EU-RISK MANAGEMENT PLAN FOR VidPrevtyn® Beta (COV2 PRES DTM-AS03 [B.1.351])

RMP version to be assessed as part of this application	
Data Lock Point (DLP)	08-NOV-2022
RMP Version number	Version 1.0
Date of final sign-off	10-NOV-2022

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	The EU-RMP v0.1, v0.2 and v0.3 were submitted in procedure EMEA/H/C/005754. The purpose of the update of EU-RMP v1.0 is to update VidPrevtyn Beta indication and posology and address EMA raised topics on EU-RMP v0.3.
Summary of significant changes in this RMP	• Part I: DLP updated to 08-Nov-2022, update of indication and dosage sections. • Part II module SI: Update of the indication. • Part VI: Update of the indication. • Part VII: Update of Annexes 4 (Update of Targeted Follow-up Form Coversheet on Myocarditis/Perimyocarditis) and 8.

DLP: Data Lock Point; EMA: European Medicines Agency; EU: European Union; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	Not applicable (initial submission)
Approved with procedure	Not applicable (initial submission)
Date of approval (opinion date)	Not applicable (initial submission)

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	Johanne-Sophie Depont-Seiller[a], PharmD
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

A/G:	Albumin/Globulin
ACCESS:	vACCine covid-19 monitoring readinESS
ADE:	Antibody Dependent Enhancement
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
ARDS:	Acute Respiratory Distress Syndrome
ATC:	Anatomical Therapeutic Chemical
BAME:	Black, Asian and Minority Ethnic
CD4:	Cluster of Differentiation 4
CDC:	Centers for Disease Control and Prevention
CFR:	Case Fatality Ratio
CI:	Confidence Interval
CMDh:	Co-ordination group for Mutual recognition and Decentralised procedures - Human
COPD:	Chronic Obstructive Pulmonary Disease
CoV2 preS dTM:	CoV-2 prefusion Spike delta TM
CSR:	Clinical Study Report
CVD:	Cardiovascular Disease
CVE:	COVID Vaccine Effectiveness
C-VIPER:	COVID-19 Vaccines International Pregnancy Exposure Registry
DART:	Developmental and Reproductive Toxicity
DLP:	Data Lock Point
DME:	Designated Medical Event
DNA:	Deoxyribonucleic Acid
DSMB:	Data and Safety Monitoring Board
EC:	European Commission
ECDC:	European Centre for Disease Prevention and Control
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EHR:	Electronic Health Record
EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
EU:	European Union
EUL:	Emergency Use Listing
F:	Female
Fc:	Fragment Crystallizable
FDA:	Food and Drug Administration
FI:	Frailty Index
GTIN:	Global Trade Item Number
GVP:	Good Pharmacovigilance Practices
H and E:	Hematoxylin and Eosin
HCoV:	Human Coronavirus
HCP:	Healthcare Professional

HIV:	Human Immunodeficiency Virus
HLT:	High Level Term
ICMRA:	International Coalition of Medicines Regulatory Authorities
ICS:	Intracellular Cytokine Staining
ICSR:	Individual Case Safety Report
ICU:	Intensive Care Unit
IgG:	Immunoglobulin G
IL:	Interleukin
IM:	Intramuscular
INN:	International Nonproprietary Name
IRR:	Incidence Rate Ratio
JAK:	Janus Kinase
LMP:	Last Menstrual Period
LTCF:	Long-Term Care Facility
M:	Male
MAAE:	Medically Attended Adverse Event
MAH:	Marketing Authorization Holder
MDV:	Multidose Vial
MedDRA:	Medical Dictionary for Regulatory Activities
MERS-CoV:	Middle East Respiratory Syndrome Coronavirus
mRNA:	Messenger Ribonucleic Acid
NHP:	Non-Human Primates
NPI:	Non-Pharmaceutical Intervention
NZW:	New Zealand White
O/E:	Observed-to-Expected
OR:	Odds Ratio
PAS:	Post-Authorization Study
PASS:	Post-Authorization Safety Study
PBRER:	Periodic Benefit-Risk Evaluation Report
PIP:	Pediatric Investigation Plan
PL:	Package Leaflet
PRAC:	Pharmacovigilance Risk Assessment Committee
PSP:	Patient Support Program
PSR:	Periodic Safety Report
PSUR:	Periodic Safety Update Report
PSUSA:	Pharmacovigilance Risk Assessment Committee
PTC:	Product Technical Complaint
QPPV:	Qualified Person Responsible for Pharmacovigilance
QR:	Quick Response
qRT-PCR:	Quantitative Reverse Transcription Polymerase Chain Reaction
RMP:	Risk Management Plan
RR:	Risk Ratio
SAE:	Serious Adverse Event
SARI:	Severe Acute Respiratory Infection
SARS-CoV-2:	Severe Acute Respiratory Syndrome Coronavirus 2
SCRI:	Self-Controlled Risk Interval

SmPC:	Summary of Product Characteristics
SPEAC:	Safety Platform for Emergency Vaccines
Th:	T-helper
UK:	United Kingdom
US:	United States
VAED:	Vaccine-Associated Enhanced Disease
VAERD:	Vaccine-Associated Enhanced Respiratory Disease
VAERS:	Vaccine Adverse Event Reporting System
VE:	Vaccine Effectiveness
VOC:	Variants of Concern
VOI:	Variants of Interest
WHO:	World Health Organization

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5: Part I.1 - Product Overview

Active substance(s) (INN or common name)	Recombinant protein derived from the SARS-CoV-2 prefusion Spike delta TM (CoV2 preS dTM) (B.1.351 strain)
Pharmacotherapeutic group(s) (ATC Code)	Vaccines, COVID-19 Vaccines (J07BX03)
Marketing Authorization Applicant	Sanofi Pasteur
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	VidPrevtyn Beta
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: CoV2 preS dTM-AS03 (B.1.351) is a recombinant adjuvanted vaccine further also referred as COVID-19 Vaccine (Recombinant, Adjuvanted).
	Summary of mode action: The mechanism of action consists of the induction of immune responses against the antigens contained in the vaccine. Following administration, the spike glycoprotein of SARS-CoV-2 associated with AS03 adjuvant is stimulating 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.
	Important information about its composition: Recombinant CoV-2 Spike Protein (B.1.351) antigen is produced in a continuous insect cell line and by recombinant DNA technology. AS03 adjuvant is an oil-in-water emulsion composed of squalene, DL-α-tocopherol and polysorbate 80. CoV2 preS dTM-AS03 (B.1.351) contains no egg proteins, antibiotics, or preservatives. CoV2 preS dTM-AS03 (B.1.351) may contain octylphenol ethoxylate, a trace residual from the manufacturing process.
Hyperlink to the product information	Refer to e-CTD, Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	Current: VidPrevtyn Beta is indicated as a booster for active immunization to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine.
	Proposed: Not applicable

Dosage in the EEA	Current: VidPrevtyn Beta is administered intramuscularly as a single dose of 0.5 mL at least 4 months after a previous COVID-19 vaccine. It is recommended to administer VidPrevtyn Beta once as a booster to adults who have received prior vaccination series with either mRNA or adenoviral vector COVID-19 vaccines.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Solution and emulsion for emulsion for injection - The volume after mixing 1 vial of antigen solution (2.5 mL) with 1 vial of adjuvant emulsion (2.5 mL) allows for delivery of 10 doses of vaccine (0.5 mL per dose). VidPrevtyn Beta 5 micrograms/Booster vaccination: One dose (0.5 mL) contains 5 micrograms of recombinant CoV-2 Spike Protein (B.1.351) antigen formulated with AS03 adjuvant for booster vaccination.
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the EU?	Yes

ATC: Anatomical Therapeutic Chemical; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; DNA: Deoxyribonucleic Acid; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; mRNA: Messenger Ribonucleic Acid; RMP: Risk Management Plan; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

RISK MANAGEMENT PLAN - PART II: SAFETY SPECIFICATION

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

A novel coronavirus, SARS-CoV-2, 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 World Health Organization (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, as of 30 September 2022, there have been 614 385 693 confirmed cases of COVID-19, including 6 522 600 deaths, reported to WHO. [1] Although all regions have reported substantive numbers of cases, the greatest cumulative numbers of confirmed cases to date (as of the 30 September 2022) have been in Europe (254 million cases), the Americas (178 million cases), and the Western Pacific (89 million cases). [1] 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. [2]

Clinical features and natural history of the disease

Coronavirus disease-2019 symptoms may vary from mild to severe, with approximately 33% to 55% [3] of known cases to be asymptomatic (varies by variant). [4] 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. [5]

Symptoms appear on average 4 to 5 days after infection, though the usual range is between 2 to 14 days. Preliminary data shows the incubation period for Omicron to be 2.9 to 3.2 days. [6] Most reported symptoms include fever, fatigue, muscle ache, cough, and shortness of breath, which can progress to pneumonia. [7] Mild acute disease tends to resolve within approximately 2 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. [8,9] 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. [10] The spectrum of symptomatic infection ranges from mild to critical, though most infections are not severe. A report published by the Chinese Center for Disease Control and Prevention concluded that out of approximately 44 500 confirmed infections, 81% of patients suffered from mild symptoms (no/mild pneumonia). 14% of patients suffered from severe disease (including dyspnea, hypoxia, or over 50% lung involvement on imaging within 24/48 hours).
Five percent (5%) of patients suffered from critical disease, defined as respiratory failure, shock

or multiorgan dysfunction. [8] Overall, as of 30 September 2022, there is an estimated global fatality rate of 1% (March 2020 to September 2022) with variations between countries and over the time period. [1]

Transmissibility and spectrum of severity have been reported to evolve according to the various variants currently circulating.

Variants of Concern (VOC)

Identification as a VOC is based on the following criteria: an increase in transmissibility or detrimental change in COVID-19 epidemiology; or an increase in virulence or change in clinical disease presentation; or a decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics. [9]

New and emerging variants are also playing an important role in local and global epidemiology. Starting from 18 December 2020, five VOCs have been identified by the WHO, namely Alpha, Beta, Gamma, Delta, and Omicron.

The European Centre for Disease Prevention and Control (ECDC) also regularly assesses the evidence on the variants and designated VOCs based on the situation in EU/EEA region.

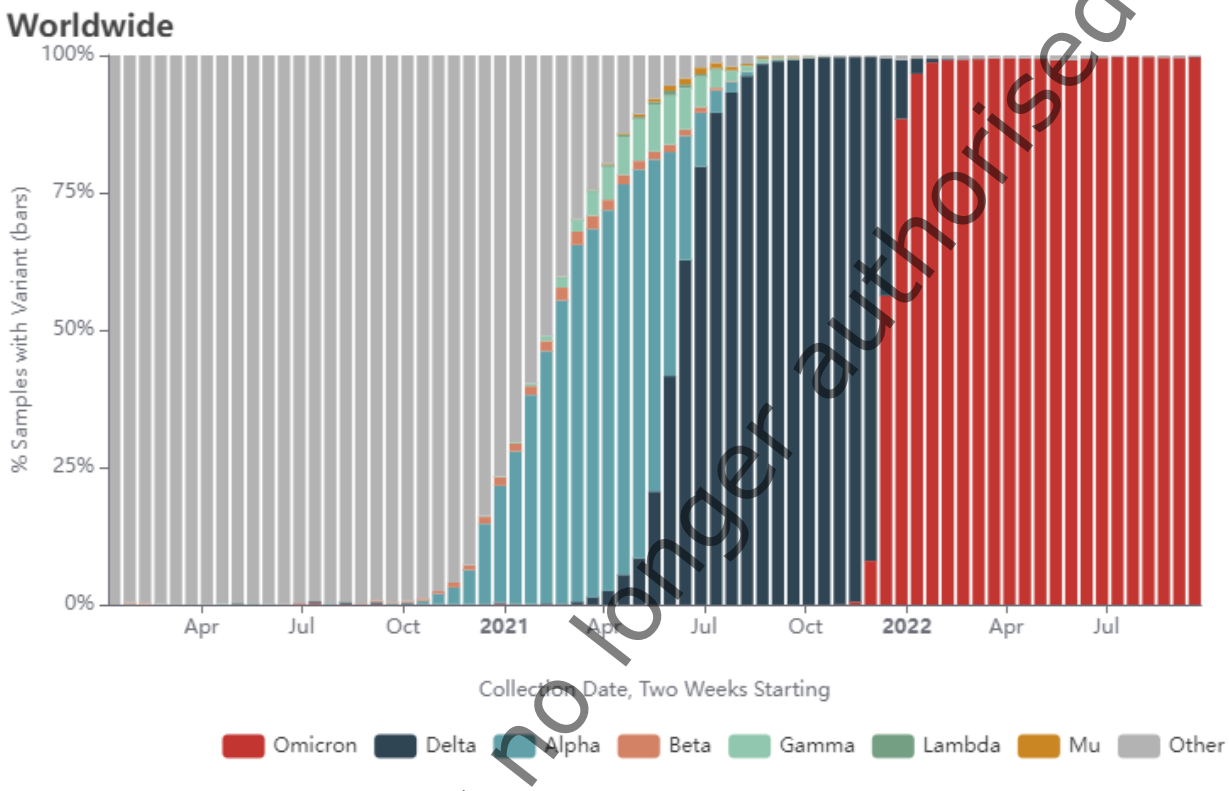
As of September 2022, the only VOC defined by WHO and ECDC is Omicron, with ECDC specifying four sub-lineages of Omicron; BA.1, BA.2, BA.4 and BA.5. [9,10,11]

There continues to be increased diversity within Omicron and within its descendent lineages. A number of these Omicron descendent lineages are under monitoring. Globally, and as of the epidemiological week 36 (05 September 2022 to 11 September 2022), BA.5 descendent lineages continue to be dominant accounting for 81.2% of sequences, followed by BA.4 descendent lineages (including BA.4.6) which account for 8.1%, and BA.2 descendent lineages (including BA.2.75) which account for 2.9% of sequences. The Omicron variant has a substantial growth advantage, due in part to a combination of immune escape and intrinsic high transmissibility, and rapidly became the predominant strain worldwide. [12]

The Omicron variant showed up to 70 times faster multiplication in the bronchus than Delta and the evidence from both the United Kingdom (UK) and Denmark showed an increased secondary attack rate compared to Delta. [13,14] In terms of severity, several studies suggested less severe outcomes compared to Delta including hospitalization, intensive care unit (ICU) admission, and mechanical ventilation. [15,16,17]

Worldwide variant distribution

Figure 1 - Variants over time worldwide



Source: Regeneron COVID-19 dashboard [18]

EU/EEA variant distribution

In the EU/EEA region, Omicron has been first reported in November 2021 and became predominant strain rapidly from the second half of December 2021 onwards.

Among the 13 countries with an adequate volume of sequencing or genotyping for weeks 36-37 (05 September to 18 September 2022), the estimated distribution of VOC or of variants of interest (VOI) was 98.8% (98.2-100.0% from 13 countries) for BA.4/BA.5, 0.9% (0.2 1.8%, 369 detections from 11 countries) for BA.2 and 0.8% (0.6-1.2%, 164 detections from 6 countries) for BA.2.75.

An analysis by the UK Health Security Agency estimates BA.2 to have 75% increased transmissibility when compared to BA.1, and BA.5 is reported to be 35% more transmissible than BA.2. [19] Currently available evidence does not suggest a difference in disease severity between the sublineages. [20]

Despite a characterized reduction in neutralizing activity of Omicron VOC as compared to previous VOCs, and between Omicron sublineages eg, BA.5 compared to BA.1, [21,22,23] vaccine effectiveness (VE) against severe disease of the primary series showed some decline over six months (10-20%) [20] suggesting protective effect of primo vaccination against Omicron VOC

severe infections. The first booster dose vaccination improved VE against severe disease: ≥70% in 34 (94%) of 36 estimates evaluating VE between 14 days and three months of receipt of a booster dose. [20]

Demographics of the population indicated and risk factors for the disease

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.

When it comes to severity of disease there is also an uneven distribution, with a higher impact on the elderly population. Results published by the ECDC show a similar pattern of infection distribution amongst age groups and sexes as the WHO. The distribution for mild cases also correlates relatively closely to total number of cases. A definition of a mild case in this instance is one that does not require hospitalization or result in death. Pooled data from EU/EEA countries show positive correlation with age, showing that as age increases, so does the risk of hospitalization. Infection with SARS-CoV-2 leading to a fatal outcome also very strongly correlates with age, with adults over 60 years of age primarily dying as a result of SARS-CoV-2 infection compared to younger age groups.

Risk factors for severe disease and death

The estimated case fatality rate varies widely between countries, influenced by a variety of factors including testing and screening approaches, demographics, healthcare availability and others. Although the global case fatality ratio (CFR) has changed overtime due to various waves of infection, variants, non-pharmaceutical intervention (NPIs) and vaccination strategies, the CFR has remained highest amongst 60 year or older groups population.

Studies have observed that the risk of COVID-19 severity is higher with the increasing age, male sex, and presence of comorbidities, especially cardiovascular disease (CVD). [1,24] Smoking was also found to be associated with increased risk of severity [5,8,25] and mortality. [26] Residents of long-term care facilities (LTCFs) have been regarded as a medically and socially vulnerable group and 72% of all COVID-19 related deaths in Europe were attributed to residents at LTCFs. [27]

Important comorbidities

The results of the systematic reviews, below in Table 6, showed the higher relative risks of both severity and mortality amongst patients with certain comorbidities upon infection with SARS-CoV-2.

Table 6 - Important comorbidities and the relative risk of both severity and mortality compared against people without any comorbidities

Comorbidities	Risk of severity (Odds Ratio)	Risk of mortality (Odds Ratio)
Diabetes	2.04 [28] to 3.27 [24] (Mostly around 2.5) [29,30,31,32,33]	1.25 [34] to 3.73 [35] (Mostly around 2.5) [24,36,37,38]
Hypertension	1.82 [39] to 3.17 [31] (Mostly around 2 to 3) [28,24,29,30,32,33,40]	2.2 to 3.5 [24,36,38,39] 1.54 (among ICU patients) [40]
Obesity	1.72 [31] to 4.17 [41] (Mostly around 2 to 3) [29,31,42,43,44,45,46]	1.14 [47] to 1.59 [34] (Mostly around 1.5) [24,42,46,48]
Chronic Kidney diseases	Around 3 [24,29,31,32]	OR 5.38 [24] 2.39 (among ICU patients) [40] RR 2.5 [49] 7.1 [50]
Cardiovascular diseases (CVDs)	2.25 [51] to 3.87 [24] (Most around 3) [28,31,32,40]	2.25 [51] 3.72 [38] 4.91 [24] 1.91 (among ICU patients) [40] 2.72 (among hospitalized patients) [52]
Cerebrovascular disease and Stroke	2.05 [52] to 5.88 [53] (Mostly around 3 to 4) [29,30,32,54]	Around 3 [54,55]
Malignancies	1.5 [44] to 2.6 [28,29,32,56]	Around 3 [38,56] 1.81 (among ICU patients) [40]
Chronic Respiratory diseases	Around 5 [24,57,58]	Around 3.5 [24,35,36]
Chronic Obstructive Pulmonary Disease	Around 3 [30,32] to 6.42 [59]	3.5 [38]
People living with HIV	1.15 [60]	1.38 (among hospitalized patients) [60]
Solid organ transplant patients	1.57 (for ICU admission) [61]	1.4 to 1.5 [61]

CVD: Cardiovascular Disease; HIV: Human Immunodeficiency Virus; ICU: Intensive Care Unit; OR: Odds Ratio; RR: Risk Ratio.

Therapeutic Treatment options

There is currently no cure for COVID-19. Multiple antivirals and therapeutic treatments that target severe COVID-19 have been authorized, however most therapeutic options are still in early stages of research (over 670 drug development programs are in planning stages and over 470 trials are being reviewed by the Food and Drug Administration [FDA]).

Antiviral treatment

Antivirals for COVID-19 are indicated for the treatment of COVID-19 in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen and in adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The antiviral, remdesivir, has been approved by the FDA. [62] The European Commission (EC) have authorized two antiviral treatments for the use in the EU: remdesivir and

PF-07321332/ritonavir (Paxlovid). A third antiviral (molnupiravir) has been submitted for marketing authorization in the EU. [63]

Therapeutic treatment

Multiple therapeutic treatments for COVID-19 have been authorized. The FDA have authorized 14 treatments for emergency use. [62] The EC has authorized six treatments for the use in the EU with several monoclonal antibodies (regdanvimab, tocilizumab, casirivimab/imdevimab, tixagevimab/cilgavimab and sotrovimab) and an anti-inflammatory molecule (anakinra). [63]
A tyrosine kinase inhibitor currently approved for the treatment of polyarthritis rheumatoid (Baricitinib) has been submitted for marketing authorization in the EU.

