 booster vaccine.

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 November 2023, there have been 772 166 517 confirmed cases of COVID-19, including 6 981 263 deaths, reported to WHO (34). Although all regions have reported substantive numbers of cases, the greatest cumulative numbers of confirmed cases to date have been in Europe (>277 million cases), the Western Pacific (>207 million cases) and the Americas (>193 million cases) (34).

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 (42).

Coronavirus disease-2019 symptoms may vary from mild to severe, with approximately 33% to 55% of known cases to be asymptomatic (varies by variant) (43), (44). 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 (45).

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 (46). 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 (47), (48). 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 (49).

New and emerging variants are playing an important role in local and global epidemiology. As of September 2022, the only 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 (37), (48). 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 (50).

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 (51).

Following the introduction of the first COVID-19 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 (50), (52), (53). 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 (54), (55), (2).

18.2 BENEFIT-RISK ANALYSIS EVALUATION

18.2.1 Methodology

The current benefit-risk evaluation, for each indication, is based on the 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 post marketing 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.

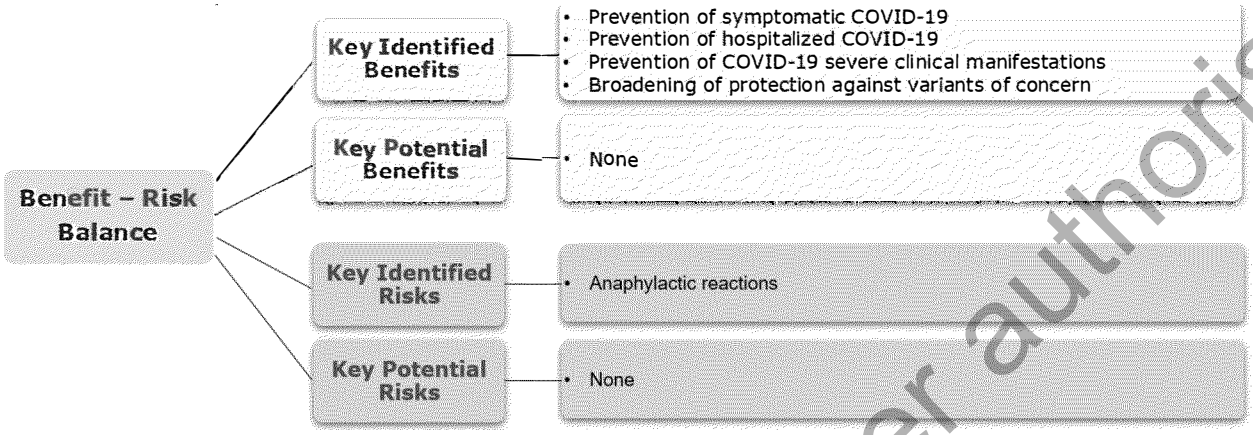
The descriptive framework emphasizes relevant metrics to enable a comprehensive discussion of benefit-risk while providing complete transparency into the origin and format of the source data. Key benefits are defined by favorable effects that contribute importantly to the overall benefit-risk evaluation 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 - The COVID-19 vaccine (recombinant, adjuvanted) key benefit-risk assessment value tree in adults from 18 years and above for booster immunization as per current recommendations



COVID-19: Coronavirus Disease-2019

The Benefit-risk assessment tables (Table 16, Table 17, Table 18, and Table 19) 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 16 - Benefit-Risk Assessment table - Analysis of condition

Evidence and Uncertainties	Conclusions and Reasons
The 2019–23 pandemic of COVID-19, was caused by SARS-CoV-2, protein-enveloped RNA virus. On 05-May-2023, WHO chief declared end to COVID-19 as a global health emergency. (56) Globally, as of 18-Oct-2023, there have been 771 407 825 confirmed cases of COVID-19, including 6 972 152 deaths, reported to WHO. (57) A fifth coronavirus wave declared mid-Nov-2021 followed by the emergence of a new variant (Omicron) first reported to WHO from South Africa (B.1.1.529). There have been subsequent peaks (both cases and hospitalizations) due to emerging Omicron sub-lineages with higher transmissibility and immune escape (58), (59). As of Sep-2023, multiple Omicron sub-lineages and variants that previously circulated have been classified as VBM by the CDC (60) and 95% or more of the population in EU and US are non-naive for COVID-19 (vaccinated or with previous infection). **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 (61), and infectiousness is estimated to last for 1-9.5 days (depending on the variant) (62). Twenty five percent (25%) of asymptomatic SARS-CoV-2 infections (63). Antibody	The 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. (66) 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
persistence demonstrated up to eight-months after COVID-19 infection and up to six-months after a second mRNA vaccine dose (64). A study from Italy showed that >98% of infected participants had antibodies up to nine-months later (65). **New emerging variants:** Emergence of new variants (previously Alpha, Beta, Gamma, Delta, and Omicron; now multiple different Omicron sub-lineages) with changes in transmissibility, severity and risk of reinfection: highly transmissible VOCs emerged and spreading globally. **Uncertainties:** Some data indicating COVID-19 will become an endemic, with opportunistic infections and seasonal pic of burden, however new variants emerging at an unprecedented rate and generating waves of infection out of season. Influential factors to determine seasonality still unknown (62).	