The recommended use of each therapeutic is based on the medical status of the patient. The WHO's guideline development group considered benefits of remdesivir to be modest and of moderate certainty for key outcomes such as mortality and mechanical ventilation, resulting in a conditional recommendation.

Recently, WHO indicated that (sotrovimab) and (casirivimab-imdevimab) initially recommended in patients who do not require supplemental oxygen but are at an increased risk of developing severe disease, have "meaningfully reduced neutralization activity of the currently circulating variants of SARS-CoV-2 and their subvariants".

World Health Organization also said that other therapies such as tocilizumab or sarilumab interleukin (IL-6 receptor blockers) and baricitinib (the Janus Kinase [JAK] inhibitor) may now be combined, in addition to corticosteroids, in patients with severe or critical COVID-19 and requiring supplemental oxygen or mechanical ventilation.

Prophylactic Treatment options

Following the introduction of the first SARS-CoV-2 vaccines in December 2020, vaccination is reducing burden of disease, but the full effect won't be realized until adequate vaccine coverages rates are achieved. Vaccine supply and access remain far short of the global need, with additional confounders such as waning immunity and emerging variants posing a challenge to establishing and maintaining herd immunity within vaccinated populations.

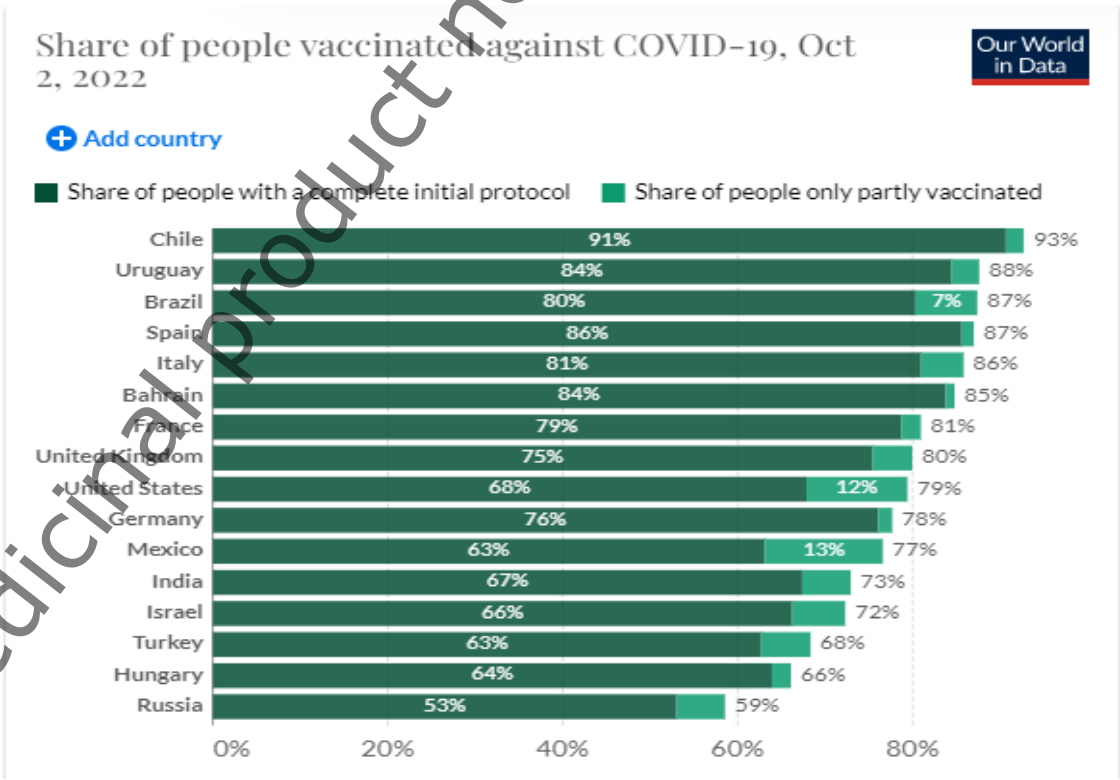
This challenge is still under debate in the scientific and medical community to establish the best way to tackle current and emerging variants. Dozens of non-profits, government agencies and vaccine makers have made a top research priority to propose in a near future booster vaccines susceptible to provide protection among a large panel of variant of concern. [64] Meanwhile, health agencies (FDA and EMA) recently approved several mRNA booster vaccine containing Omicron (Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5 [BioNTech and Pfizer]; Spikevax bivalent Original/Omicron BA.1 [Moderna]).

World Health Organization issued emergency use listing (EUL) for 11 COVID-19 vaccines developed by Pfizer/BioNTech, AstraZeneca/SK Bioscience, Janssen-Cilag, Moderna Biotech, Beijing Institute of Biological Products, Sinovac Life Sciences, Bharat Biotech, Serum Institute of India Pvt. Ltd, Novavax and, CanSino Biologics. [62,63] In Europe, the EC has so far granted 6 marketing authorizations, following the positive assessment of the EMA regarding their safety and their effectiveness: [65] two COVID-19 mRNA vaccines, one developed by BioNTech and Pfizer, (BNT162b2) and another by Moderna, (mRNA 1273), two viral vector vaccines,

one developed by Oxford University and AstraZeneca (ChAdOx1 nCOV 19) and one developed by Janssen (Ad26 COV2.S), one recombinant protein vaccine developed by Novavax and one inactivated, adjuvanted vaccine manufactured by Valneva. Several other vaccines are at different stages of their evaluation by the EMA: Inactivated Vaccine (Vero Cell) by Sinovac Life Sciences Co. Ltd, COVID-19 vaccine HIPRA (PHH-IV) by HIPRA Human Health S.L.U., VidPrevtyn Beta by Sanofi Pasteur, Sputnik V (Gam-COVID-Vac) by Russia's Gamaleya National Centre of Epidemiology and Microbiology and Skycovion (SK Chemicals GmbH). [66] The United States (US) FDA currently only recommend three COVID-19 vaccines for general use, BioNTech and Pfizer (BNT162b2), [67,68] Moderna (mRNA 1273) [69,70] and Janssen vaccine (Ad26 COV2.S). [71]

With the introduction of vaccines starting in December 2020, the impact of vaccination programs is continuing to play a role in local trends. As of 23 June 2022, a total of 12.1 billion doses of vaccines have been administered worldwide, and the highest coverage countries have achieved over 95% of the population fully vaccinated with a primary series, with the UK at 73% and the US at 67% coverage; however, most countries are still much lower than this. Europe as a continent has an average coverage rate of 66%, however the range within Europe extends from 86% (Portugal) to 30% (Bulgaria). Vaccine coverage in particularly affected European countries varies considerably, with high and upper middle-income countries at >75%, lower middle-income countries at 55%, and many low-income countries at 15% of the population receiving two doses. [72]

Figure 2 - Vaccination coverage by regions



Source: Our World in Data [73]

Waning of SARS-CoV-2 immunity

One of the remaining unknowns of COVID-19 is the durability of immunity including the time taken to be susceptible to reinfection. Research is being conducted on this subject, and preliminary data has been published, however due to the relatively short time since the beginning of the pandemic, longer-term data is not yet available. This is further confounded by the emergence of new VOCs and VOIs, especially with Omicron, with observed reductions in VE either being attributed to waning immunity, or reduced effectiveness against variants due to immune escape, or both.

Natural infection

Direct data remain limited for the durability of immunity after natural infection with SARS-CoV-2, although a recent comparative evolutionary study examining durability of immunity to SARS-CoV-2 and related viruses (SARS-CoV, middle east respiratory syndrome coronavirus [MERS-CoV], human coronavirus [HCoV]-229E, HCoV-OC43, HCoV-NL63) concluded that there is a phylogenetic relationship between human-infecting coronaviruses, and that reinfection by SARS-CoV-2 specifically under endemic conditions can occur between 3 and 63 months after peak antibody response, with a median time of 16 months. [74] Another study looked into immunological memory to SARS-CoV-2 up to 8 months after infection and found that each component of immune memory in convalescent patients exhibited distinct kinetics, with spike-specific memory B cells becoming more abundant at 6 months compared to 1 month. Immunoglobulin G to spike protein was also relatively stable over a 6-month period and cluster of differentiation 4 (CD4)+ and CD8+ T cells declined with a half-life of 3 to 5 months. [75]

Vaccine induced protection

When directly comparing the magnitude of responses to either vaccination or natural infection, currently licensed vaccines have been shown to produce peak neutralizing antibody responses up to four-times those seen in convalescent patients. [76] It has also been observed that the decay of a neutralizing titre of antibodies in vaccinated subjects over the first 3 to 4 months after vaccination was at least as rapid as the decay observed in convalescent patients. [77]

There is also a growing body of evidence that indicates a reduction in VE over time. Several studies, across a range of approved COVID-19 vaccines, have shown that although VE against symptomatic disease peaks in the early weeks after the second dose, it gradually declines from as little as 3 months after the second dose. [78] This waning is also more pronounced in the over 65-year-olds, as well as those in a clinically extremely vulnerable group, and 40 to 64-year-olds with underlying conditions compared to healthy adults. [79] This gradual declining of VE was also observed with respect to specific variants, including Beta, Delta, and Mu previously. [80] Emergence of Omicron has made waning immunity more prominent with the improved ability to escape both natural as well as vaccine induced protection. [81]

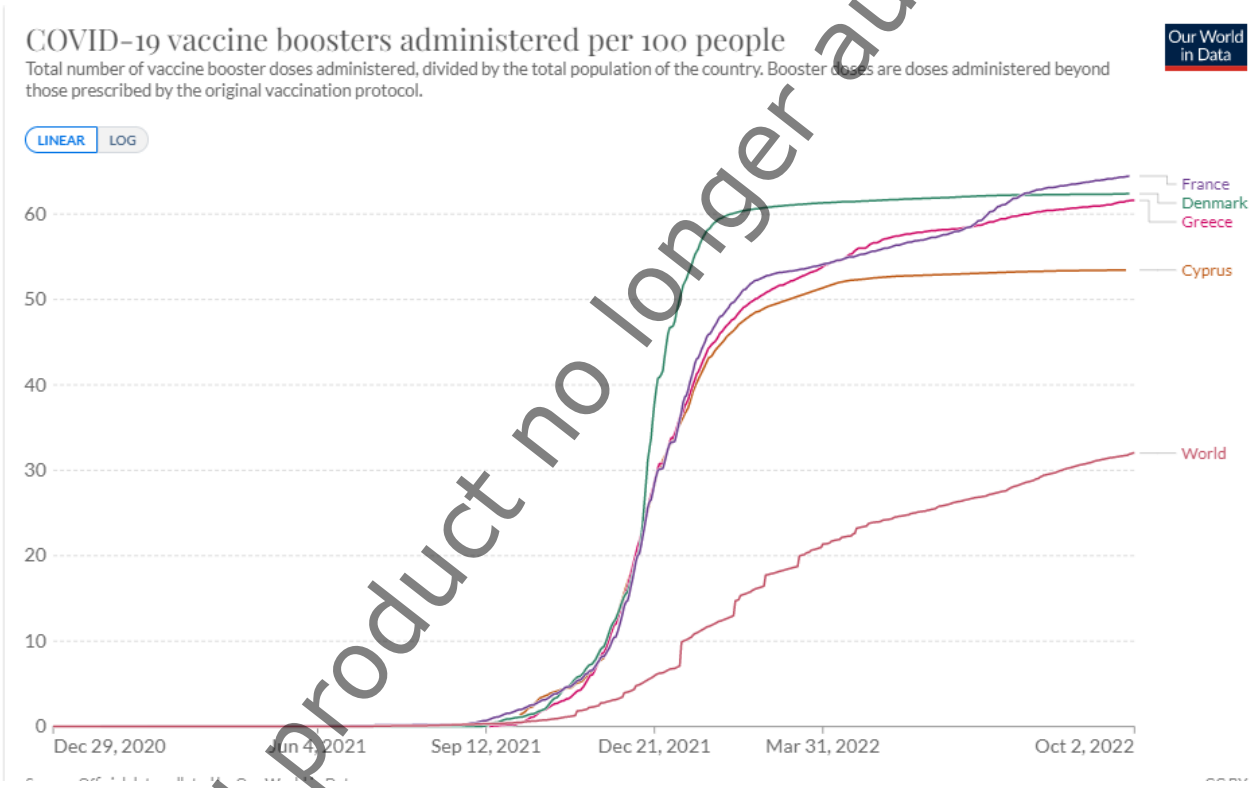
Booster Dose

Considering the evidence on waning immunity, most EU countries are offering additional doses of vaccine with priority for all adults (18+). The EMA has published guidance on the populations requiring a booster, as well as the recommended time interval for each group. [81] The minimal interval after the primary vaccination schedule is between 1 to 8 months and is dependent on the

target population and by country. Both homologous (same vaccine) and heterologous (different vaccines/platforms) booster doses are being provided. The heterologous booster vaccinations are recommended by multiple health agencies globally, with some initial evidence of higher effectiveness of heterologous primary + booster series against severe and symptomatic disease. [82,83] Real world effectiveness studies have shown both homologous and heterologous boosters reinforce significant protection against severe disease and hospitalization following waning of primo-vaccination. [82]

It is important to note that waning immunity against the currently dominant Omicron variant has also been observed after administration of a parental booster dose. [17,84,85]

Figure 3 - Proportion of booster doses by regions



Source: Our World in Data [73]

Indication

CoV2 preS dTM-AS03 (B.1.351) is indicated as a booster for active immunization to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine.

The epidemiology of the disease is summarized in the following table:

Table 7 - Epidemiology of Coronavirus Disease-2019 (COVID-19)

Indication	Active immunization to prevent COVID-19 (Booster dose)
Incidence	As of 30-Sep-2022, there have been more than 614 million confirmed cases of COVID-19 and over 6.5 million deaths reported. [1] Daily new confirmed incident cases peaked at 2196 confirmed cases per million population in Europe (01/22), 2445/million in North America (01/22), 1025/million in South America (01/22), 188/million in Asia (01/22), 44/million in Africa (12/21) and 4074/million in Oceania (01/22). However, regional-level estimates conceal the substantive variation experienced by country, with daily incidence rates reaching >6000/million population per day in Denmark and France at their highest peaks. Daily incidence rates have varied over time since the emergence of SARS-CoV-2 in Dec-2019, with most countries having experienced either four or five pandemic waves. In Jun-2022, regional incidence rates ranged 0 to 24 000/million population, with incidence trends varying across regions due to a rise in circulation of BA.4 and BA.5.
Prevalence	Given the acute nature of COVID-19 disease and the rapidly changing pandemic epidemiology, prevalence estimates have not been the key measure for tracking COVID-19. However, seroprevalence surveys have provided valuable insights into the cumulative proportion of the population infected. [86] Seroreversion has been documented, so data are mostly reflective of infection within the previous 4-6 months. Modeled estimates by regions based on the available studies showed a range of 17% in Europe in Jul-2021 to 68% in Southeast Asia in May-2021. [87] Substantive regional variation has been documented within countries, for example in the UK seroprevalence estimates varied from 2.8% to 23.3% in regional household and community regional surveillance between Sep-2020 to May-2021.
Demographics of the population in the authorized/proposed indication	The proposed indication is broad, including: • individuals 18 years of age and older previously vaccinated against COVID-19. 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. This age-based distribution however does not correlate acrsoss gender-based distribution, with infections occurring at similar rates between males and females.
Main existing treatment options	Curative options: There is currently no cure for COVID-19. The antiviral treatment, remdesivir, has been approved by both the FDA and EC. The EC has also authorized other treatments: anakinra, regdanvimab, tocilizumab, casirivimab/imdevimab, tixagevimab/cilgavimab, sotrovimab and PF-07321332/ritonavir. Scientists are also studying a wide range of other potential treatments. Most therapeutic options however are still in early stages of research. Prophylaxis options in addition to social distancing and masking: The EC has so far granted 6 marketing authorizations, following the positive assessment of the EMA regarding their safety and their effectiveness: • Two COVID-19 mRNA vaccines, one developed by BioNTech and Pfizer, (BNT162b2) and another by Moderna, (mRNA-1273). • Two viral vector vaccines: one developed by Oxford University and AstraZeneca (ChAdOx1-nCOV19) and one developed by Janssen (Ad26.COV2.S). • One recombinant protein vaccine developed by Novavax. • One inactivated vaccine developed by Valneva.

Indication	Active immunization to prevent COVID-19 (Booster dose)
	Several other vaccines are at different stages of their evaluation by the EMA (Verocell by Sinovac, COVID-19 Vaccine HIPRA (PHH-1V) by HIPRA, VidPrevtyn Beta by Sanofi Pasteur, Sputnik V by Gamaleya and Skycovion [SK Chemicals GmbH]). Dozens of non-profits, government agencies and vaccine makers have made a top research priority to propose in a near future booster vaccines susceptible to provide protection among a large panel of variant of concern. [64] Meanwhile, health agencies (FDA and EMA) recently approved several mRNA booster vaccines containing Omicron (Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5 [BioNTech and Pfizer]; Spikevax bivalent Original/Omicron BA.1 [Moderna]).
Natural history of the indicated condition in the untreated population including mortality and morbidity	The spectrum of symptomatic infection ranges from mild to critical, though most infections are not severe. Symptoms may vary from mild to severe, and many infections are known to be asymptomatic. Of those with laboratory confirmed symptomatic disease, approximately 80% experience mild-to-moderate symptoms. Symptoms appear on average 4-5 days after infection, though the usual range is between 2 to 14 days. Most reported symptoms include fever, fatigue, muscle ache, cough, and shortness of breath, which can progress to pneumonia, ARDS, cardiovascular sequalae and other severe symptoms. [7] Mild acute disease tends to resolve within approximately 2 weeks, whereas severe cases may last 3-6 weeks. However, data are emerging indicative of long-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. [8,9] The estimated CFR varies widely between countries, ranging from 0.04% in Greenland and 0.08% in Iceland and Bhutan, to 6.93% and 6.5% in Peru and Mexico respectively with differences influenced by demographics, testing/reporting and health care availability. [88] When it comes to severity of disease there is also an uneven distribution, with the elderly suffering much more than the younger population. Results published by the ECDC show a similar pattern of infection distribution amongst age groups and sexes as the WHO. Transmissibility and spectrum of severity have been reported to evolve according to the various variants currently circulating. Studies have observed that the risk of COVID-19 severity is higher with the increasing age, male sex, and presence of comorbidities, especially CVD. [1,24] Smoking was also found to be associated with increased risk of severity [5,8,25] and mortality. [26] Residents of LTCFs have been regarded as a medically and socially vulnerable group and 72% of all COVID-19 related deaths in Europe were attributed to residents at LTCFs. [27] Race and ethnicity also affect COVID-19 mortality rates. Native American and African American community members have higher mortality rates when compared to the White community in the US. [89] Public Health England reported that the mortality rate in BAME groups were higher than those in White ethnic groups. [90]
Important co-morbidities and risk factors for the disease	Key risk factors for severe COVID-19 disease include but not limited to CVD, diabetes, chronic respiratory disease, COPD, hypertension, malignancies, obesity, chronic kidney disease, cerebrovascular disease and stroke, with higher risk of severity and mortality ranging 1.14 to 7.1 times higher in these risk groups (Table 6). Older age (particularly ≥65 years) is a recognized risk factor for more severe COVID-19 disease and death, with populations aged 65-74 years at 5 times higher risk of hospitalization and 90 times higher risk of death than population aged 18-29 years old in the US. [87]

Indication	Active immunization to prevent COVID-19 (Booster dose)
	This relative risk increases with age, peaking in the 85+ group at 15 times and 570 times the risk of hospitalization and death. Frailty is theoretically defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday activities or acute stressors. In the absence of a gold standard, frailty has been operationally defined as meeting three out of five phenotypic criteria indicating compromised energetics: low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss. [25,91] Alternatively, frailty has been operationalized as a risk index by counting the number of deficits accumulated over time (termed "FI") including disability, diseases, physical and cognitive impairments, psychosocial risk factors, and geriatric syndromes (eg, falls, delirium, and urinary incontinence). [92] It was argued that, compared to Fried's frailty phenotype, the FI is a more sensitive predictor of adverse health outcomes due to its finer graded risk scale, and its robustness in clinical inferences with regard to the number and actual composition of the items in the FI. [93] However, all ages and those without pre-existing co-morbidities are still at risk of severe COVID-19 disease and death. Additionally, "long-COVID" or "post-acute COVID syndrome" has been documented in younger and older adults. Therefore, it is possible that vaccines may be prioritized to risk groups given the higher risk of severe disease, but there is a clear medical need for vaccination of all age groups and regardless of the existence of co-morbidities.

ARDS: Acute Respiratory Distress Syndrome; BAME: Black, Asian and Minority Ethnic; CFR: Case Fatality Rate; COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease-2019; CVD: Cardiovascular Disease; EC: European Commission; ECDC: European Centre for Disease Prevention and Control; EMA: European Medicines Agency; FDA: Food and Drug Administration; FI: Frailty Index; LTCF: Long-Term Care Facility; mRNA: Messenger Ribonucleic Acid; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; UK: United Kingdom; US: United States; WHO: World Health Organization.

RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The SARS-CoV-2 vaccine consists of preS-dTM antigen adjuvanted with AS03 (GlaxoSmithKline's Adjuvant System composed of alpha-tocopherol, squalene and polysorbate 80 in an oil-in-water emulsion).

The majority of non-clinical data was generated using the monovalent, original strain (D614), CoV2 preS dTM AS03 (D614) vaccine.

The non-clinical assessment of CoV2 preS dTM-AS03 original strain vaccine was based on immunogenicity, efficacy, and safety evaluation in laboratory animals.

The variant vaccine (CoV2 preS dTM AS03 [B.1.351 or Beta strain]) is manufactured using the same technology and production process as parental vaccine (D614). The only change is the new immunogen B.1.351 while the rest of the vaccine formulation remains unaltered. This new component represents the same prefusion Spike protein antigen target as the parental (D614), with a drift in the amino acid sequence to match the B.1.351 variant strain. Therefore, no new toxicological findings are expected. Thus, a new toxicology study was not deemed necessary to support progression to registration. This approach is aligned with the conclusions from emergency use authorization for vaccines to prevent COVID-19 Guidance for Industry (October 2020, revised in 2022), the International Coalition of Medicines Regulatory Authorities (ICMRA) COVID-19 Virus variants workshop (February 2021) together with the Medicines and Healthcare products Regulatory Agency Guidance on strain changes in authorized COVID-19 vaccines (March 2021).

The prototype (D614) vaccine immunogenicity was evaluated in naive mice, hamsters and macaques as well as in previously vaccinated macaques to document the benefit of a late booster. The Monovalent (B.1.351) vaccine immunogenicity was evaluated in naive and primed macaques, and the efficacy in hamsters. In naive animals, the different studies established the need for a second dose and the use of AS03 adjuvant to induce a potent neutralizing antibody response and efficacy against SARS-CoV-2 infection (in hamsters and macaques). [94] In previously vaccinated macaques, the results demonstrated a strong increase of the responses against the original virus (D614) and robust broadening of the neutralizing antibody responses to the VOCs Alpha, Beta, Gamma and Delta, as well as against Omicron. The studies also showed higher cross-neutralization of VOCs when the Monovalent (B.1.351) vaccine booster was formulated with AS03. [95]

The neutralizing antibody persistence and Spike-specific memory B cells were evaluated over 6 months after the booster immunization. Six months post-booster, the neutralizing antibody titers against Omicron were more than 20-fold greater than baseline titers (pre-booster), and the memory B cells responses were increased to robust levels, especially in animals with low responses at baseline.

For the non-clinical safety evaluation, the local tolerance and potential systemic toxicity of the (D614) vaccine was assessed in two repeated dose toxicity studies as well as in a developmental and reproductive toxicity (DART) study in rabbits, and the potential of vaccine-associated enhanced respiratory disease (VAERD) was evaluated in immunogenicity and efficacy studies conducted in Non-Human Primates (NHP) and Golden Syrian Hamsters.

This (D614) vaccine has been assessed in two repeated dose toxicity studies in New Zealand White (NZW) rabbits, which are known to develop an immune response to CoV2 preS dTM antigen. These studies were conducted by the intramuscular (IM) route, which is the clinical route, and each injection consisted of one 0.5 mL dose of the CoV2 preS dTM-AS03 (D614) vaccine. A total of 2 or 3 IM injections were given every 2 weeks to the animals. The key safety findings from these studies are reported in the summary table below.

In the first repeated dose toxicity study (Study No. 5003471), following a single dose administration, S-specific Immunoglobulin G (IgG) response was detected on Day 15 in four out of ten animals injected with the CoV2 preS dTM (D614) antigen alone and in all animals injected with the CoV2 preS dTM (D614) antigen in combination with AS03. After three injections, S-specific IgG titers were detected in 14 out of 20 animals dosed with CoV2 preS dTM (D614) antigen alone, and in all animals dosed with CoV2 preS dTM (D614) adjuvanted with AS03. In comparison to animals dosed with CoV2 preS dTM (D614) alone, an overall increase in S-specific titers was observed on Day 15, Day 31, and Day 45 in all animals dosed with the CoV2 preS dTM-AS03 (D614) adjuvanted vaccine.

In this study (Study No. 5003471), a single or repeated (three times) IM injection(s) of CoV2 preS dTM (D614) at a dose level of 15 µg/dose (targeted dose; representing an effective dose of 3.9 µg of the CoV2 preS dTM (D614) protein after recalculation) either alone or with AS03 adjuvant were well tolerated in rabbits. Administration of CoV2 preS dTM (D614) with AS03 resulted in transient and non-adverse changes in hematology, coagulation and clinical chemistry parameters indicative of a transient acute phase response/inflammation. These changes correlated with non-adverse histopathology findings of increased severity of acute/subacute to subacute/chronic mixed cell inflammation at the injection site and in the overlying skin of animals administered CoV2 preS dTM (D614) with AS03. Animals injected on three occasions, also showed increased lymphoid cellularity in the spleen (correlating with increased spleen weights) and lymph nodes. After the 2 weeks recovery period (single or repeated doses), only changes in laboratory parameters related to immunization were noted, and the inflammation at the injection site was less pronounced (ie, partial reversibility) but still observed, as expected with the ongoing healing process. These results are expected for an adjuvanted vaccine and suggested that it does not represent any special hazard for humans.

In the second repeated dose toxicity study (Study No. 5003591), two IM injections of CoV2 preS dTM (D614) at a dose level of 5 µg/dose (targeted dose; representing an effective dose of 2.4 µg of the SARS-CoV-2 Spike protein content after recalculation) adjuvanted with AS03 was well tolerated in rabbits. It induced very slight erythema and/or edema observed at the injection sites. In addition, non-adverse minimal to mild increases in absolute neutrophil count, fibrinogen, globulin, mild to marked increases in C-reactive protein and minimal decreases in albumin/globulin (A/G) ratio in males and females were noted. These changes correlated with microscopic changes as evidenced by an increase in severity of mixed cell inflammation (subacute/chronic) at the injection sites accompanied by multifocal aggregates of vacuolated macrophages. In addition, an increase in incidence and severity of fibrosis/fibroplasia was also observed in treated rabbits. Increased lymphoid cellularity in various lymph nodes and/or mixed inflammatory cell infiltration were also seen as well as an increase in adrenal gland and spleen weights that was noted in treated males but did not correlate with any macroscopic or microscopic change different from controls. Overall, this second toxicology study did not elicit any new

findings on top of those already seen with the CoV2 preS dTM (D614) adjuvanted with AS03. The key non-clinical findings are presented in Table 8.

In the DART study (Study No. 20288238), IM administration of CoV2 preS dTM (D614) adjuvanted with AS03 at 10 and 15 µg preS dTM/dose before and during gestation (total of five administrations) to female NZW rabbits was associated with non-adverse dose-related transient lower body weight gain during the pre-mating period after the second injection only. Vaccine-related local reactions at the injection site, such as oedema and induration of increasing severity after repeated administration, and microscopic inflammation, hemorrhage, muscular degeneration/necrosis, vacuolation of macrophages, and/or fibroplasia, were observed in both vaccine groups. 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.

The potential risk for VAERD or Vaccine-Associated Enhanced Disease (VAED) was assessed indirectly through the documentation of the immune responses, specifically the CD4 T-helper (Th) cell responses: type I (Th1) versus type 2 (Th2) and directly through challenges with SARS-CoV-2 in susceptible animal species that had been vaccinated prior to viral exposure.

The CD4 Th1/Th2 responses were evaluated in naive Rhesus macaques after immunization with 2 doses of CoV2 preS dTM-AS03 (D614). Two weeks post-immunization (D35), the peripheral blood mononuclear cells containing the CD4 T cells were sampled, stimulated with the Spike antigen and the Th1 and Th2 cytokines secreted by the activated CD4 T cells were measured using intracellular cytokine staining (ICS). The results indicated a mixed population of Th1 and Th2 CD4 T cells, with mainly a “Th0” population secreting tumor necrosis factor alpha and IL-2. There was no evidence of a Th2 dominant responses which was previously associated to VAERD with inactivated SARS-CoV vaccines. [96] Similar T-cell response profile is expected for the variant CoV2 preS dTM-AS03 (B.1.351), as the B.1.351 spike showed no impact on CD4 or CD8 responses in previously infected or vaccinated individuals.

The absence of VAERD was then confirmed by directly looking at the pathology caused by SARS-CoV-2 infection in vaccinated animals. Two species, namely Rhesus macaques (CoV2-04_NHP study) and Golden Syrian Hamsters (CoV2-03_Hm study) were utilized for assessment of VAERD and vaccine efficacy. In macaques, animals were vaccinated with CoV2 preS dTM-AS03 (D614) (down to lowest antigen doses of 4 µg) and exposed to a non-attenuated, qualified stock of SARS-CoV-2, Wuhan strain. In hamsters, animals were vaccinated with the parental Monovalent D614 or Monovalent B.1.351 CoV2 preS dTM-AS03 vaccine formulations, with 1 µg or 2 µg and exposed to D614 strain, Alpha variant or Beta (B.1.351) variant strains. The assessment of VAERD was based on viral replication in upper and lower respiratory tract, lung histopathology evaluation (Hematoxylin and Eosin [H and E] staining and Viral N protein immunochemistry) and any clinical signs (body weight and general behavior) in the vaccine groups as compared to an unvaccinated control group. The results showed that the viral loads in lungs and nares measured using quantitative reverse transcription polymerase chain reaction (qRT-PCR) were reduced or below the level of detection in all immunized animals, confirming no enhancement of viral replication in vaccinated animals. In NHPs, the histological and immunohistochemical staining of the lung samples collected at D7 or D8 and D14 or D15 post-challenge showed reduction of inflammation and eosinophil infiltration in the lungs of the AS03-adjuvanted vaccine groups compared to the non-vaccinated control group. In addition, the

lung samples of the vaccinated animals had a marked reduction of the infected cells at D7/8, consistent with the finding of reduced viral loads by qRT-PCR. These findings suggested a consistent correlation between viral infection and histopathology, and there was no enhancement of viral replication nor lung pathology due to vaccination. Importantly, no increase of the inflammatory cytokines and chemokines levels in the lungs was detected post-challenge in the vaccinated Rhesus, except for a transient slight increase of IL-5 on D2 that resolved on D4 and was not associated to eosinophilia as evidenced by histopathology. Altogether, the various analyses combined provided direct confirmation that no signs of enhanced inflammation due to vaccination were observed as compared to the controls after challenge with a virulent viral stock in rhesus macaques, a species with an immune system highly analogous to human. Similar reduction of viral replication and lung pathology was observed in hamsters using the Monovalent B.1.351vaccine, whatever the viral strain used for the challenge. Altogether the non-clinical studies showed no signs of disease enhancement in vaccinated animals.

The key non-clinical safety findings are presented in the following table.

Table 8 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Repeated dose toxicity study with CoV-2 preS dTM either alone or with AS03	• CoV2 preS dTM-AS03 (D614) vaccine was well tolerated locally and did not induce any vaccine-related systemic toxicity findings after 2 or 3 IM injections in rabbits covering for priming and booster indications. • These data did not demonstrate local or systemic effects other than reversible signs of inflammation which are expected due to induction of the immune response upon vaccination (vaccine reactogenicity).
• Reproductive/developmental toxicity study	• CoV-2 preS dTM-AS03 (D614) vaccine did not induce any effects on mating performance or fertility in female rabbits, or on embryo-fetal (including teratogenicity) and early postnatal development of the offspring. High S-specific IgG response was detected in dams, fetuses and pups indicating placental transfer of maternal antibodies. No data are available on vaccine excretion in milk.
• Genotoxicity	• No genotoxicity study requested for vaccines according to WHO guidelines (WHO, 2005). CoV-2 preS dTM-AS03 is not expected to be genotoxic in humans. • Genotoxicity of the AS03 alone was assessed in two in vitro tests (reverse mutation test in bacteria; gene mutation in mouse cells) and one in vivo test (micronucleus test in the rat after intravenous administration). No indication of genotoxicity was evident. The vaccine was not tested.
• Carcinogenicity	• No carcinogenicity study requested for vaccines according to WHO guidelines (WHO, 2005) (WHO, 2013). CoV-2 preS dTM-AS03 is not expected to be carcinogenic in humans.
Safety pharmacology	• Consistent with usual vaccine development programs, no safety pharmacology studies will be conducted, unless there are significant findings in the toxicology studies that would require further investigation of the safety pharmacology of the vaccine assets.
Other toxicity-related information or data	• No additional specific toxicity studies were or will be conducted.
VAED including VAERD	• The available non-clinical data do not indicate any risk related to potential VAED including VAERD in humans. No signs of any

Key Safety Findings	Relevance to human usage
	enhanced immunopathology were observed following SARS-CoV-2 infection in immunized animals in the different studies performed in hamsters (CoV2-03_Hm) and Rhesus macaques (CoV2-04_NHP) compared to controls. After viral challenge, the viral replication and pathology in the lungs were reduced or abrogated in CoV2 preS dTM-AS03 (D614) or (B.1.351) immunized animals.

CoV2 preS dTM: CoV-2 prefusion Spike delta TM; IM: Intramuscular; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine Associated Enhanced Respiratory Disease; WHO: World Health Organization.

Summary of non-clinical safety concerns

Important identified risk	None
Important potential risk	None
Missing information	No data available on vaccine excretion in milk.

The overall non-clinical assessment of the CoV2 preS dTM-AS03 vaccine is considered to support the registration. No findings in the non-clinical testing raised suspicion of a safety concern in humans.

RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

SIII.1. BRIEF OVERVIEW OF DEVELOPMENT

The clinical development of the CoV2 preS dTM AS03-adjuvanted vaccine (SARS-CoV2 preS dTM, the SARS-CoV-2 recombinant protein vaccine) has been the following:

The first Phase I/II Clinical Study (VAT00001) has been conducted in adults and elderly to document the safety and the immunogenicity of vaccine formulations as primary series using CoV2 preS dTM AS03 (D614).

The lower-than-expected immunogenicity in combination with the higher-than-expected reactogenicity observed in the Phase I/II study indicated that assessment of optimized antigen formulations (with higher antigen dose and lower host cell protein content) was necessary to select a formulation to progress to Phase III evaluation, [97] which was then evaluated in the VAT00002 Phase II Original Cohort primary series.

VAT00001 Phase I/II exposure data has not been included in clinical trial exposure due to the suboptimal formulation. The interim data are considered as not relevant for safety assessment.

A Phase II (VAT00002 - Original Cohort, primary series) 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 2 injections of 5 µg, 10 µg, or 15 µg of the CoV2 preS dTM (D614) vaccine, adjuvanted with AS03. Interim data from this Phase II study was used to decide on progression to Phase III and to select an antigen dose formulation for further clinical development evaluating the vaccines when used as a late booster. [98]

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

- Supplemental Phase III Cohort 1 to evaluate the safety and immunogenicity of a booster dose of the parental strain (Monovalent D614) vaccine among adults previously vaccinated with a primary series of mRNA (Pfizer/BioNTech or Moderna) or adenovirus-vectored vaccines (Janssen or AstraZeneca).
- Supplemental Phase III Cohort 2 to evaluate the safety and immunogenicity of a booster dose of a variant vaccine (Monovalent B.1.351 [Beta variant] or Bivalent [D614/B.1.351]) in adults previously primed with mRNA or adenovirus-vectored vaccines.
- In addition, available and willing individuals previously primed with the adjuvanted recombinant protein vaccine (different formulations) as part of the Phase II Original Cohort were enrolled into the Supplemental Phase III Cohort 2 and randomized to a booster dose of the parental strain booster vaccine or Monovalent variant booster vaccine.
- Selection of the 5 µg dose was based on the immunogenicity results in non-naive participants of the original cohort of VAT00002.

A Phase III Clinical Study (VAT00008) randomized, modified double-blind, placebo-controlled, multi-stage, multi-center, multi-country study is being conducted to assess the efficacy, safety, and immunogenicity of 2 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 2 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 selection mitigates the risk of having lower antibody titers against variants that would be circulating at the time of the efficacy study with potential to result in lower observed vaccine efficacy 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 bivalent vaccine. Thus, by design, the inclusion of the B.1.351 antigen with the D614 antigen in the bivalent vaccine mitigates the risk of lower antibody 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 adverse events (AE), medically attended adverse event [MAAEs], serious adverse event [SAEs] and adverse event of special interests [AESIs]).

An Investigator Sponsored Study (VAT00013/COVIBOOST), randomized, single-blinded multicenter clinical trial has been conducted to assess the immunogenicity and safety following a booster dose of the COVID-19 mRNA vaccine original formulation (Pfizer/BioNTech) and two adjuvanted sub-unit vaccines (Monovalent D614 or Monovalent B.1.351) administered in adults who received 2 doses of Pfizer/BioNTech mRNA original formulation vaccine as a primary vaccination. The safety data are considered as supportive data owing to the differences in safety data collection methods with VAT00002 Phase II/III and VAT00008 Phase III Clinical Studies (type of safety data, duration of collection and the coding were different, which precludes their integration in the tables).

A Phase III Clinical Study in pregnant women (VAT00006) to assess the safety and immunogenicity of the B.1.351 vaccine in pregnant women during pregnancy and safety in post-partum including breast-feeding period, if applicable is also planned.

SIII.2. CLINICAL TRIAL EXPOSURE

Data from the following trials were used for characterization of exposure and safety up to the DLP:

B.1.351 Monovalent vaccine, Booster immunization data:

- Phase II/III trial (VAT00002): Supplemental Phase III Cohort 2 (Booster Monovalent B.1.351) (unblinded data)
- Supportive data from VAT00013/COVIBOOST Investigator Sponsored Study: Randomized Booster study (Monovalent D614 or B.1.351) (unblinded data)

- A total of 85 participants received one dose of 5 μg of D614 + AS03 formulation, 80 participants received one dose of 5 μg of B.1.351 + AS03 formulation, and 82 participants received one dose of 30 μg of BTN162b2 formulation as a booster dose after priming vaccination with the Pfizer/BioNTech BNT vaccine. These data are not included in Exposure tables below.

Supportive data with other formulations:

- Phase II/III trial (VAT00002): Original Phase II Cohort and Supplemental Phase III Comparator Cohort (D614) (open-label)
  - Over 3200 participants enrolled and stratified according to different cohorts
- Phase III trial (VAT00008): both stages (unblinded data)
  - 23 038 participants enrolled in the full analysis set population (1:1 randomization to vaccine and placebo in both stages)

Exposure data presented below refer to safety analysis set population (different than randomization population).

B.1.351 Monovalent vaccine, Booster immunization data:

Duration of exposure and person-time are not provided as these notions are not relevant for vaccines.

Table 9 - Exposure by Dose - Safety Analysis Set - Booster series

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Dose of exposure	Participants (n)
VAT00002	Supplemental Cohort 2	Pfizer/BioNTech Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				Dose 1	378
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				Dose 1	375
		Moderna Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				Dose 1	111
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				Dose 1	108

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Dose of exposure	Participants (n)
		AZ Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				Dose 1	100
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				Dose 1	100
		Janssen Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				Dose 1	38
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				Dose 1	38
		CoV2 preS dTM-AS03 (D614) Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				Dose 1	78
		All			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				Dose 1	705
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				Dose 1	621

Prior prime vaccination: AZ = Oxford University/AstraZeneca
Study: VAT00002 Program: t001_rmp_july_b1351 Output: t001_rmp_july_b1351.RTF DATE: 05JUL2022 11:23
CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 10 - Exposure by age group and gender- Safety Analysis Set - Booster series

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Age group	Participants n(%)	
					M	F
VAT00002	Supplemental Cohort 2	Pfizer/BioNTech Primed				

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Age group	Participants n(%)	
					M	F
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)			
				18-55 years	140 (82.4)	178 (85.6)
				≥56 years	30 (17.6)	30 (14.4)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)			
				18-55 years	142 (80.2)	173 (87.4)
				≥56 years	35 (19.8)	25 (12.6)
		Moderna Primed				
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)			
				18-55 years	33 (64.7)	45 (75.0)
				≥56 years	18 (35.3)	15 (25.0)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)			
				18-55 years	32 (72.7)	44 (68.8)
				≥56 years	12 (27.3)	20 (31.3)
		AZ Primed				
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)			
				18-55 years	40 (69.0)	24 (57.1)
				≥56 years	18 (31.0)	18 (42.9)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)			
				18-55 years	29 (55.8)	35 (72.9)
				≥56 years	23 (44.2)	13 (27.1)

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Age group	Participants n(%)	
					M	F
		Janssen Primed				
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)			
				18-55 years	14 (73.7)	14 (73.7)
				≥56 years	5 (26.3)	5 (26.3)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)			
				18-55 years	15 (83.3)	13 (65.0)
				≥56 years	3 (16.7)	7 (35.0)
		CoV2 preS dTM-AS03 (D614) Primed				
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)			
				18-55 years	33 (48.5)	25 (39.1)
				≥56 years	35 (51.5)	39 (60.9)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)			
				18-55 years	2 (5.0)	2 (5.3)
				≥56 years	38 (95.0)	36 (94.7)
		All				
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)			
				18-55 years	229 (67.8)	263 (71.7)
				≥56 years	109 (32.2)	104 (28.3)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)			
				18-55 years	218 (74.9)	265 (80.3)
				≥56 years	73 (25.1)	65 (19.7)

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Age group	Participants n(%)	
					M	F

Prior prime vaccination: AZ = Oxford University/AstraZeneca
Study: VAT00002 Program: t003_rmp_july_b1351 Output: t003_rmp_july_b1351.RTF DATE: 05JUL2022 11:23
CoV2 preS dTM: CoV-2 prefusion Spike delta TM; F: Female; M: Male.