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: Variants of Concern; US: United States; EU: European Union; UN: United Nations; mRNA: Messenger Ribonucleic Acid; VBM: Variants Being Monitored.

Table 17 - Benefit-Risk Assessment table - Current Treatment Options

Evidence and Uncertainties	Conclusions and Reasons
Currently, seven other COVID-19 booster vaccines received MA in multiple countries including Europe: COMIRNATY® (BioNTech and Pfizer), SPIKEVAX® (Moderna), NUVAXOVID (NOVAVAX), BIMERVAX® (HIPRA), COVID-19 Vaccine (inactivated, adjuvanted) Valneva, JCOVDEN® (Janssen), VAXZEVRIA® (AstraZeneca). Of note, more than 380 vaccine candidates around the world (348 in clinical development and 32 in use). (57) **Post-exposure treatments:** Recommended use of each therapeutic based on medical status of the patient, age and health conditions: eg, antivirals should be used in 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. Currently only one drug treatment for use in COVID-19 (REMDESIVIR®) approved by FDA and 14 treatments authorised for emergency use (67). REMDESIVIR with/without dexamethasone or in combination with baricitinib (Cytokine inhibitor) with an FDA authorization (in adults and pediatric patients 12+ and >40kg). 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] (68). • Bebtelovimab: mAb for treatement that retains activitity against Omicron (Bebtelovimab) may offer an alternative in adults and paediatric patients aged 12+ and >40kg).	Widespread vaccine deployment in many countries reduced burden of disease and burden on healthcare system. (71)

Evidence and Uncertainties	Conclusions and Reasons
• KINERET® (anakinra), OLUMIANT® (baricitinib) or GOHIBIC® (vilobelimab) or Molnupiravir introducing mutations into the viral genome during viral replication (69)also offer alternative treatments in COVID-19 hospitalized adults requiring supplemental oxygen. Recommendations for treating non-hospitalized patients are listed. (70)	

US: United States; FDA: Food and Drug Administration; EUA: Emergency Use Authorization; mAb: Monoclonal Antibody; 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; MA: Marketing Authorization

Table 18 - 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 VOC **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 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. **VAT00008 Phase III Booster extension:** The study is ongoing. Key secondary immunogenicity objective is to describe the neutralizing antibody profile at D01 and D21 and at six-months after crossover or booster injection. Exploratory objectives will further evaluate relative efficacy after crossover/booster vaccination. **VAT00013 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) vaccine, and Pfizer/BioNTech vaccines. The results 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.	Robust immunogenicity results in booster vaccination (VAT00002 supplemental cohorts) in adults 18 years and older (all age groups).
Clinical Evidence: Primary series to demonstrate efficacy Study undertaken in real-word setting of high SARS-CoV-2 seropositivity in participants. Global study to span all VOC including Alpha, Gamma, Mu, Delta and Omicron: Circulation of variants during the conduct of the study predominantly	Significant vaccine efficacy demonstrated to prevent symptomatic COVID-19, including COVID-19 caused by Omicron.