Table 11 - Summary of Exposure by Racial Origin - Safety Analysis Set - Booster series

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
VAT00002	Supplemental Cohort 2	Pfizer/BioNTech Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				White	247 (65.3)
				Asian	12 (3.2)
				Black or African American	54 (14.3)
				American Indian or Alaska native	5 (1.3)
				Native Hawaiian or other Pacific Islander	2 (0.5)
				Multiple	6 (1.6)
				Not Reported	44 (11.6)
				Unknown	8 (2.1)
				Total	378 (100)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				White	239 (63.7)
				Asian	13 (3.5)
				Black or African American	60 (16.0)
				American Indian or Alaska native	6 (1.6)
				Native Hawaiian or other Pacific Islander	1 (0.3)

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
				Multiple	6 (1.6)
				Not Reported	48 (12.8)
				Unknown	2 (0.5)
				Total	375 (100)
		Moderna Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				White	78 (70.3)
				Asian	1 (0.9)
				Black or African American	16 (14.4)
				American Indian or Alaska native	6 (5.4)
				Native Hawaiian or other Pacific Islander	0
				Multiple	3 (2.7)
				Not Reported	1 (0.9)
				Unknown	6 (5.4)
				Total	111 (100)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				White	61 (56.5)
				Asian	3 (2.8)
				Black or African American	32 (29.6)
				American Indian or Alaska native	2 (1.9)
				Native Hawaiian or other Pacific Islander	0
				Multiple	1 (0.9)
				Not Reported	6 (5.6)

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
				Unknown	3 (2.8)
				Total	108 (100)
		AZ Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				White	91 (91.0)
				Asian	4 (4.0)
				Black or African American	3 (3.0)
				American Indian or Alaska native	0
				Native Hawaiian or other Pacific Islander	0
				Multiple	0
				Not Reported	1 (1.0)
				Unknown	1 (1.0)
				Total	100 (100)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				White	86 (86.0)
				Asian	7 (7.0)
				Black or African American	2 (2.0)
				American Indian or Alaska native	0
				Native Hawaiian or other Pacific Islander	0
				Multiple	1 (1.0)
				Not Reported	2 (2.0)
				Unknown	2 (2.0)
				Total	100 (100)

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
		Janssen Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				White	15 (39.5)
				Asian	2 (5.3)
				Black or African American	16 (42.1)
				American Indian or Alaska native	4 (10.5)
				Native Hawaiian or other Pacific Islander	1 (2.6)
				Multiple	0
				Not Reported	0
				Unknown	0
				Total	38 (100)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				White	21 (55.3)
				Asian	2 (5.3)
				Black or African American	10 (26.3)
				American Indian or Alaska native	2 (5.3)
				Native Hawaiian or other Pacific Islander	0
				Multiple	0
				Not Reported	2 (5.3)
				Unknown	1 (2.6)
				Total	38 (100)

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
		CoV2 preS dTM-AS03 (D614) Primed			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				White	80 (60.6)
				Asian	2 (1.5)
				Black or African American	7 (5.3)
				American Indian or Alaska native	20 (15.2)
				Native Hawaiian or other Pacific Islander	0
				Multiple	0
				Not Reported	0
				Unknown	23 (17.4)
				Total	132 (100)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				White	37 (47.4)
				Asian	2 (2.6)
				Black or African American	2 (2.6)
				American Indian or Alaska native	14 (17.9)
				Native Hawaiian or other Pacific Islander	0
				Multiple	1 (1.3)
				Not Reported	0
				Unknown	22 (28.2)
				Total	78 (100)

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
		All			
			CoV2 preS dTM-AS03 (B.1.351) (5 μg antigen)		
				White	468 (66.4)
				Asian	21 (3.0)
				Black or African American	91 (12.9)
				American Indian or Alaska native	29 (4.1)
				Native Hawaiian or other Pacific Islander	3 (0.4)
				Multiple	10 (1.4)
				Not Reported	46 (6.5)
				Unknown	37 (5.2)
				Total	705 (100)
			CoV2 preS dTM-AS03 (2.5 μg D614 antigen + 2.5 μg B.1.351 antigen)		
				White	407 (65.5)
				Asian	25 (4.0)
				Black or African American	104 (16.7)
				American Indian or Alaska native	10 (1.6)
				Native Hawaiian or other Pacific Islander	1 (0.2)
				Multiple	8 (1.3)
				Not Reported	58 (9.3)
				Unknown	8 (1.3)
				Total	621 (100)

Prior prime vaccination: AZ = Oxford University/AstraZeneca
Study: VAT00002 Program: t005_rmp_july_b1351 Output: t005_rmp_july_b1351.RTF DATE: 05JUL2022 13:22
CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Supportive data with other formulations:

Table 12 - Exposure by Dose - Safety Analysis Set - Primary series

STUDY	Cohort/Stage	Study Intervention Groups	Dose of exposure	Participants (n)
VAT00008	Stage 2			
		CoV2 preS dTM-AS03 (2.5 µg D614 antigen + 2.5 µg B.1.351 antigen)		
			Dose 1	6724
			Dose 2	5928
			Total number of doses received	12652
		Placebo		
			Dose 1	6696
			Dose 2	5877
			Total number of doses received	12573

Study: VAT00002 Program: t002_rmp_july_b1351 Output: t002_rmp_july_b1351.RTF DATE: 05JUL2022 11:23
CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 13 - Exposure by age group and gender - Safety Analysis Set - Primary series

Study	Cohort/Stage	Study Intervention Groups	Age group	Participants n(%)	
				M	F
VAT00008	Stage 2				
		CoV2 preS dTM-AS03 (2.5 µg D614 antigen + 2.5 µg B.1.351 antigen)			
			18-59 years	3763 (94.7)	2544 (92.5)
			≥60 years	210 (5.3)	207 (7.5)
		Placebo			
			18-59 years	3734 (94.9)	2557 (92.5)
			≥60 years	199 (5.1)	206 (7.5)

Study: VAT00002 Program: t004_rmp_july_b1351 Output: t004_rmp_july_b1351.RTF DATE: 05JUL2022 11:23
CoV2 preS dTM: CoV-2 prefusion Spike delta TM; F: Female; M: Male.

Table 14 - Summary of Exposure by Racial Origin - Safety Analysis Set - Primary series

STUDY	Cohort/Stage	Study Intervention Groups	Ethnic origin	Participants n(%)
VAT00008	Stage 2			
		CoV2 preS dTM-AS03 (2.5 µg D614 antigen + 2.5 µg B.1.351 antigen)		

STUDY	Cohort/Stage	Study Intervention Groups	Ethnic origin	Participants n(%)
			White	287 (4.3)
			Asian	2562 (38.1)
			Black or African American	2873 (42.7)
			American Indian or Alaska Native	408 (6.1)
			Native Hawaiian or Other Pacific Islander	2 (<0.1)
			Multiple	5 (<0.1)
			Not Reported	95 (1.4)
			Unknown	492 (7.3)
			Total	6724 (100)
		Placebo		
			White	283 (4.2)
			Asian	2567 (38.3)
			Black or African American	2854 (42.6)
			American Indian or Alaska Native	402 (6.0)
			Native Hawaiian or Other Pacific Islander	3 (<0.1)
			Multiple	6 (<0.1)
			Not Reported	82 (1.2)
			Unknown	499 (7.5)
			Total	6696 (100)

Study: VAT00002 Program: t006_rmp_july_b1351 Output: t006_rmp_july_b1351.RTF DATE: 05JUL2022 11:23
CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 15 - Exposure by Dose - Safety Analysis Set - Booster series

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Dose of exposure	Participants (n)
VAT00002	Supplemental Cohort 1	Pfizer/BioNTech Primed			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				Dose 1	328
		Moderna Primed			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				Dose 1	113

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Dose of exposure	Participants (n)
		AZ Primed			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				Dose 1	127
		Janssen Primed			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				Dose 1	103
		All			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				Dose 1	671
VAT00002	Supplemental Cohort 2	CoV2 preS dTM-AS03 (D614) Primed			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				Dose 1	132

Prior prime vaccination: AZ = Oxford University/AstraZeneca
Study: VAT00002 Program: t001_rmp_july_d614 Output: t001_rmp_july_d614.RTF DATE: 06JUL2022 15:29
CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 16 - Exposure by Dose - Safety Analysis Set - Primary series

STUDY	Cohort/Stage	Study Intervention Groups	Dose of exposure	Participants (n)
VAT00002	Original Prime Cohort			
		Group 1: CoV2 preS dTM-AS03 (5 μg antigen)		
			Dose 1	240
			Dose 2	233
			Total number of doses received	473
		Group 2: CoV2 preS dTM-AS03 (10 μg antigen)		
			Dose 1	240
			Dose 2	228
			Total number of doses received	468

STUDY	Cohort/Stage	Study Intervention Groups	Dose of exposure	Participants (n)
		Group 3: CoV2 preS dTM-AS03 (15 μg antigen)		
			Dose 1	241
			Dose 2	227
			Total number of doses received	468
	Supplemental Cohorts 1 and 2 Comparator Group			
		CoV2 preS dTM-AS03 (D614) (10 μg antigen)		
			Dose 1	473
			Dose 2	445
			Total number of doses received	918
VAT00008	Stage 1			
		CoV2 preS dTM-AS03 (D614) (10 μg antigen)		
			Dose 1	5050
			Dose 2	4719
			Total number of doses received	9769
		Placebo		
			Dose 1	5064
			Dose 2	4722
			Total number of doses received	9786

Study: VAT00002 Program: t002_rmp_july_d614 Output: t002_rmp_july_d614.RTF DATE: 05JUL2022 11:11
CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 17 - Exposure by age group and gender - Safety Analysis Set - Booster series

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Age group	Participants n(%)	
					M	F
VAT00002	Supplemental Cohort 1	Pfizer/BioNTech Primed				
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)			

STUDY	Cohort/Stage	Prime vaccination	Study Intervention Groups	Age group	Participants n(%)	
					M	F
				18-55 years	92 (62.2)	129 (71.7)
				≥56 years	56 (37.8)	51 (28.3)
		Moderna Primed				
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)			
				18-55 years	26 (57.8)	49 (72.1)
				≥56 years	19 (42.2)	19 (27.9)
		AZ Primed				
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)			
				18-55 years	38 (56.7)	35 (58.3)
				≥56 years	29 (43.3)	25 (41.7)
		Janssen Primed				
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)			
				18-55 years	30 (73.2)	45 (72.6)
				≥56 years	11 (26.8)	17 (27.4)
		All				
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)			
				18-55 years	186 (61.8)	258 (69.7)
				≥56 years	115 (38.2)	112 (30.3)
VAT00002	Supplemental Cohort 2	CoV2 preS dTM-AS03 (D614) Primed				
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)			
				18-55 years	33 (48.5)	25 (39.1)
				≥56 years	35 (51.5)	39 (60.9)

Prior prime vaccination: AZ = Oxford University/AstraZeneca
Study: VAT00002 Program: t003_rmp_july_d614 Output: t003_rmp_july_d614.RTF DATE: 06JUL2022 15:29
CoV2 preS dTM: CoV-2 prefusion Spike delta TM; F: Female; M: Male.

Table 18 - Exposure by age group and gender - Safety Analysis Set - Primary series

STUDY	Cohort/Stage	Study Intervention Groups	Age group	Participants n(%)	
				M	F
VAT00002	Original Prime Cohort				
		Group 1: CoV2 preS dTM-AS03 (5 µg antigen)			
			18-59 years	56 (47.9)	65 (52.8)
			≥60 years	61 (52.1)	58 (47.2)
		Group 2: CoV2 preS dTM-AS03 (10 µg antigen)			
			18-59 years	65 (51.6)	55 (48.2)
			≥60 years	61 (48.4)	59 (51.8)
		Group 3: CoV2 preS dTM-AS03 (15 µg antigen)			
			18-59 years	68 (57.1)	51 (41.8)
			≥60 years	51 (42.9)	71 (58.2)
	Supplemental Cohorts 1 and 2 Comparator Group				
		CoV2 preS dTM-AS03 (D614) (10 µg antigen)			
			18-55 years	253 (96.2)	206 (98.1)
			≥56 years	10 (3.8)	4 (1.9)
VAT00008	Stage 1				
		CoV2 preS dTM-AS03 (D614) (10 µg antigen)			
			18-59 years	2614 (92.1)	2022 (91.4)
			≥60 years	224 (7.9)	190 (8.6)
		Placebo			
			18-59 years	2662 (92.1)	1982 (91.1)
			≥60 years	227 (7.9)	193 (8.9)

Study: VAT00002 Program: t004_rmp_july_d614 Output: t004_rmp_july_d614.RTF DATE: 05JUL2022 11:11
CoV2 preS dTM: CoV-2 prefusion Spike delta TM; F: Female; M: Male.

Table 19 - Summary of Exposure by Racial Origin - Safety Analysis Set - Booster series

STUDY	Cohort/ Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
VAT00002	Supplemental Cohort 1	Pfizer/BioNTech Primed			

STUDY	Cohort/ Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				White	251 (76.5)
				Asian	19 (5.8)
				Black or African American	15 (4.6)
				American Indian or Alaska native	5 (1.5)
				Native Hawaiian or other Pacific Islander	0
				Multiple	1 (0.3)
				Not Reported	33 (10.1)
				Unknown	4 (1.2)
				Total	328 (100)
		Moderna Primed			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				White	100 (88.5)
				Asian	7 (6.2)
				Black or African American	3 (2.7)
				American Indian or Alaska native	2 (1.8)
				Native Hawaiian or other Pacific Islander	0
				Multiple	1 (0.9)
				Not Reported	0
				Unknown	0
				Total	113 (100)
		AZ Primed			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				White	104 (81.9)
				Asian	11 (8.7)
				Black or African American	2 (1.6)
				American Indian or Alaska native	0

STUDY	Cohort/ Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
				Native Hawaiian or other Pacific Islander	0
				Multiple	0
				Not Reported	10 (7.9)
				Unknown	0
				Total	127 (100)
		Janssen Primed			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				White	97 (94.2)
				Asian	0
				Black or African American	5 (4.9)
				American Indian or Alaska native	1 (1.0)
				Native Hawaiian or other Pacific Islander	0
				Multiple	0
				Not Reported	0
				Unknown	0
				Total	103 (100)
		All			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				White	552 (82.3)
				Asian	37 (5.5)
				Black or African American	25 (3.7)
				American Indian or Alaska native	8 (1.2)
				Native Hawaiian or other Pacific Islander	0
				Multiple	2 (0.3)
				Not Reported	43 (6.4)
				Unknown	4 (0.6)
				Total	671 (100)

STUDY	Cohort/ Stage	Prime vaccination	Study Intervention Groups	Ethnic origin	Participants n(%)
VAT00002	Supplemental Cohort 2	CoV2 preS dTM-AS03 (D614) Primed			
			CoV2 preS dTM-AS03 (D614) (5 μg antigen)		
				White	80 (60.6)
				Asian	2 (1.5)
				Black or African American	7 (5.3)
				American Indian or Alaska native	20 (15.2)
				Native Hawaiian or other Pacific Islander	0
				Multiple	0
				Not Reported	0
				Unknown	23 (17.4)
				Total	132 (100)

Prior prime vaccination: AZ = Oxford University/AstraZeneca
Study: VAT00002 Program: t005_rmp_july_d614 Output: t005_rmp_july_d614.RTF DATE: 06JUL2022 15:29
CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 20 - Summary of Exposure by Racial Origin - Safety Analysis Set - Primary series

STUDY	Cohort/Stage	Study Intervention Groups	Age group	Participants n(%)
VAT00002	Original Prime Cohort			
		Group 1: CoV2 preS dTM-AS03 (5 μg antigen)		
			White	156 (65.0)
			Asian	13 (5.4)
			Black or African American	13 (5.4)
			American Indian or Alaska native	22 (9.2)
			Native Hawaiian or other Pacific Islander	2 (0.8)
			Multiple	5 (2.1)
			Not Reported	4 (1.7)
			Unknown	25 (10.4)
			Total	240 (100)

STUDY	Cohort/Stage	Study Intervention Groups	Age group	Participants n(%)
		Group 2: CoV2 preS dTM-AS03 (10 μg antigen)		
			White	150 (62.5)
			Asian	10 (4.2)
			Black or African American	23 (9.6)
			American Indian or Alaska native	24 (10.0)
			Native Hawaiian or other Pacific Islander	1 (0.4)
			Multiple	2 (0.8)
			Not Reported	4 (1.7)
			Unknown	26 (10.8)
			Total	240 (100)
		Group 3: CoV2 preS dTM-AS03 (15 μg antigen)		
			White	155 (64.3)
			Asian	10 (4.1)
			Black or African American	20 (8.3)
			American Indian or Alaska native	20 (8.3)
			Native Hawaiian or other Pacific Islander	2 (0.8)
			Multiple	4 (1.7)
			Not Reported	2 (0.8)
			Unknown	28 (11.6)
			Total	241 (100)
	Supplemental Cohorts 1 and 2 Comparator Group			
		CoV2 preS dTM-AS03 (D614) (10 μg antigen)		
			White	370 (78.2)
			Asian	18 (3.8)
			Black or African American	50 (10.6)
			American Indian or Alaska native	15 (3.2)
			Native Hawaiian or other Pacific Islander	0

STUDY	Cohort/Stage	Study Intervention Groups	Age group	Participants n(%)
			Multiple	8 (1.7)
			Not Reported	3 (0.6)
			Unknown	9 (1.9)
			Total	473 (100)
VAT00008	Stage 1			
		CoV2 preS dTM-AS03 (D614) (10 μg antigen)		
			White	114 (2.3)
			Asian	2219 (43.9)
			Black or African American	1057 (20.9)
			American Indian or Alaska native	1641 (32.5)
			Native Hawaiian or other Pacific Islander	1 (<0.1)
			Multiple	8 (0.2)
			Not Reported	1 (<0.1)
			Unknown	9 (0.2)
			Total	5050 (100)
		Placebo		
			White	116 (2.3)
			Asian	2226 (44.0)
			Black or African American	1052 (20.8)
			American Indian or Alaska native	1645 (32.5)
			Native Hawaiian or other Pacific Islander	3 (<0.1)
			Multiple	6 (0.1)
			Not Reported	3 (<0.1)
			Unknown	13 (0.3)
			Total	5064 (100)

Study: VAT00002 Program: t006_rmp_july_d614 Output: t006_rmp_july_d614.RTF DATE: 05JUL2022 11:11
CoV2 preS dTM: CoV 2 prefusion Spike delta TM.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

In below table important exclusion criteria for the phase III Clinical Study (VAT00002) Supplemental Cohort 2 are described.

Table 21 - Important exclusion criteria in pivotal studies in the development program

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to a vaccine containing any of the same substances	To avoid potentially severe and life-threatening allergic reactions.	No	Anaphylactic reaction is considered as a potential risk. Severe hypersensitivity to any of the vaccine components constitutes a contraindication for the vaccine. This is described in the EU-SmPC section 4.3 Contraindications and 4.4 Special warnings and precautions for use.
Dementia or any other cognitive condition at a stage that could interfere with following the study procedures based on Investigator's judgment	These conditions could interfere with the participant's ability to follow study procedures (potential non-compliance consequences).	No	Exclusion criterion is related to study procedures compliance and not to the vaccine itself as safety profile of the vaccine is not expected to be different in this population when properly administered.
Self-reported thrombocytopenia, contraindicating IM vaccination based on Investigator's judgment	On the basis of underlying thrombocytopenia IM vaccination may lead to hematoma.	No	It is common medical practice not to administer a product by the IM route in patients with underlying severe thrombocytopenia. This is described in EU-SmPC section 4.4 Special warnings and precautions for use.
Bleeding disorder, or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating IM vaccination based on Investigator's judgment	On the basis of underlying bleeding disorder or receipt of anticoagulants in the past 21 days, IM vaccination may lead to an increased risk of bleeding.	No	It is common medical practice not to administer a product by the IM route in patients with underlying bleeding disorder/receipt of anticoagulants in the past 21 days. This is described in the EU-SmPC section 4.4 Special warnings and precautions for use.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnant and breast-feeding women	To avoid any potential harm to the fetus or to the breastfed infant	Yes	Pregnant and breast-feeding women are usually excluded from clinical trials to avoid use in vulnerable population. Pregnant and breast-feeding women population is considered as missing information. This is described in the EU-SmPC section 4.6 Fertility, Pregnancy and Lactation. A Phase III Clinical Study in pregnant and breast-feeding women as well as observational studies are planned.
Unstable acute or chronic illness that in the opinion of the Investigator or designee poses additional risk as a result of participation	To avoid any confounding factors in the analysis of safety and efficacy data. Participants with well-controlled conditions are not excluded.	Yes	Participants with unstable acute or chronic illness were excluded from clinical trials as these conditions could be considered as an additional risk for the participant as a result of clinical trial participation. Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) is considered as missing information.
Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥38.0°C [≥100.4°F]). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided	Temporary exclusion criterion to collect the most accurate safety data and to ensure adequate immune response.	No	Participants with moderate or severe acute illness/infection are usually excluded from clinical trials. This is only a temporary exclusion resulting in postponement of vaccination until recovery. This is described in the EU-SmPC section 4.4 Special warnings and precautions for use.
Receipt of any vaccine in the 30 days preceding or on the day of the first study vaccination or planned receipt of any vaccine between the first study vaccination and in the 30 days following the second study vaccination except for influenza vaccination, which may be received at any time in relation to study intervention	To avoid any interference with the safety as well as the immunogenicity evaluation within the study.	Yes	Interactions with other vaccines is considered as missing information. This is described in the EU-SmPC section 4.5 Interaction with other medicinal products and other forms of interaction.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Receipt of immunoglobulins, blood or blood-derived products in the past 3 months	The immunogenicity of the vaccine may be reduced by receipt of immunoglobulins, blood or blood-derived products in the past 3 months	No	These participants were excluded from clinical studies to obtain unconfounded immunogenicity results.
Receipt of solid-organ or bone marrow transplants in the past 180 days	The immunogenicity of the vaccine may be reduced by immunosuppressive treatment required for solid-organ or bone marrow transplants.	Yes	These participants were excluded to obtain unconfounded immunogenicity results. Immunocompromised population is considered as missing information. Receipt of immunosuppressive treatment is described in the EU-SmPC section 4.4 Special warnings and precautions for use.
Receipt of anti-cancer chemotherapy in the last 90 days	The immunogenicity of the vaccine may be reduced by anti-cancer chemotherapy.	Yes	These participants were excluded to obtain unconfounded immunogenicity results. Immunocompromised population is considered as missing information. Receipt of immunosuppressive treatment is described in the EU-SmPC section 4.4 Special warnings and precautions for use.

COPD: Chronic Obstructive Pulmonary Disease; EU: European Union; IM: Intramuscular; SmPC: Summary of Product Characteristics.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Clinical studies are limited in size and in time, therefore, unlikely to detect very rare adverse reactions, or adverse reactions with a long-latency.

B.1.351 Monovalent vaccine data, Booster immunization:

Mean follow-up after booster vaccination was 144 days at the time of the primary analysis of Phase III Clinical Study (VAT00002, Supplemental Cohort 2, Monovalent B.1.351 booster group).

Of note, all subjects completed their visit at Day 28 from VAT00013/COVIBOOST Investigator Sponsored Randomized Booster study (Monovalent B.1.351).

One year follow-up after last vaccination is ongoing.

Limitations to detect uncommon adverse reactions:

It is acknowledged that Monovalent B.1.351 Booster safety database is limited in size (N = 705), however the safety profile observed with the Monovalent B.1.351 Booster is not different from the safety profile observed in the larger safety dataset of participants having received Beta-variant containing formulations (Monovalent B.1.351 Booster, Bivalent B.1.351/D614 Priming and Booster) of the vaccine (N = 7093, also including participants of VAT00008 stage 2).

Adverse reactions section of the SmPC accurately reflect the totality of safety data available on Beta-variant containing vaccines (N = 7093). The safety profile of Monovalent B.1.351 Booster was established based on safety data from 705 participants vaccinated with 5 µg Monovalent B.1.351 booster formulation (VAT00002 Booster Cohort 2). It was confirmed with the pooled dataset, including data from 7798 participants having received vaccine formulations containing the same Beta antigen (VAT00008 stage 2; reactogenicity data collected in 3759 participants). The lists of adverse reactions were identical regardless of the dataset used (705 or 3759 participants).

Monovalent B.1.351 safety database (N = 705) did allow a complete characterization of common (≥1/100 to <1/10) and very common (≥1/10) adverse reactions. In particular, all solicited events are included in the list of adverse reactions of the SmPC, all of them being common or very common. For uncommon (≥1/1000 to <1/100) adverse reactions, Monovalent B.1.351 Booster vaccine safety database (N = 705) did not allow a robust characterization. Extended safety database analysis including clinical studies with vaccine formulation containing the same Beta antigen, resulting in a total of 3759 participants (Monovalent B.1.351 Booster, Bivalent B.1.351/D614 Priming and Booster) was thus considered to support the characterization of uncommon adverse reactions. Extended safety database of 3759 participants is sufficient to define the list of Monovalent B.1.351 uncommon adverse reactions while their frequency needs to be confirmed. Based on the extended safety database analysis, no significant impact on Monovalent B.1.351 Booster benefit/risk is expected when further characterizing uncommon adverse reactions.

The safety database of Monovalent (B.1.351) vaccine is expended with Monovalent (B.1.351) vaccine used as a booster dose as part of the VAT00008 Clinical Study (Open Label Extension): all participants will be offered the opportunity to be part of this phase of the study and can therefore receive the Monovalent (B.1.351) booster vaccine. This extension will allow a more robust estimation of the frequency estimates.

Supportive data with other formulations

Mean follow-up after booster vaccination was:

- One hundred fifty-two (152) days at the time of the primary analysis of Phase III Clinical Study (VAT00002, Supplemental Cohort 1).

Mean follow-up after primary vaccination was:

- Forty-four (44) days at the time of the primary analysis of Phase II Clinical Study (VAT00002, Original Cohort). In addition, 365 days at the time of the analysis to support initial submission (partially cleaned data).

- Two hundred twenty-eight (228) days at the time of the primary analysis of Phase III Clinical Study (VAT00002, Supplemental Comparator Cohort).
- One hundred sixty-five (165) days in both vaccine and placebo groups at the time of the primary analysis of Phase III Clinical Study (VAT00008) stage 1.
- Eighty-five (85) days in both vaccine and placebo groups at the time of the primary analysis of Phase III Clinical Study (VAT00008) stage 2.

For the Phase III efficacy Clinical Study (VAT00008), the assumed incidence rate of COVID-19 cases was based on available epidemiological data in the public domain in Clinical Study participating countries (2.25%). This resulted in a planned enrollment number of 5080 participants in the vaccine group (Monovalent D614 vaccine) in stage 1 which would provide 92.1% probability to detect at least one AE with 0.05% rate. In stage 2 a planned enrollment number of 6783 participants in vaccine group (Bivalent D614/B.1.351 vaccine), would provide 96.6% probability to detect at least one AE with 0.05% rate. A total of 23 141 participants in the two different stages were enrolled and randomized with allocation ratio (1:1) into vaccine group and placebo group. Owing to the ongoing war in Ukraine, data completeness could not be confirmed for the four Ukrainian sites in VAT00008; it was agreed with the Center for Biologics Evaluation and Research that none of the participants from these sites were included in the main analyses.[1]

One year follow-up after last vaccination is ongoing.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 22 - Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant and breast-feeding women	CoV2 preS dTM-AS03 has not yet been studied in pregnant or breast-feeding women (this population was excluded from Phase II/III and Phase III Clinical Studies). Pregnant and breast-feeding women are part of the target population. A Phase III Clinical Study in pregnant and breast-feeding women (VAT00006) as well as observational studies are planned. Animal studies do not indicate any finding 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. Few pregnancy exposures were reported in ongoing Clinical Studies. Based on these data, no safety concern has been observed in this population.

[1] Due to exclusion of Ukrainian participants, the enrollment number decreased since the last RMP version (1.1).

Type of special population	Exposure
	The use of CoV2 preS dTM-AS03 (B.1.351) in pregnancy and while breast-feeding is considered as missing information until sufficient evidence is available to demonstrate that potential benefits outweigh any potential risks for the mother and fetus.
Elderly subjects	Elderly participants were included in Clinical Studies from Phase II/III to Phase III: Refer to [Part II SIII.2] for more detailed exposure data. Elderly patients are part of the target population. To date, there is no information to suggest that elderly patients are adversely affected by CoV2 preS dTM-AS03 (B.1.351), no increased risk of adverse reactions has been observed.
Populations with relevant different ethnic origin	Populations with relevant different ethnic origin are included in Clinical Studies from Phase II/III to Phase III: Refer to [Part II SIII.2] for more detailed exposure data. Race or ethnic origin did not show any impact on the safety profile.
Subpopulations carrying known and relevant genetic polymorphisms	CoV2 preS dTM-AS03 has not been evaluated in participants carrying known and relevant genetic polymorphisms. No data are available. To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of CoV2 preS dTM-AS03 (B.1.351) in the currently proposed indication(s).
Children and Adolescents	CoV2 preS dTM-AS03 has not yet been studied in patients below 18 years of age. Patients below 18 years of age are not part of the target population. A Clinical Study in pediatric population is planned. A PIP/PSP has been agreed with the EMA and FDA. [99]
Individuals with relevant co-morbidities	
Patients with relevant comorbidities • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Patients with a disease severity different from inclusion criteria in clinical trials	CoV2 preS dTM-AS03 has not been studied in participants with hepatic impairment, renal impairment, cardiovascular impairment, and immunocompromised status or with a disease severity different from inclusion criteria in clinical trials. Since vaccines are not metabolized by the liver, not eliminated by the kidney, no specific safety issue is expected in these populations. Participants with stable medical conditions/co-morbidities increasing the risk of severe COVID-19 were included in Phase II/III and Phase III Clinical Studies (high-risk medical conditions include eg, hepatic disease, chronic kidney disease, heart conditions such as heart failure and immunocompromised status). B.1.351 Monovalent vaccine data, Booster immunization: 58.9% in Cohort 2 Monovalent (B.1.351) belonged to the high-risk medical condition group. Supportive data with other formulations: • At the date of primary analysis of Phase III Clinical Study VAT00008: - 31.7% of the participants belonged to a high-risk medical condition group in stage 1 and - 32.2% belonged to a high-risk medical condition in stage 2. • For Phase II/III VAT00002 Clinical Study, at the date of primary analysis, - 60.5% of participants in the Original Cohort, - 47.5% of participants in Cohort 1, - 67.4% in Cohort 2 Homologous (D614) Primed group and, - 59.8% in the comparator group

Type of special population	Exposure
	belonged to the high-risk medical condition group. Individuals with medical conditions/co-morbidities increasing the risk of severe COVID-19 are part of the target population. To date, there is no information to suggest that these patients are adversely affected by CoV2 preS dTM-AS03, no increased risk of adverse reactions has been observed. The use of CoV2 preS dTM-AS03 (B.1.351) in frail patients which includes individuals with medical conditions/co-morbidities increasing the risk of severe COVID-19 is considered as missing information until sufficient evidence is available to demonstrate that potential benefits outweigh any potential risks in this population.
Frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	Frailty has been defined as a physiological syndrome characterized by decreased reserve and diminished resistance to stressors, resulting from cumulative decline across multiple physiological systems, and causing vulnerability to adverse outcomes. [100] Frailty is more common in women than in men, more common with age [101] is related to disability and to co-morbidity and self-rated health. Frail subjects are part of the target population. Elderly subjects and subjects with comorbidities including those at increased risk of severe COVID-19 were enrolled in Clinical Studies. Individuals with unstable acute or chronic illness were excluded from phase II/III (VAT00002, Original Cohort and Supplemental Cohorts) and phase III Clinical Studies (VAT00008). Immune function could be impaired in frail subjects. To date, there is no information to suggest that these subjects are adversely affected by CoV2 preS dTM-AS03, no increased risk of adverse reactions has been observed. The use of CoV2 preS dTM-AS03 (B.1.351) in frail subjects with unstable health conditions and co-morbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) is considered as missing information until sufficient evidence, notably in individuals with unstable acute or chronic illness, is available to demonstrate that potential benefits outweigh any potential risks in this population.
Immunocompromised subjects	CoV2 preS dTM-AS03 was not studied in subjects with known or suspected immunodeficiency, including organ transplant subjects. In VAT00002 phase II/III Clinical Study, participants with receipt of solid-organ or bone marrow transplants in the past 180 days or receipt of anti-cancer chemotherapy in the last 90 days were excluded (only persons living with HIV, stable HIV infection determined by participant currently on antiretrovirals with CD4 count >200/mm^3 could be included). In VAT00008 phase III Clinical Study, immunocompromised participants were eligible for enrollment (participants with immunocompromised state from solid organ transplant or from other causes [blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of immunosuppressors]). In Phase III VAT00008 stage 1 and 2, immunocompromised state was one of the high-risk medical conditions as defined in the study protocol. B.1.351 Monovalent vaccine data, Booster immunization: 1.7% in Cohort 2 Monovalent (B.1.351) group belonged to the immunocompromised state group. Supportive data with other formulations: At the date of primary analysis of Phase III Clinical Study VAT000008: • 0.5% of the participants belonged to immunocompromised state as defined in the study protocol in stage 1 and • 5.1% belonged to immunocompromised state in stage 2.

Type of special population	Exposure
	For Phase II/III VAT00002 Supplemental Cohorts, at the date of primary analysis, the below percentage of participants belonged to the immunocompromised state group (including both participants with immunocompromised state from solid organ transplant or from other causes) • 3.0% of participants in Cohort 1, • 1.5% in Cohort 2 Homologous (D614) Primed group and, • 1.1% in the Comparator Group. Immunocompromised subjects are part of the target population. While efficacy may be compromised in this population, no specific safety issue is expected. To date, there is no information to suggest that these subjects are adversely affected by CoV2 preS dTM-AS03, no increased risk of adverse reactions has been observed. The use of CoV2 preS dTM-AS03 (B.1.351) in immunocompromised subjects is considered as missing information until sufficient evidence is available to demonstrate that potential benefits outweigh any potential risks in this population.
Subjects with autoimmune or immune-inflammatory diseases	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 and phase III at the discretion of the investigator. Individual with auto-immune or immune-inflammatory disease are part of the target population. To date, there is no information to suggest that these subjects are adversely affected by CoV2 preS dTM-AS03, no increased risk of adverse reactions has been observed. The use of CoV2 preS dTM-AS03 (B.1.351) in subjects with autoimmune or immune-inflammatory diseases has been defined as missing information until sufficient evidence is available to demonstrate that potential benefits outweigh any potential risks in these populations.

CD4: Cluster of Differentiation 4; COPD: Chronic Obstructive Pulmonary Disease; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; EMA: European Medicines Agency; FDA: Food and Drug Administration; HIV: Human Immunodeficiency Virus; PIP: Pediatric Investigation Plan; PSP: Patient Support Program.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

The vaccine is not yet registered in any market worldwide.

SV.1. POST-AUTHORIZATION EXPOSURE

Not applicable

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Potential for misuse of VidPrevtyn Beta for illegal purposes is considered low as this product is not known to have attributes that make it a candidate for intentional overdose, abuse, or illegal use, such as known pharmacological addictive effects. There is no evidence that vaccines would have the potential to induce drug abuse behaviors. Furthermore, it is a product available only through prescription and administered by healthcare professionals (HCPs) and not by self-administration.

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

In accordance with EMA's "([Consideration on core requirements for RMPs of COVID-19 vaccines v3.1 {dated 01 September 2022}])" guidance, the below factors were taken into consideration for the generation of the safety specifications and are not determined to be identified or potential risks.

The vaccine construct and the formulation: As with most vaccines for active immunization, the mechanism of action consists of the induction of immune responses against the antigens contained in the vaccine. The antigen of the CoV2 preS dTM (B.1.351) vaccine is a stabilized prefusion trimer of the SARS-CoV-2 Spike protein (B.1.351 strain). The coronavirus spike protein is the major viral surface glycoprotein and mediates attachment and entry into host cells. The spike protein precursor is cleaved to form non-covalently associated subunits, S1 and S2. [102] In the case of SARS-CoV-2, the receptor is angiotensin-converting enzyme 2, [103] a membrane-bound carboxypeptidase localized to vascular endothelial as well as epithelial surfaces. The magnitude and quality of the immune response to the antigen is enhanced through the inclusion of AS03 (GlaxoSmithKline's adjuvant system containing alpha-tocopherol and squalene in an oil-in-water emulsion). The adjuvant is anticipated to further enhance the magnitude of neutralizing antibody responses and to further induce balanced Th1/Th2 cell responses.

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The following safety topics will be discussed in this section and will be presented in Section SVII.1.1 as the risks did not meet the criteria of important risks for inclusion in the list of safety concerns in the RMP:

- Potential harm from overdose
- Potential for medication errors
- Potential for transmission of infectious agents
- Potential for off-label use
- Effect on fertility
- Pediatric safety issues
- Risks with minimal clinical impact on patients (in relation to the severity of the disease prevented)

The following safety topics will be discussed in this section and will be presented in Section SVII.1.2 as the risks met the criteria for inclusion in the list of safety concerns in the RMP.

- Important identified risk:
  - None

- Important potential risks:
  - Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
  - 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 [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
  - Use in subjects with autoimmune or inflammatory disorders
  - Interaction with other vaccines
  - Long-term safety

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not all potential or identified risks for the vaccine met the criteria of important risks for inclusion in the list of safety concerns in the RMP.

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

- **Anaphylactic reactions:**

Anaphylactic reactions are considered as a potential risk, not important in alignment with Guideline on Good pharmacovigilance practices (GVP) Module V - Risk management systems (Rev. 2) (28 March 2017 EMA/838713/2011 Rev 2) and removed from the list of safety concerns.

- **Potential harm from overdose:**

CoV2 preS dTM-AS03 (B.1.351) will be available in a multidose vial (MDV) presentation for 10 times 0.5 ml dose.

Multidose presentation implies the possibility of overdose. As the vaccine is injected by qualified medical personnel, situations of overdose should be exceptional. Furthermore, as CoV2 preS dTM-AS03 (B.1.351) is a vaccine there is no narrow therapeutic margin or major dose-related toxicity expected.

This specific situation of overdose is mitigated through the information available in particular in Instruction for use section (EU-SmPC section 6.6 where Instructions of use are described) and on vaccine packaging (vial and carton).

Overdose will be monitored via routine activities and will be presented in each periodic benefit-risk evaluation report (PBRER)/periodic safety update report (PSUR).

- **Potential for medication errors:**

CoV2 preS dTM-AS03 (B.1.351) will be available as two vials: one MDV containing the (B.1.351) antigen and second MDV containing adjuvant AS03 to be mixed at time of vaccination. This presentation implies the potential for medication errors via mixing error, ie, possibility to inject only the antigen or only the adjuvant or using a diluent rather than the supplied adjuvant. This would result in insufficient immunogenicity of the vaccine(s) in case of "failure to vaccinate" (due to immunization error) leading to lack of anticipated clinical benefit (related to efficacy).

As the vaccine is injected by qualified medical personnel, medication errors following preparation error should be exceptional. Presentation as liquid-liquid product for mixing is well-established for vaccines.

This specific situation of medication errors is mitigated through the information available in particular in instruction for use section (EU-SmPC section 6.6 where instructions of use are described) and on packaging (warning on a need to mix the contents of 2 vials is presented on each packaging element, including the vials).

CoV2 preS dTM-AS03 (B.1.351) will be available with 1 unique posology: 5 µg for booster immunization.

Medication errors will be monitored via routine activities and will be presented in each PBRER/PSUR.

- **Potential for transmission of infectious agents:**

No potential for transmission of infectious agents is anticipated (sterility-controlled manufacturing process and strict recommendations regarding the use once the vial is opened).

- **Potential for off-label use:**

This potential for off-label use is mainly concerning the potential use of CoV2 preS dTM-AS03 (B.1.351) in another age group (eg, children) that is not indicated or use in special populations.

This specific situation of off-label use mitigated through the information available in EU-SmPC (section 4.1 for age indication).

Off-label use will be monitored via routine activities and will be presented in each PBRER/PSUR.