Evidence and Uncertainties	Conclusions and Reasons
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 IRR, with the lower bound of the 95% CI > 30%; modified Full Analysis Set post-dose two: all participants regardless of serostatus at baseline). VE 72.5% (95% CI: 49.5; 86.0) for prevention of Omicron symptomatic COVID-19 (all participants regardless of serostatus at baseline). The VE 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. VE in the older adults (60+ years): -47.7% (-1668.0; 83.1) (2 cases in Placebo group versus 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. **Effectiveness:** Vaccine effectiveness of VidPrevtyn Beta against hospitalization of 43.6% (95% C.I.; 20.1 to 60.2%), with no significant difference found with the effectiveness of the Pfizer BA.4/5 booster [56.4% (95% C.I; 25.8 to 74.4%)]. VidPrevtyn Beta demonstrated similar waning of effectiveness to Pfizer BA.4/5 vaccine at post-nine weeks after vaccination (72), (73). **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 (74), (75), (76), (77). **Emerging variants:** Need for broadened protection Using MV Beta vaccine as a booster (third dose) in primed NHPs (mRNA-primed study CoV2-07_NHP and subunit-primed study CoV2-08_NHP), neutralising 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-three months after primary immunization with the Beta MV and D614/Beta BiV 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.	Immunocompromised patients allowed to be included into the phase III Clinical Study VAT00008. Pregnancy exposures in VAT00002 and VAT00008 to followed and assessed. Post-marketing data to be assessed through pregnancy registry (VAT00012). Exploratory analysis of VAT00008 will be efficacy by SARS-CoV-2 variant. Duration of protection monitored in post-authorization effectiveness studies.

Evidence and Uncertainties	Conclusions and Reasons
• Efficacy against infection and disease in at-risk groups (eg, immunocompromised participants) and special population (eg, pregnant women). • Efficacy against new emergent variants.	

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: Variants of Concern; VE: Vaccine Efficacy; IRR: Incidence Rate Ratio; Ab: Antibody; NHP: Non-Human Primates; S: Spike; MV: Monovalent; BiV: Bivalent.

Table 19 - Benefit-Risk Assessment table - Risk and Risk Management

Evidence and Uncertainties	Conclusions and Reasons
VidPrevtyn Beta Key identified risk • Anaphylaxis: Class-effect for all vaccines. The AESI within the clinical studies. No safety concern identified with regards to anaphylaxis based on review of available Pivotal Clinical Studies data (B.1.351) including VAT00008 open label extension. Based on medical review of postmarketing safety data, a signal on allergic including anaphylactic reactions has been detected, evaluated, and confirmed as an identified risk. Anaphylactic reactions re-classified as non-important identified risk (for RMP). **VidPrevtyn Beta Key potential risk** None. Of note, VAED/VAERD theoretical key potential risk no more considered as key based on cumulative evidence gathered with VidPrevtyn Beta supported by evidence with other COVID-19 vaccines. **AESIs** No increased risk of AESIs from clinical studies or postmarketing setting including on Myocarditis/Pericarditis **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 (78), (79). **Baculovirus platform Evidence** • Strongly characterized protein manufacturing platform (Baculovirus) 23 million doses of recombinant flu vaccines distributed in adults up to Jun-2022 with no safety concern. Other COVID-19 vaccine Evidence: Other COVID-19 AS03 adjuvanted vaccines demonstrated an acceptable safety profile (80), (81). **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 participants, in frail participants with unstable health conditions and co-morbidities (e.g. COPD, diabetes, chronic	Based on medical review of postmarketing case data, detected signal of allergic including anaphylactic reactions which was confirmed as an identified risk and reflected in the Product Information. No other safety concerns detected from clinical and postmarketing setting data. 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 including by age group (below 70 years old and above 70 years old). Risk management includes ongoing PV activities: • Safety in immunocompromised patients (VAT00002 and VAT00008) • Long-term safety including AESIs monitored during pivotal Clinical Studies follow-up and in PASS. • 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 MV (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. Current Risk Management Strategy considered adequate to document the risk management system set-up for VidPrevtyn Beta and to

Evidence and Uncertainties	Conclusions and Reasons
neurological disease, cardiovascular disorders), in participants with autoimmune or inflammatory disorders. • Limited safety database to assess very rare events identified for other COVID-19 vaccines in post-marketing setting (other platforms) • Long-term safety.	ensure a safe use of the vaccine in real-life setting.

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; PV: Pharmacovigilance; RMP: Risk Management Plan.

Benefit-Risk conclusion:

Considering 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.
- VAT00008 stage 2, VAT00008 open-label booster extension.
- 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.
- Postmarketing safety data up to DLP with more than two million doses administered in the postmarketing setting, and effectiveness data generated during the 2023 Spring COVID-19 vaccination campaign in the UK.

The benefits associated with COVID-19 vaccine (recombinant, adjuvanted) as booster given in adults from 18 years and older outweigh the potential risks of the vaccine. The COVID-19 vaccine (recombinant, adjuvanted) benefit-risk balance remains positive in its current indication in individuals 18 years of age and older.

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), 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 remains positive in the currently approved conditions of use.

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