- **Effect on fertility:**

Developmental and reproductive toxicity study conducted in rabbits do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Available information is provided in EU-SmPC (section 4.6 fertility, pregnancy and lactation).

- **Pediatric safety issues:**

The safety of CoV2 preS dTM-AS03 has not been yet established in pediatric population. CoV2 preS dTM-AS03 (B.1.351) is indicated for 18 years and above (Please refer to off-label use).

Based on interim analysis results from Phase III Clinical Study (VAT00008) stage 1 and stage 2 and from Phase II/III Clinical Study (VAT00002) Supplemental Cohorts, a Clinical Study in pediatric population is being planned. A PIP has been agreed with the EMA and FDA. [99]

- **Risks with minimal clinical impact on patients (in relation to the severity of the disease prevented):**

Syncope (fainting) and other anxiety-related reactions can occur following, or even before, any vaccination as a psychogenic or vasovagal response to the needle injection.

Injection site reactions may include injection site pain, injection site erythema, injection site swelling, injection site pruritus, injection site bruising, injection site warmth, upper limb edema, and, possibly, the extensive swelling of the vaccinated limb.

Systemic reactions may include fever, headache, malaise, myalgia, arthralgia, chills, fatigue, nausea, diarrhea and lymphadenopathy as separate events or a combination of events.

Aligned with EMA's "([Consideration on core requirements for RMPs of COVID-19 vaccines v3.1 {dated 01 September 2022}])", [104] CoV2 preS dTM-AS03 (B.1.351) reactogenicity profile is presented below. The reactogenicity profile does not impact the overall safety profile of the vaccine, has minimal clinical impact on patients (in relation to the severity of the disease prevented) and is not proposed to be included in the list of safety concerns.

Reactogenicity: Clinical impact on the safety profile is assessed as minimal in relation to the severity of the disease prevented.

B.1.351 Monovalent vaccine data, Booster immunization:

- VAT00002 Phase III Supplemental Cohort 2:

The majority of solicited reactions were of short duration (1 to 3 days after study vaccination), were of mild to moderate intensity and did not require medical intervention. Solicited reactions were reported less frequently in the ≥60 years of age group compared to the 18-59 years of age group. Overall, a low frequency of grade 3 solicited injection site or systemic reactions (less than 10% of participants experienced any grade 3 solicited reaction for both booster groups, blinded data) was observed. Injection site pain was the most frequently reported injection site reaction overall and the most frequently reported grade 3 intensity injection site reaction. Headache, myalgia, and malaise were the most frequently reported solicited systemic reactions of any grade. Malaise was the most frequently reported grade 3 solicited systemic reaction.

- Supportive data from VAT00013:

The reactogenicity profiles of the three booster vaccines utilized in the study (D614G + AS03 formulation, B.1.351 + AS03 formulation, and Pfizer–BioNTech BTN162b2) [105] was similar as the one observed in VAT00002 Cohort 2 Clinical Study.

Supportive data with other formulations:

Overall, a similar reactogenicity was seen between the Monovalent and Bivalent groups.

- **Primary immunization**
  - VAT00002 Phase II (Original Cohort, primary series):

From VAT00002 Phase II D1-D43 interim clinical study report (CSR), most of the solicited reactions were of grade 1 and grade 2 intensity. A higher frequency of solicited reactions was reported after the second injection than after the first injection, with comparable values across dose groups (5, 10 and 15 µg). The majority of solicited reactions occurred between D01 and D04

and resolved without intervention. Grade 3 solicited reactions occurred in 20.4% of all participants, with comparable values across dose groups. The proportion of participants reporting at least one Grade 3 solicited reaction was higher in the 18 to 59 years age group (27.3%) compared to the ≥60 years age group (13.6%). No grade 3 solicited reactions were considered as a SAE or a MAAE and all resolved.

Injection site pain was the most frequently reported injection site reaction of any intensity and of grade 3 intensity in all treatment groups. Grade 3 injection site reactions were overall reported with a low frequency and increased following the second injection. The proportion of participants reporting solicited systemic reactions of any grade were highest for malaise, myalgia, and headache in all treatment groups. [98]

Increase of the active substance quantity did not impact the reactogenicity as the reactogenicity was similar across treatment groups.

- VAT00002 Phase III Supplemental Comparator Group:

In the Comparator Group (aged 18 to 55 years only), solicited reactions were frequent with similar frequency following first injection and second injection, but tended to be transient and self-limited. The frequency of grade 3 solicited reactions increased between first injection (13.9%) and second injection (22.6%).

Solicited injection site reactions were reported with similar frequency following first injection and second injection. For solicited systemic reactions, frequency increased between first injection and second injection. The frequency of grade 3 reactions increased between first injection and second injection for both solicited injection site reactions (Post-dose 1: 3.9%, Post-dose 2: 10.7%) and solicited systemic reactions (Post-dose 1: 12.3%, Post-dose 2: 20.2%).

Injection site pain was the most frequently reported injection site reaction overall and the most frequently reported grade 3 intensity injection site. Headache, myalgia, and malaise were the most frequently reported solicited systemic reactions of any grade. Headache was the most frequently reported grade 3 solicited systemic reaction.

The safety data was consistent with and further supports the safety profile established with the primary series formulation seen in the VAT00002 Original Phase II Cohort.

- VAT00008 Phase III Stage 1:

Overall, lower frequencies of solicited reactions were observed after the second injection compared to after the first injection, and similar frequencies were observed in the older age group (≥60 years) compared to the younger age group (18 to 59 years of age). Intensities of solicited reactions were similar after both injections and in both age groups (18 to 59 years of age and ≥60 years). Reactogenicity was higher in the vaccine group than in the placebo group, as observed with other vaccines. Grade 3 solicited reactions occurred in 6.1% in the vaccine group and 2.9% in the placebo group. With regards to the age groups, grade 3 solicited reactions occurred in a similar proportion in the younger age group (18 to 59 years: 6.2% in the vaccine group) compared to the older age group (≥60 years: 5.4% in the vaccine group). The majority of solicited reactions were of short duration (1 to 3 days after study vaccination), were of mild to moderate intensity and did not require medical intervention.

Injection site pain was the most frequently reported solicited injection site reaction, in both age groups and after the first as well as after the second injection. Headache was the most frequently

reported solicited systemic reaction overall and in the younger age group (18 to 59 years of age), myalgia is most frequently reported in the older age group (≥60 years). In the overall population (irrespective of age group) and after any injection, headache, myalgia and malaise were the most frequently reported solicited systemic reactions. Overall, a low frequency of grade 3 solicited injection site or systemic reactions (below 10% in the vaccine group) was observed, applicable to both the 18 to 59 years of age and the ≥60 years age group. Grade 3 fever was reported in a low percentage of the participants, below 2% in the vaccine group (applicable to both the 18 to 59 years of age and the ≥60 years age group). The majority of reactions was short-lasting (up to 3 days).

Frequencies and intensities of solicited reactions (injection site and systemic reactions) were lower in both stage 1 and stage 2 of VAT00008 phase III study compared to the VAT00002 phase II (Original Cohort, primary Series) and Phase III (Supplemental Comparator Cohort). This can likely be explained by the difference in study design (phase III study is placebo-controlled, whereas in the phase II/III study all participants received an antigen dose), by difference in participating countries, enrollment at different time periods during the pandemic and by an influence of serostatus at baseline: In VAT00008 stage 1 and also in stage 2, a higher reactogenicity was observed in participants naive (with regard to SARS-CoV-2 infection) at baseline compared to non-naive participants at baseline. As more non-naive participants were enrolled into VAT000008 phase III study than in the previous VAT00002 phase II study, this contributed also to the difference in reactogenicity observed.

- VAT00008 Phase III Stage 2:

Overall, an acceptable reactogenicity profile was observed in Stage 2 (Bivalent D614 + B.1.351 versus Placebo). Slightly lower frequencies of solicited reactions were observed after the second injection compared to after the first injection. The frequencies of solicited reactions (injection site and systemic) were similar in both age groups (18-59 years and ≥60 years) and after both injections. When looking at the reactogenicity by age group and comparing the 2 injections, a comparable reactogenicity after the first and second injection was observed in the younger age group (18-59 years), whereas in the older age group ≥60 years a slightly lower systemic reactogenicity was seen after the second injection.

The majority of solicited reactions were of short duration (1 to 3 days after study vaccination), were of mild to moderate intensity and did not require medical intervention.

Injection site pain was the most frequently reported solicited injection site reaction, in both age groups and after the first as well as after the second injection. Headache was the most frequently reported solicited systemic reaction overall, after both injections and in both age groups. Overall, a low frequency of grade 3 solicited injection site or systemic reactions (below 10%) was observed, applicable to both the 18 to 59 years of age group and the ≥60 years age group. Grade 3 fever was reported in a low percentage of the participants (below 2%).

- **Booster immunization**

- VAT00002 Phase III Supplemental Cohort 1 (Protein primed group):

Overall, solicited reactions were frequent, but transient and mainly mild to moderate. The percentage of participants who experienced at least one solicited reaction was comparable across all priming groups. Participants aged ≥60 years reported solicited reactions less frequently than participants aged 18 to 59 years. Grade 3 solicited reactions were reported in 8.0% of booster

group participants across all priming groups. With regards to the age groups, grade 3 solicited reactions occurred less frequently in the older age group (≥60 years: 5.3% across all booster groups) compared to the younger age group (18 to 59 years: 9.2% across all booster groups).

Injection site pain is the most frequently reported solicited injection site reaction across all priming groups and in both age groups. Headache was the most frequently reported solicited systemic reaction overall and in the younger age group (18 to 59 years of age), myalgia is the most frequently reported in the older age group (≥60 years). Overall, a low frequency of grade 3 solicited injection site or systemic reactions (2.5% for injection site and 6.6% for systemic reactions across all priming groups) was observed, applicable to both the 18 to 59 years of age and the ≥60 years age groups.

Adverse Event of Special Interests (AESIs)

For clinical development, AESIs were considered for CoV2 preS dTM-AS03 (B.1.351) according to Brighton Collaboration (Safety Platform for Emergency Vaccines [SPEAC]), [106] vACCine covid-19 monitoring readinESS (ACCESS) protocol, [107] US CDC (preliminary list of AESI for Vaccine Adverse Event Reporting System [VAERS] surveillance), [108] WHO and FDA Guidance's. [109,110] and also safety data from other manufacturers including from COVID-19 vaccine platforms and selected as appropriate. [111,112,113,114]

No safety concern was raised from Clinical Development including on AESIs.

For postmarketing surveillance, list of AESIs is adapted from ACCESS project list [107] available in [Annex 7.2], Brighton Collaboration (SPEAC), [106] US CDC (preliminary list of AESI for VAERS surveillance), [108] WHO and FDA Guidance's. [109,110] safety data from COVID-19 vaccine Clinical Studies and also safety data from other manufacturers including from COVID-19 vaccine platforms and selected as appropriate. [111,112,113,114]

These AESIs are taken in consideration for routine and additional pharmacovigilance activities.

Observed/Expected analysis will be conducted as feasible. The list is considered dynamic and may be incremented following the evolving safety profile of the vaccine.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

There are no important identified risks for CoV2 preS dTM-AS03 (B.1.351) at EU-RMP DLP based on the B.1.351 Monovalent vaccine Clinical Study interim results (VAT00002 Phase III Supplemental Cohort 2 and VAT00013), Supportive data from other CoV2 preS dTM-AS03 formulations Clinical Study interim results extensive postmarketing experience with the manufacturing platform [115] and with the use of AS03 adjuvant. [116]

The important potential risks for CoV2 preS dTM-AS03 (B.1.351) are the following:

Table 23 - Important potential risk considered for inclusion in the list of safety concerns: Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	
Scientific evidence that has led to the inclusion	A theoretical concern with coronavirus vaccines is VAED. [117,118,119,120] This is the potential (hypothetical) increased disease severity in naïve vaccinees upon exposure to wild-type virus. [120,121] This disease enhancement of viral infection is also not fully understood. Mostly in the context of non-clinical beta coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the Th cell response. [96,122,123] Animal models of SARS-CoV-2 infection have not shown evidence of VAED disease after immunization. [94] Available data for other COVID-19 vaccines from different platforms do not indicate a risk of vaccine enhanced disease. [94,124,125,126] However, considering limited long-term safety data and in the absence of effectiveness data, the available evidence is not yet sufficient to fully rule out VAED including VAERD as a safety concern. Thus, it remains an important potential risk.
Risk-benefit impact	At this time, VAED including VAERD is a theoretical (hypothetical) concern without any evidence in humans. Therefore, there is currently no impact on the risk-benefit balance. Participants of ongoing Clinical Studies are followed up on any COVID-19 outcome (active and passive surveillances). No evidence of VAED including VAERD was found based on review of available data from Clinical Studies. Of note, in D614 containing vaccines (Monovalent) formulation and specifically in VAT00008 stage 1, an increased number of Omicron symptomatic COVID-19 cases in the naive vaccine group compared to the naive placebo group was observed. When scrutinizing this observation, there was no increase in severe outcomes, hospitalization, or mortality in the naive vaccinees. The clinical presentation (intensity of symptoms as measured in 3 intensity grades, number of symptoms per Omicron case and the duration of symptoms) was similar in the naive vaccine and placebo groups. No evidence of an increased viral load (naive vaccinees versus naive placebo recipients) was found. Most likely explanation for the observation is a lack of efficacy of the Monovalent D614 formulation against Omicron (lower level of neutralizing antibodies for this variant, additionally a long period between administration of the 2 doses of the study vaccine in VAT00008 stage 1 and the start of the Omicron wave (approximately 5 months after study start). In VAT00008 stage 2, no increased number of Omicron cases in the vaccine group were reported as compared to the placebo group. This was not seen neither in Booster formulations. In addition, VAED including VAERD might not apply to booster vaccine if referring to Brighton definition (VAED including VAERD risk would concern only SARS-CoV-2 seronegative individuals or individuals with unknown serostatus and no previous COVID-19 infection). [120] Any change in the available evidence (risk re-evaluation as per incidence and severity), could negatively impact the benefit/risk assessment for the concerned population.

Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

COVID-19: Coronavirus Disease-2019; Fc: Fragment Crystallizable; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine-Associated Enhanced Respiratory Disease.

Table 24 - Important potential risk considered for inclusion in the list of safety concerns: Myocarditis and Pericarditis

Myocarditis and Pericarditis	
Scientific evidence that has led to the inclusion	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. [127] 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. [128,129] 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. [130] 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 adjuvant system than the CoV2 preS dTM vaccine. [131] 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.
Risk-benefit 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. [130] 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. [132]

CI: Confidence Interval; CoV2 preS dTM: CoV 2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; IRR: Incidence Rate Ratio; mRNA: Messenger Ribonucleic Acid; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

Table 25 - Missing information considered for inclusion in the list of safety concerns: Use in pregnancy and while breast-feeding

Use in pregnancy and while breast-feeding	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in pregnant or breast-feeding women is not yet known as these populations have been excluded from Clinical Studies (phase II/III and phase III). It is not yet known whether CoV2 preS dTM-AS03 (B.1.351) could cause any fetal harm when administered to a pregnant woman or if any detrimental effects could occur when administered in breast-feeding women.

Use in pregnancy and while breast-feeding	
	Developmental and reproductive toxicology 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. Few pregnancy exposures were reported in ongoing Clinical Studies. Based on these data, no safety concern has been observed in this population. A Phase III study in pregnant and breast-feeding women (VAT00006) as well as observational studies are planned.
Risk-benefit impact	In general, it is recognized that the anticipated risk and consequence of missing information in pregnant and breast-feeding women is low and only considered for some live attenuated vaccines. [133]

CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 26 - Missing information considered for inclusion in the list of safety concerns: Use in immunocompromised subjects

Use in immunocompromised subjects	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in immunocompromised subjects is not yet known as these populations have been excluded from phase II/III Clinical Study (VAT00002). The immunogenicity of the vaccine may be reduced in individuals with immunocompromised conditions. This population is included in phase III Clinical Study (VAT00008) allowing the participation of individuals with a range of medical conditions including immunocompromised state (from solid organ transplant or from other causes (blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of immunosuppressors). In the phase II/III study (VAT00002) and phase III study (VAT00008), participants with a controlled HIV infection could be included.
Risk-benefit impact	This is not a safety risk per se outside of a potential decrease of efficacy in case of severe impairment of immune function.

CoV2 preS dTM: CoV-2 prefusion Spike delta TM; HIV: Human Immunodeficiency Virus.

Table 27 - Missing information considered for inclusion in the list of safety concerns: Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)

Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) is not fully known. The immunogenicity of the vaccine may be reduced in frail individuals. Whereas individuals who are frail considering their age or co-morbidities [134] or conditions increasing the risk of severe COVID-19 were included in phase II/III (VAT00002) and phase III Clinical Studies (VAT00008) (medical

Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	
	conditions of cancer, chronic kidney disease, COPD, obesity (body mass index 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), individuals with unstable acute or chronic illness were excluded from phase II/III (VAT00002, Original Cohort and Supplemental Cohorts) and phase III Clinical Studies (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.
Risk-benefit impact	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 due to the condition or treatment of the condition.

COPD: Chronic Obstructive Pulmonary Disease; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019.

Table 28 - Missing information considered for inclusion in the list of safety concerns: Use in subjects with autoimmune or inflammatory disorders

Use in subjects with autoimmune or inflammatory disorders	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in subjects with autoimmune or inflammatory disorders is not fully known. 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.
Risk-benefit impact	Individuals with autoimmune or inflammatory disorders may experience a different outcome than achieved in healthy individuals administered vaccines.

CoV2 preS dTM: CoV-2 prefusion Spike delta TM; HIV: Human Immunodeficiency Virus.

Table 29 - Missing information considered for inclusion in the list of safety concerns: Interaction with other vaccines

Interaction with other vaccines	
Scientific rationale for anticipating a different safety	CoV2 preS dTM-AS03 (B.1.351) will be used in patients who also may receive other vaccines.

Interaction with other vaccines	
profile in the particular subpopulation/use that has led to the inclusion	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 may be received at any time in relation to study intervention and influenza vaccination is part of concomitant medications that are collected.
Risk-benefit impact	It is not yet known if CoV2 preS dTM-AS03 (B.1.351) interacts with other vaccines with regards to safety or immunogenicity.

CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 30 - Missing information considered for inclusion in the list of safety concerns: Long-term safety

Long-term safety	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	Despite extensive experience with the manufacturing platform and AS03 adjuvant, long-term safety data available with CoV2 preS dTM-AS03 (B.1.351) are limited. Vaccines targeting SARS-CoV-2 are a new class of vaccines, with first vaccines authorized in Dec-2020 and 2021.
Risk-benefit impact	The long-term safety of CoV2 preS dTM-AS03 (B.1.351) is limited. Safety follow-up is ongoing in the Phase II/III and phase III Clinical Studies. Follow-up Duration: **B.1.351 Monovalent vaccine, Booster immunization** VAT00002 Phase III (Supplemental Cohorts): approximately 365 days post-booster injection **Supportive data with other formulations** VAT00002 Phase II (Original Cohort): 365 days post-injection 2 VAT00002 Supplemental Cohorts Comparator Group: approximately 365 days post-injection 2 VAT00008 Phase III stage 1: Approximately 387 days post injection 1 VAT00008 Phase III stage 2: Approximately 387 days post injection 1 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.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable since no previous version was approved (B.1.351).

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for CoV2 preS dTM-AS03 (B.1.351):

- Important identified risk:
  - None
- Important potential risks:
  - Vaccine Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
  - 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 [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
  - Use in subjects with autoimmune or inflammatory disorders
  - Interaction with other vaccines
  - Long-term safety

SVII.3.1 Presentation of important identified risks and important potential risks

Table 31 - Important potential risk: Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Important potential risk	Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
Potential mechanism	This potential risk has not been described with any SARS-CoV-2 vaccine from any other late phase Clinical Studies nor in animal models with SARS-CoV-2 infection. Historically, cellular immunopathology associated to either Th2 or inflammatory T cell responses has been observed after viral challenge in some animal models administered SARS-CoV-1 (murine, ferret and non-human primate models) or MERS-CoV (mice model) early-stage vaccine candidates. [117,118] No similar observations were reported for any of the SARS-CoV-2 vaccines, in animal models or in humans. This potential risk has been included based on these animal data with these related beta coronaviruses. Historically, disease enhancement in vaccinated children following infection with natural virus has been observed with an inactivated respiratory syncytial virus vaccine. [135] Vaccine-associated disease enhancement in humans has been described for two investigational formalin inactivated vaccines; against Respiratory Syncytial Virus and measles, and one licensed vaccine, the tetravalent live attenuated dengue vaccine. [106,117] Two different mechanisms have been identified to trigger disease enhancement. • Antibody Dependent Enhancement is the result of vaccine-elicited antibodies that do not effectively neutralize the virus because of low affinity, wrong specificity, or inadequate concentration. Virus-antibody complexes can gain entry to cells via Fc-receptor-mediated uptake and lead to a more severe disease.

Important potential risk	Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
	• A second mechanism involves triggering of allergic inflammation, characterized by Th2 biased immune response over Th1. [117,119] The molecular mechanism for this phenomenon, sometimes termed ADE, VAERD, or Immune Enhancement of viral infection, is also not fully understood. In the context of coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the Th cell response. [96,122,123,117]
Evidence source(s) and strength of evidence	A theoretical concern with coronavirus vaccines is VAED. [117,118,119,120] This is the potential (hypothetical) increased disease severity in naive vaccinees [120] upon exposure to wild-type virus. [121] This disease enhancement of viral infection is also not fully understood. Mostly in the context of non-clinical beta coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the Th cell response. [96,122,123] Animal models of SARS-CoV-2 infection have not shown evidence of VAED disease after immunization. [94] Available data for other COVID-19 vaccines from different platforms do not indicate a risk of vaccine enhanced disease. [94,124,125,126] However, considering limited long-term safety data and in the absence of effectiveness data, the available evidence is not yet fully sufficient to rule out VAED including VAERD as a safety concern. Thus, it remains an important potential risk.
Characterization of the risk	Vaccine-Associated Enhanced Disease including VAERD is a theoretical safety concern based on the currently available information for COVID-19 vaccines. Within the Clinical Studies for CoV2 preS dTM-AS03 (B.1.351), active surveillance (phone calls with the study participants) and passive surveillance (study participants instructed to contact the site if the experience COVID-19-like illness symptoms or have a positive COVID-19 test from any other source) for COVID-19-like illness was implemented. For the VAT00008 phase III stage 1 and stage 2 efficacy study, a harm monitoring with regards to symptomatic and severe COVID-19 cases was implemented. These provisions within the Clinical Studies allow detection of any evidence of VAED including VAERD caused by CoV2 preS dTM-AS03 (B.1.351). No evidence of VAED including VAERD was found based on review of available data from clinical studies. • Of note, in D614 containing vaccines (Monovalent) formulation and specifically in VAT00008 stage 1, an increased number of Omicron symptomatic COVID-19 cases in the naive vaccine group compared to the naive placebo group was observed. When scrutinizing this observation, there was no increase in severe outcomes, hospitalization, or mortality in the naive vaccinees. The clinical presentation (intensity of symptoms as measured in 3 intensity grades, number of symptoms per omicron case and the duration of symptoms) was similar in the naive vaccine and placebo groups. No evidence of an increased viral load (naive vaccinees versus naive placebo recipients) was found. Most likely explanation for

Important potential risk	Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
	the observation is a lack of efficacy of the Monovalent D614 formulation against Omicron (lower level of neutralizing antibodies for this variant, additionally a long period between administration of the 2 doses of the study vaccine in VAT00008 stage 1 and the start of the Omicron wave (approximately 5 months after study start). In VAT00008 stage 2, no increased number of Omicron cases in the vaccine group were reported as compared to the placebo group. This was not seen neither in Booster formulations. In addition, VAED including VAERD might not apply to booster vaccine if referring to Brighton definition (VAED including VAERD risk would concern only SARS-CoV-2 seronegative individuals or individuals with unknown serostatus and no previous COVID-19 infection). [120]
Risk factors and risk groups	Individuals with lower neutralizing antibodies titers or those with waning immunity. [119,120,134]
Preventability	This risk remains unpredictable and may depend on the immune response of the patient. [117,136] Potential risk may be decreased with an efficacious vaccine generating an adequate immune response is expected to mitigate this theoretical risk. Clinical study participants are informed of this theoretical risk during the informed consent process. Occurrence of COVID-19 cases and especially severe COVID-19 cases are monitored in the Clinical Studies and in postmarketing setting. This will allow early detection of any evidence of VAED including VAERD.
Impact on the benefit-risk balance of the product	Available data for mRNA COVID-19 vaccines (Pfizer/BioNTech and Moderna, [124,125] for an adenovirus-vectored vaccine (Janssen) [126] as well as for a protein adjuvanted vaccine [137] do not indicate a risk of vaccine enhanced disease. As VAED including VAERD is a theoretical (hypothetical) safety concern there is no deleterious impact on the benefit-risk balance anticipated for this product.
Public health impact	No public health impact is identified currently.
MedDRA Term	Standardized MedDRA Query (broad) COVID-19.

ADE: Antibody Dependent Enhancement; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; Fc: Fragment Crystallizable; MedDRA: Medical Dictionary for Regulatory Activities; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; mRNA: Messenger Ribonucleic Acid; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; Th: T-helper; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine-Associated Enhanced Respiratory Disease.

Table 32 - Important potential risk: Myocarditis and Pericarditis

Important potential risk	Myocarditis and Pericarditis
Potential mechanism	Myocarditis is a rare disease with an estimated annual incidence prior to COVID-19 vaccine pandemic of 16 per 100 000 persons in the general population. The true incidence may be higher, as signs and symptoms vary, and it therefore can be challenging to make the diagnosis. Viruses are the primary cause of myocarditis, including amongst others adeno- and enteroviruses. Severe acute respiratory syndrome coronavirus 2 has been associated with myocarditis as well, and multiple cases have been described since the outbreak of the COVID-19 pandemic. [132] The majority of patients are young, healthy males. [138] 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

Important potential risk	Myocarditis and Pericarditis
	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. [139] Several mechanisms have been hypothesised to account for COVID-19 mRNA vaccine associated myocarditis including autoimmunity triggered by molecular mimicry, [138,139] immune-mediated pathology, [130] pro-inflammatory cascade. [140]
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. [127] 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. [128,129] 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. [130] 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 adjuvant system than the CoV2 preS dTM vaccine. [131] 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.
Characterization of the risk	No case of myocarditis and pericarditis has been observed in ongoing clinical studies with CoV2 preS dTM (B.1.351) vaccine. However, based on potential risk from other COVID-19 vaccines, participants of ongoing clinical studies with CoV2 preS dTM (B.1.351) vaccine are advised to seek immediate medical attention and notify study site staff if symptoms compatible with myocarditis and pericarditis occur following vaccination. Participants with events of myocarditis and pericarditis will be discontinued from further vaccination and followed for subsequent visits as per the protocol for safety, immunogenicity, and efficacy endpoints. No postmarketing data are yet available with CoV2 preS dTM (B.1.351) vaccine. The most important published cohort studies to date demonstrate that myocarditis is a very rare side effect after COVID-19 mRNA vaccination, with an incidence of approximately 1-4 cases per 100 000 vaccinated persons. [132] 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. [130]

Important potential risk	Myocarditis and Pericarditis
	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. [128,129] Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of the Novavax COVID-19 vaccine, which is manufactured using a protein/adjuvant platform and a different adjuvant system than the CoV2 preS dTM vaccine. [131] In the placebo-controlled safety dataset of Novavax COVID-19 vaccine (participants 12 years of age and older) with 30 058 subjects receiving active vaccine and 19 892 subjects receiving placebo, two cases of myocarditis were reported following exposure to Novavax COVID-19 vaccine and one case was reported following exposure to placebo. In the post-crossover phase of studies, three cases of myocarditis were reported. The Sponsor assessed the causality as not related for the five cases occurring after exposure to COVID-19 vaccine with all cases attributed to alternative etiologies, including reasonable infectious and/or non-infectious causes. There were no cases of myocarditis and pericarditis assessed as related by the Sponsor.
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk. [138,139]
Preventability	As the mechanism is not fully understood, preventative measures cannot be defined at this time.
Impact on the benefit-risk balance of the product	Balanced with the risk of death and illness seen with COVID-19 itself, the vaccine has a favorable risk-benefit balance.
Public health impact	Myocarditis and pericarditis are events which may be serious or non-serious and are generally mild but may be potentially life-threatening. Most vaccine-associated myocarditis events have been mild and self-limiting. [130] 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. [132]
MedDRA Term	High Level Term Noninfectious myocarditis, HLT Noninfectious pericarditis.

CI: Confidence Interval; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; HLT: High Level Term; IRR: Incidence Rate Ratio; MedDRA: Medical Dictionary for Regulatory Activities; mRNA: Messenger Ribonucleic Acid; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; Th: T-helper.

SVII.3.2 Presentation of the missing information

Table 33 - Missing information: Use in pregnancy and while breast-feeding

Missing Information	Use in pregnancy and while breast-feeding
Evidence source(s) and strength of evidence	Pregnant or breast-feeding women are excluded from Clinical Studies (phase II/III and phase III). A pregnancy test is systematically being performed in these women before each study vaccine administration and the vaccine or placebo dose is not injected in case of a positive pregnancy test. Use of CoV2 preS dTM-AS03 (B.1.351) in pregnancy and while breast-feeding is considered as missing information until sufficient evidence is available. Safety data with other vaccine manufactured with the same platform and safety data with other AS03 adjuvanted vaccines administered during pregnancy have

Missing Information	Use in pregnancy and while breast-feeding
	shown no evidence of an increased risk of adverse outcomes in the mother or child. [141] 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.
Anticipated risk/consequence of the missing information	It is not yet known whether CoV2 preS dTM-AS03 (B.1.351) could cause any fetal harm when administered to a pregnant woman or if any detrimental effects could occur when administered in breast-feeding women. Pregnant women are part of the clinical development plan (VAT00006 safety and immunogenicity Clinical Study in pregnant women during pregnancy and safety in post-partum including breast-feeding period, if applicable). 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. [133] Preliminary findings in pregnant persons who received mRNA COVID-19 vaccines did not show obvious safety signals. However, more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes. [142,143]

COVID-19: Coronavirus Disease-2019; DART: Developmental and Reproductive Toxicity; mRNA: Messenger Ribonucleic Acid.

Table 34 - Missing information: Use in immunocompromised subjects

Missing Information	Use in immunocompromised subjects
Evidence source(s) and strength of evidence	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in immunocompromised patients is not yet known as these populations have been excluded from some phase II/III Clinical Studies. This population is included in phase III Clinical Study allowing the participation of individuals with a range of medical conditions including immunocompromised state. In the phase II/III study (VAT00002) and in the phase III study (VAT00008), participants with a controlled HIV infection could be included.
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.

CoV2 preS dTM: CoV-2 prefusion Spike delta TM; HIV: Human Immunodeficiency Virus.

Table 35 - Missing information: Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)

Missing Information	Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
Evidence source(s) and strength of evidence	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in frail patients is not yet known even though elderly population and individuals with co-morbidities [134] or high-risk conditions were represented in Clinical Studies. Individuals with co-morbidities [134] or high risk conditions are considered to be associated with an increased risk of severe COVID-19 (cancer, chronic kidney disease, COPD, obesity (body mass index 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.
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; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; HIV: Human Immunodeficiency Virus.

Table 36 - Use in subjects with autoimmune or inflammatory disorders

Missing Information	Use in subjects with autoimmune or inflammatory disorders
Evidence source(s) and strength of evidence	The safety profile of CoV2 preS dTM-AS03 (B.1.351) in subjects with autoimmune or inflammatory disorders is not fully known even if individuals with autoimmune or immune-inflammatory diseases could be included in Clinical Studies: Participants with stable clinical conditions under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) could be enrolled in phase II/III (VAT00002) and phase III (VAT00008) at the discretion of the investigator. Individual with auto-immune or immune-inflammatory disease are part of the target population.
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.

CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 37 - Missing information: Interactions with other vaccines

Missing Information	Interactions with other vaccines
Evidence source(s) and strength of evidence	Receipt of any vaccine in the 30 days preceding the first study vaccination, except for influenza vaccination, is part of the exclusion criteria in the Clinical Studies. From phase II/III and phase III Clinical Studies (VAT00002 and VAT00008), influenza vaccination could be received at any time in relation to study intervention and influenza vaccination is part of concomitant medications that are collected. Vaccination with CoV2 preS dTM-AS03 (B.1.351) together or in close temporal connection with other vaccines is likely to occur later in a postmarketing setting.
Anticipated risk/consequence of the missing information	It is not yet known if CoV2 preS dTM-AS03 (B.1.351) interacts with other vaccines with regards to safety or immunogenicity.

CoV2 preS dTM: CoV-2 prefusion Spike delta TM.

Table 38 - Missing information: Long-term safety

Missing Information	Long-term safety
Evidence source(s) and strength of evidence	Despite extensive experience with the manufacturing platform and AS03 adjuvant, there is limited long-term safety data available with CoV2 preS dTM-AS03 (B.1.351). Vaccines targeting SARS-CoV-2 are a new class of vaccines, with first vaccines authorized in 2020 and 2021.
Anticipated risk/consequence of the missing information	The long-term safety data of CoV2 preS dTM-AS03 (B.1.351) is limited, however safety follow-up is ongoing in the phase II/III (with supportive data from phase I/II) and phase III study Clinical Studies. Based on currently available information, there is no evidence of any potential risks with late onset after vaccination.

CoV2 preS dTM: CoV-2 prefusion Spike delta TM; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	None
Important potential risks	Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
	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 [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in subjects with autoimmune or inflammatory disorders
	Interactions with other vaccines
	Long-term safety

COPD: Chronic Obstructive Pulmonary Disease; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine-Associated Enhanced Respiratory Disease.

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The safety profile of CoV2 preS dTM-AS03 (B.1.351) will be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of ADRs in periodic safety reports (PSRs), product technical complaints (PTCs) relating to AEs, and signal detection.

Routine pharmacovigilance activities: Standard pharmacovigilance processes in place will be followed. Due to special circumstances of COVID-19 pandemic and according to "([Consideration on core requirements for RMPs of COVID-19 vaccines v3.1 {dated 01 September 2022}])", [104] routine pharmacovigilance activities are enhanced through different means.

The applicant maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from Clinical Studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepares reports for regulatory authorities (eg, individual case safety reports [ICSRs], PBRER, etc,), and maintains continuous reporting of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities). The marketing authorization holder (MAH) maintains a pharmacovigilance system master file which contains further details of these systems and standard practices.

Individual Case Safety Report (ICSR) Processing: Individual case safety reports will be submitted in accordance to GVP Module VI, GVP Product or Population Specific Considerations I: Vaccines for prophylaxis against infectious diseases, and the detailed guidance on ICSRs in the context of COVID-19 (EMA 2020c). [144]

Adverse Event of Special Interest:

Adverse Event of Special Interest from Brighton Collaboration (SPEAC), [106] ACCESS, [107] US CDC, [108] US Guidance for Adjuvanted vaccines (preliminary list of AESI for VAERS surveillance, WHO and FDA Guidance's) [109,110,145] and also safety data from other manufacturers including from COVID-19 vaccine platforms [111,112,113,114,146,147] have been considered and selected as appropriate.

The ongoing clinical trial program (from phase I to phase III) includes safety assessment with collection of AESIs, defined as AEs, serious or nonserious, that needed to be monitored, documented, and managed in a pre-specified manner.

No specific safety concerns have been identified from the clinical trial program including AESIs.

For postmarketing surveillance, the list of AESIs has been adapted from ACCESS project list [107] available in [Annex 7.2], Brighton Collaboration (SPEAC), [106] US CDC, [108] US Guidance for Adjuvanted vaccines (preliminary list of AESI for VAERS surveillance, WHO and FDA Guidance's) [109,110,145] safety data from COVID-19 vaccine Clinical Studies and also safety data

from other manufacturers including from COVID-19 vaccine platforms [111,112,113,114,146,147] and selected as appropriate. Observed-to-Expected (O/E) analysis will be conducted as feasible. [148]

These AESIs are taken in consideration for routine and additional pharmacovigilance activities as appropriate. The list is considered dynamic and may be incremented following the evolving safety profile of the vaccine.

In addition to the Sponsor, an external data and safety monitoring board (DSMB) is responsible for monitoring the safety of participants enrolled in the phase III Clinical Study (VAT00008).

Follow-up (including Targeted Follow-up Questionnaires): Individual Case Safety Reports are followed-up to obtain the necessary information for a complete description of the AE and an adequate assessment following Standard Operational Procedures. Planned follow-up attempts to document ICSRs involving COVID-19 vaccine will follow a risk-based approach with priority given to serious unlisted and AESIs cases: for non-valid cases, two attempts will be made for serious unlisted cases, and one attempt for the others. For valid cases, two attempts will be made for serious unlisted and serious cases with a specific follow-up questionnaire, one attempt will be made for serious listed cases, non-serious unlisted cases and non-serious listed cases with a specific follow-up questionnaire or considered as medication errors with no AE, and no attempt will be made for non-serious listed cases unless neither patient age or age group was collected or if case batch number is missing (in these situations, one attempt will be made). Targeted Follow-up Questionnaires will be used to document COVID-19 Like illness (in the context of vaccination failure/lack of efficacy including occurrence of VAED and VAERD) and to document Myocarditis and Pericarditis. [Annex 4]

For AESIs, additional request for information to the standard follow-up may be conducted on a case-by-case basis.

“Vaccine Associated Enhanced Disease (VAED) including Vaccine Associated Enhanced Respiratory Disease (VAERD)”, is a theoretical (hypothetical) safety concern for CoV2 preS dTM-AS03 based on available evidence in naive vaccinees [120]. A targeted follow-up questionnaire of COVID-19 Like illness will be implemented for postmarketing surveillance in the context of vaccination failure/lack of efficacy including VAED and VAERD.

“Myocarditis and Pericarditis”, is a theoretical safety concern for CoV2 preS dTM-AS03 based on available evidence in Clinical studies with other COVID-19 vaccines. It is thus recommended to be included as important potential risk as Myocarditis and pericarditis event were discovered only in the widespread use of other COVID-19 vaccines. A targeted follow-up questionnaire of Myocarditis and Pericarditis will be implemented for postmarketing surveillance.

Periodic review of aggregated safety data: According to “([Consideration on core requirements for RMPs of COVID-19 vaccines v3.1 {dated 01 September 2022}])” [104] and in addition to routine PBRERs/PSURs, the applicant aims to submit Summary Safety Reports containing a review of interval safety information during the reporting period, as well as cumulative data.

Summary Safety Reports will include:

- Exposure data stratified by regions, age groups, gender, by dose number (when applicable). Exposure data based on administered doses rather than distributed doses will be used whenever possible (eg, ECDC Vaccine Tracker). [104,145,149]

- Details of the MAH's search strategy, case definitions etc. for all provided reviews and methodology for O/E analyses including source of background rates, risk windows, etc.
- Data in Summary Tabulations
  - Reports per EU country.
  - Interval and cumulative number of reports stratified by report type (medically confirmed or not) and by seriousness (including fatal reports separately).
  - Interval and cumulative number of reports per high level term and system organ class.
  - Interval and cumulative number of reports, overall and by age groups and in special populations (eg, pregnant women).
- Summaries of reported cases of selected AESI considered relevant for periodic review with the Summary safety report submission and RMP Safety concerns: report numbers and relevant cases, including O/E analyses as applicable. Observed-to-Expected analyses will be performed cumulatively using appropriate background rates (eg, European background rates provided by ACCESS available from and [150] US background rates), [151,152] an appropriate risk window and when appropriate, should be stratified by age groups, or presented per region (eg, if background rates vary), and complemented with a sensitivity analysis. If an increased O/E ratio is detected, a further evaluation of the concern should be presented.
- Fatal reports if any unusual pattern is observed during initial postmarketing use.
- Data on medication errors should be included only if a pattern of errors leading to harm is identified and/or risk minimization activities are considered warranted (eg, changes to the Product Information; DHCP); otherwise, this data should be included with the (six monthly) PSURs;
- Ongoing and closed signals in the interval including a summary of their evaluation. Reviews of signals identified during the period or of safety topics identified by EMA and requested to be addressed in the summary safety report.
- Changes to reference safety information and actions taken in the interval for safety reasons.
- Risk/Benefit considerations.

The submission of summary safety reports complements the submission of 6-monthly PBRERs/PSURs. Given the current COVID-19 vaccination patterns, the initiation of summary safety reports submission requirement for new vaccines should only be triggered by the start of mass vaccination using the product in any EU Member State. The need and periodicity of continuing the submission of the summary safety reports will be initiated by the rapporteur and re-evaluated based on the available postmarketing evidence for each vaccine, and at the request of the MAH, as soon as the safety data enables a decision to be made.

Literature review:

Literature monitoring for CoV2 preS dTM-AS03 (B.1.351) will allow the identification of any new potential, safety findings at least on a weekly basis (eg, class AEs or class effects,

epidemiological published studies, publications with Clinical Study data suggesting significant changes in incidences of AEs or severity of outcome, or non-clinical data that may correlate to risk in humans).

Global pre-configured and validated product searches are performed on a regular basis against two international literature databases (Embase and Medline) within embase.com.

Literature monitoring for CoV2 preS dTM-AS03 (B.1.351) includes an automated twice a week search for published and pre-publication/online first references in 2 commercial database products (Embase and Medline). Search criteria include any COVID-19 vaccine product, irrespective of manufacturer or vaccine technology, and a report of AE(s) without restriction by seriousness or severity. Patient demographics are unrestricted by age group, ethnicity, and pregnancy status. Level of evidence (eg, clinical trials, longitudinal observational data, case reports/case series) is likewise unrestricted. References retrieved by the above search strategies are reviewed and escalated based on reporting of either new safety observations or new aspects of known risks that require further assessment. As knowledge of the SARS-CoV-2 virus, COVID-19, and vaccines evolves, it is expected that the above search strategies will likewise evolve. Monitoring of other sources including non-clinical studies, quality or manufacturing reports is performed through periodic reviews part of signal detection processes in place.

Signal detection and investigations

Given the specific requirements of COVID-19 vaccines and the need to early identify any potential safety issues, routine signal detection activities are supplemented as described below:

Data sources used for signal detection, type and frequency of reviews are listed in the following table:

Table 39 - Data Source for signal detection and frequency of monitoring

Data source	Frequency and Type of monitoring
Company Global Safety Database restricted to vaccines cases	Daily medical review of fatal/life-threatening/pre-selected “key” AESIs during case processing. Weekly qualitative review of ICSRs (Other AESIs, serious unexpected events as per CCDS, cases reported in special populations including pregnancy, special use such as medication errors). Weekly inter-product disproportionality analyses Monthly temporal intra-product analysis: review of aggregate data with proportional reporting ratio to raise any alert in case of substantial increase of events received during the reporting period versus reference previous period and cumulative period. Monthly Time to onset analysis Monthly O/E analysis on pre-selected AESIs At least every 4 months aggregate manufacturing lot review
Literature (covering Embase and Medline)	At least weekly screening of global and local literature: • Twice a week screening of Global Literature • Weekly screening of Local Literature • Medical assessment of non-ICSR scientific literature publications with new relevant safety information
CMDh/EMA websites	Weekly screening of CMDh conclusions from PSUSAs (CMDh)

Data source	Frequency and Type of monitoring
	Monthly screening of PRAC conclusions regarding the product and similar products.
Eudravigilance	Bi-weekly (ie, every 2 weeks) screening of new fatal event or new DME (as per EMA DME list). Bi-weekly disproportionality analyses on cumulative data.
VAERS	Bi-weekly disproportionality analyses on last data released available in data mining tool. Adhoc qualitative and quantitative reviews in VAERS in case of potential safety signal.
WHO VigiBase restricted to vaccines cases	Quarterly disproportionality analyses on last data released available in data mining tool.

AESI: Adverse Event of Special Interest; CCDS: Company Core Data Sheet; CMDh: Co-ordination group for Mutual recognition and Decentralised procedures - Human; DME: Designated Medical Event; EMA: European Medicines Agency; ICSR: Individual Case Safety Report; O/E: Observed-to-Expected; PRAC: Pharmacovigilance Risk Assessment Committee; PSUSA: Periodic Safety Update Report Single Assessment; VAERS: Vaccine Adverse Event Reporting System; WHO: World Health Organization.

The selected frequency for quantitative review has been determined to permit an optimal amount of data to be able to have significant scores (considering the "stability" of quantitative scores) and increase the performance of signal detection activities to complement to the already strengthened qualitative review.

This signal detection strategy is based on the current risk profile of the vaccine and might evolve over time as postmarketing safety data is accumulated.

Competent authorities will be informed as per applicable standards and regulation. Any new information that may affect the benefit-risk balance of the product will be communicated promptly to the competent authorities of the member states in which the product is authorized and to the Agency via email (P-PVemerging-safety-issue@ema.europa.eu).

Traceability

The EU-SmPC includes instructions for HCPs to record the name and the batch number of the administered product (section 4.4) and to report any suspected adverse reactions (section 4.8).

In EU, the vaccine carton box (containing antigen and adjuvant boxes) includes a 2D matrix barcode which has the brand name, batch/lot number, Global Trade Item Number (GTIN) product code, serial number and expiry date, should there be capability at a vaccination site to utilize this as an information source. Further, the Applicant will make available vaccination cards on website (accessible with quick response [QR] code) for printing and printed vaccination cards will be provided in the Member States where required. The vaccination cards contain the following elements:

- Printed vaccine brand name and manufacturer name.
- Placeholder space for name of vaccinee.
- Placeholder space for date of vaccination, and associated batch/lot number.
- For EEA countries, reference to the National Reporting System for AE reporting.
- Quick Response code and Uniform Resource Locator (https://vidprevtyn-beta.info.sanofi) for additional information on product use.

In EU, in addition to the vaccination cards, 2 stickers per dose, containing printed vaccine brand name, dosage, lot information, and a 2D matrix barcode will be made available to support documentation of the lot information on both the vaccination cards for vaccinees and in the vaccinee medical records. It is acknowledged that some countries may require utilization of nationally-mandated vaccination cards or electronic systems to document the lot number; therefore, the available vaccination cards and stickers with printed lot information may not be utilized in all countries. The use will depend on national requirements and/or national competent authority guidance. The sticker sheets with printed lot information will be provided inside the vaccine box from initial launch.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance activities mentioned below are all relevant for CoV2 preS dTM-AS03 (B.1.351) vaccine formulation:

Table 40 - Additional pharmacovigilance activities (category 1 to 3) summary

VAT00002 Supplemental Cohort 2 Clinical Study (Cat. 3)
Study short name and title: VAT00002 Phase III Supplemental Cohort 2 Clinical Study: A modified double blind, multi-armed study to assess the immunogenicity and safety of a booster dose of B.1.351 SARS-CoV-2 adjuvanted recombinant protein vaccines in adults 18 years of age and older.
Rationale and study objectives: The purpose of this Phase III Supplemental Cohort Clinical Study is: • To assess the safety profile of all participants in each study intervention group. • To demonstrate that a booster dose of Monovalent (B.1.351) vaccine given to adults previously vaccinated with the Pfizer/BioNTech mRNA COVID-19 vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with the Monovalent (D614) vaccine, and superior to that observed immediately before booster.
Study design: Open-label Supplemental Cohort 2, multistage, multicenter, multi-country study. Size: 707 participants in Cohort 2 Monovalent B.1.351 Booster arm.
Study populations: Adults 18 years of age and older
Milestones: Final CSR: 31-Dec-2023
VAT00008 - Open Label Extension (Cat. 3)
Study short name and title: VAT00008 Phase III Clinical Study: Open-label extension to assess immunogenicity, safety, efficacy of a monovalent (B.1.351) booster dose of SARS-CoV2 adjuvanted recombinant protein vaccine for prevention against COVID-19 in adults 18 years of age and older.
Rationale and study objectives: The purpose of this study is to assess the safety of a monovalent booster dose (B.1.351) of SARS-CoV-2 adjuvanted recombinant protein vaccine in adults 18 years of age and older.

Secondary safety objectives:

- To describe the frequency and spectrum of disease in episodes of symptomatic COVID-19 in SARS-CoV-2 non-naive adults after the booster vaccination.
- To assess the safety of the CoV2 preS dTM-AS03 vaccine after booster vaccination.

Study design:

Multistage, multi-center, multi-country, unblinded, Monovalent Booster study.

Open-label extension (crossover/booster).

Size

All participants who are eligible and consent to the booster extension are offered a Monovalent B.1.351 booster dose and followed for 12 months after receipt of booster.

The size of the exposed population will depend on the use of the CoV2 preS dTM-AS03 (B.1.351) vaccine during the study period. The follow-up will be for 12 months after receipt of a booster dose and the estimated number of participants is between 3800 and 4200.

Study populations:

Adults 18 years of age and older

Milestones:

Final CSR: 30-Sep-2024

VAT00007 - Post-Authorization Safety Study (Cat. 3)

Study short name and title:

VAT00007 Post-Authorization Safety Study: Observational study using secondary database.

Rationale and study objectives:

This PASS will assess the occurrence of pre-specified AESIs and safety concerns following administration of VidPrevtyn Beta as a booster dose in a real-world setting.

Primary objective:

To determine whether there is an increased risk of AESIs and safety concerns following vaccination with VidPrevtyn Beta as a booster dose.

Secondary objective:

To assess whether there is an increased risk of AESIs and safety concerns following vaccination with VidPrevtyn Beta as a booster dose stratified by characteristics including age, sex, comorbidities, previous SARS-CoV-2 vaccination or infections, concomitant vaccinations, concomitant medications, immunocompromised status, autoimmune or inflammatory disorder status, frailty (with unstable conditions or co-morbidities), if feasible.

Exploratory objective:

To describe the safety profile of VidPrevtyn Beta in pregnant or breast-feeding women, if feasible.

Study design:

Multi-country retrospective cohort study using existing European Secondary Health Data Sources (health insurance claims and/or EHR database[s]).

The selected databases are the Danish Registries, Denmark, the Systeme National de Donnees de Sante, France; the Agenzia Regionale di Sanita' della Toscana database, Italy; the Società Italiane di Medicina Generale Health Search Database, Italy; the Clinical Practice Research Datalink, UK.

The risk assessment stage will be based on a SCRI design. Self-controlled risk interval will compare specific AESI incidence rate during an immediate post-vaccination period - the risk window - to AESI incidence rate from a subsequent control window, to generate an incident rate ratio.

Size:

The size of the exposed population will depend on the use of the VidPrevtyn Beta during the study period.

Study populations:

The study population will comprise all individuals registered in the selected European health care data sources during the study period from the first date of VidPrevtyn Beta administration in the real-world setting. A feasibility assessment will first be conducted to ensure there is sufficient exposure to VidPrevtyn Beta in the healthcare databases.

Milestones:

Protocol submission: 30-Nov-2022

Final study report: 31-Dec-2025

VAT00006 - Clinical Study (Cat. 3)

Study short name and title:

VAT00006 Phase III Clinical Study: To assess immunogenicity and safety of a monovalent booster dose (B.1.351) of SARS-CoV-2 adjuvanted recombinant protein vaccine in healthy pregnant women aged 18 to 35 years.

Rationale and study objectives:

- To describe the safety profile of all healthy pregnant participants aged 18 to 35 years.
- To assess immunogenicity 21 days following booster dose of SARS-CoV-2 recombinant protein (B.1.351) vaccine with AS03 adjuvant vaccine in pregnant participants.

Exploratory objective:

To describe the safety of a monovalent booster dose (B.1.351) of SARS-CoV-2 adjuvanted recombinant protein vaccine for study participants and their infants in the period following delivery and during the breast-feeding period.

Study design:

Randomized, modified double-blind, crossover, multi-center study.

Size:

300 participants

Study populations:

Healthy pregnant female in their 2nd or 3rd trimester and aged 18 to 35 years.

Milestones:

Protocol submission: 30-Nov-2022

Final CSR: 31-Mar-2025

VAT00012 - Post-Authorization Safety Study(Cat. 3)

Study short name and title:

VAT00012 Post-Authorization Safety Study: COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)

Rationale and study objectives:

COVID-19 vaccines will be used in pregnant populations. Scientific evidence regarding their safety for pregnant women and the developing fetus is lacking.

The objective of C-VIPER is to evaluate the occurrence of obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with VidPrevtyn Beta. Specifically, the C-VIPER will estimate the risk of common obstetric outcomes, neonatal outcomes, and infant outcomes among pregnant women exposed to VidPrevtyn Beta from 30 days prior to the first day of the LMP to end of pregnancy and their offspring from birth and up to the first 12 months of life relative to a matched reference group who received no COVID-19 vaccines during pregnancy.

Study design:

International, non-interventional, postmarketing cohort study designed to collect prospective safety data among women vaccinated with VidPrevtyn Betaduring pregnancy or within 30 days prior to the first day of the LMP.

Size:

At least 200 pregnancies exposed to each branded COVID-19 vaccine during the first trimester and 300 exposed thereafter during pregnancy are projected. For each exposed pregnancy, 2 unexposed pregnancies enrolled in the

"Pregistry International Pregnancy Exposure Registry (PIPER)" will be matched by country and gestational age at enrollment (±2 weeks).

Study populations:

The source population will comprise women vaccinated with VidPrevtyn Beta at any time during pregnancy who are aged 18 years of age or older and their offspring.

The data are collected using a web data collection system. The list countries of potential interest will be based on distribution and policy position of VidPrevtyn Beta in Europe and outside Europe.

The study period will be defined as from the first date of VidPrevtyn Beta administration in the real-world setting through 48 months thereafter (3 years following the start of vaccination plus 12 months of infant follow-up time).

Milestones:

Protocol submission: 30-Jul-2022 (Refer to [Annex 3])

Final study report planned for submission within 12 months after study completion (Study details can be accessed at the EU PAS register of ENCePP EUPAS39096).

Final study report: 16-May-2028 [a]

VBA00003 Post-Licensure Effectiveness Study (Cat. 3)

Study short name and title:

VBA00003 Post-Licensure Effectiveness Study: COVID-19 Vaccine Effectiveness study (Effectiveness is not a safety concern).

Rationale and study objectives:

As part of its European regulatory obligations, benefit of VidPrevtyn Beta will be monitored in real-life setting using the COVIDRIVE platform and partnership (https://covidrive.eu/) [153,154]

Master protocol coprimary objectives:

To estimate CVE of VidPrevtyn Beta against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed a primary series with any COVID-19 vaccine and have received at least one additional dose of VidPrevtyn Beta as last dose, compared to unvaccinated patients or patients who previously completed at least a primary series with any COVID-19 vaccine but did not receive the last additional dose of interest.

Study design:

A multi-country prospective hospital-based case-control study with test-negative controls (test-negative case-control study).

Study populations:

Individuals presenting at the participating hospitals who are hospitalized and meet the SARI case definition and who meet the inclusion criteria (eligible according to national/regional immunization program, informed consent).

Milestones:

Final protocol version shared with the EMA in EU-RMP version 0.2 [Annex 3]

Final study report: 31-Mar-2025

a Enrollment period of pregnant women exposed to CoV2 preS dTM-AS03 and date of final study report, may vary depending on vaccine availability, policy positions on CoV2 preS dTM-AS03 vaccines in pregnancy and other external factors.

AESI: Adverse Event of Special Interest; CoV2 preS dTM: CoV2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; CSR: Clinical Study Report; CVE: COVID Vaccine Effectiveness; C-VIPER: COVID-19 Vaccines International Pregnancy Exposure Registry; EHR: Electronic Health Record; EMA: European Medicines Agency; EU: European Union; LMP: Last Menstrual Period; mRNA: Messenger Ribonucleic Acid; PAS: Post-Authorization Study; PASS: Post-Authorization Safety Study; SARI: Severe Acute Respiratory Infection; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SCRI: Self-Controlled Risk Interval; UK: United Kingdom.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance activities mentioned below are all relevant for Monovalent B.1.351 Booster vaccine formulation:

Table 41 - Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
VAT00002 Supplemental Cohort 2 Clinical Study Ongoing	The purpose of this Phase III Supplemental Cohort 2 Clinical study is: • To assess the safety profile of all participants in each study intervention group. • To demonstrate that a booster dose of Monovalent (B.1.351) given to adults previously vaccinated with the Pfizer/BioNTech mRNA COVID-19 vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with the Monovalent (D614) vaccine, and superior to that observed immediately before booster.	• Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD) • Myocarditis and Pericarditis • Use in immunocompromised subjects • Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders • Interaction with other vaccines • Long-term safety	Final CSR	31-Dec-2023
VAT00008 Open Label Extension Ongoing	The purpose of this study is to assess the safety of a monovalent booster dose (B.1.351) of SARS-CoV-2 adjuvanted recombinant	• Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	Final CSR	30-Sep-2024

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	protein vaccine in adults 18 years of age and older Secondary safety objectives: • To describe the frequency and spectrum of disease in episodes of symptomatic COVID-19 in SARS-CoV-2 non-naive adults after the booster vaccination. • To assess the safety of the CoV2 preS dTM AS03 (B.1.351) vaccine after booster vaccination.	• Myocarditis and Pericarditis • Use in immunocompromised subjects • Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders • Interaction with other vaccines • Long-term safety		
VAT00007 Post-Authorization, Safety Study Planned	To assess the occurrence of pre-specified AESIs and safety concerns following administration of VidPrevtyn Beta as a booster dose in a real-world setting. Primary objective: To determine whether there is an increased risk of AESIs and safety concerns following vaccination with VidPrevtyn Beta, as a booster dose. Secondary objective: To assess whether there is an increased risk of AESIs and safety conerns following vaccination with VidPrevtyn Beta as a booster dose stratified by characteristics including age, sex, comorbidities, previous SARS-CoV-2 vaccination or infections, concomitant vaccinations, concomitant medications, immunocompromised status, autoimmune or	• Myocarditis and Pericarditis • Pre-defined AESI (Refer to [Annex 7.2]) • 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 [COPD], diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders • Interaction with other vaccines • Long-term Safety	Protocol submission Final study report	30-Nov-2022 31-Dec-2025

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	inflammatory disorder status, frailty (with unstable conditions or co-morbidities), if feasible. Exploratory objective: To describe the safety profile of VidPrevtyn Beta in pregnant or breast-feeding women, if feasible.			
VAT00006 Clinical Study Planned	• To describe the safety profile of all healthy pregnant participants aged 18 to 35 years. • To assess immunogenicity 21 days following booster dose of SARS-CoV-2 recombinant protein (B.1.351) vaccine with AS03 adjuvant vaccine in pregnant participants. • Exploratory objective: To describe the safety of a monovalent booster dose (B.1.351) of SARS-CoV-2 adjuvanted recombinant protein vaccine for study participants and their infants in the period following delivery and during the breast-feeding period.	• Myocarditis and Pericarditis • Use in pregnancy and while breast-feeding • Long-term safety	Protocol submission Final CSR	30-Nov-2022 31-Mar-2025
VAT00012 Post-Authorization Safety StudyPlanned	To evaluate the occurrence of obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with VidPrevtyn Beta. Specifically, the C-VIPER will estimate the risk of common obstetric outcomes, neonatal outcomes, and infant outcomes among pregnant women exposed to VidPrevtyn Beta from 30 days prior to the first day of the LMP to end of pregnancy and their offspring from birth and up to the first 12 months of life	• Use in pregnancy	Protocol submission Final study report	30-Jul-2022 (Refer to [Annex 3]) Final study report planned for submission within 12 months after study completion (Study details can be accessed at the EU PAS register of ENCePP EUPAS39096). 16-May-2028[a]

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	relative to a matched reference group who received no COVID-19 vaccines during pregnancy.			
VBA00003 Post-Licensure Effectiveness Study Planned	To continuously monitor CVE of VidPrevtyn Beta against severe disease using the public private collaboration in Europe: the COVIDRIVE platform (https://covidrive.eu/) constituted of a network of hospitals across Europe. *153,154* Master protocol coprimary objectives: To estimate CVE of VidPrevtyn Beta against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed a primary series with any COVID-19 vaccine and have received at least one additional dose of VidPrevtyn Beta as last dose, compared to unvaccinated patients or patients who previously completed at least a primary series with any COVID-19 vaccine but did not receive the last additional dose of interest.	• Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD) (Exploratory)	Protocol submission Final study report	In EU-RMP version 0.2 [Annex 3] 31-Mar-2025

a Enrollment period of pregnant women exposed to CoV2 preS dTM-AS03 and date of final study report, may vary depending on vaccine availability, policy positions on CoV2 preS dTM-AS03 vaccines in pregnancy and other external factors.

AESI: Adverse Event of Special Interest; COPD: Chronic Obstructive Pulmonary Disease; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; CSR: Clinical Study Report; CVE: COVID Vaccine Effectiveness; C-VIPER: COVID-19 Vaccines International Pregnancy Exposure Registry; EU: European Union; LMP: Last Menstrual Period; mRNA: Messenger Ribonucleic Acid; PAS: Post-Authorization Study; SARI: Severe Acute Respiratory Infection; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine-Associated Enhanced Respiratory Disease.

RISK MANAGEMENT PLAN - PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for CoV2 preS dTM-AS03 (B.1.351).

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 42 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Myocarditis and Pericarditis	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Use in pregnancy and while breast-feeding	**Routine risk communication:** EU-SmPC section 4.6 (Fertility, pregnancy and lactation) PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Use in immunocompromised subjects	**Routine risk communication:** EU-SmPC section 4.4 (Special warning and precautions for use) PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information:** None

Safety concern	Routine risk minimization activities
Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Use in subjects with autoimmune or inflammatory disorders	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Interaction with other vaccines	**Routine risk communication:** SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Long-term safety	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None

COPD: Chronic Obstructive Pulmonary Disease; EU: European Union; PL: Package Leaflet; SmPC: Summary of Product Characteristics; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine Associated Enhanced Respiratory Disease.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Section V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 43 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Vaccine-Associated Enhanced Disease (VAED) including Vaccine Associated Enhanced Respiratory Disease (VAERD)	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Adverse event follow-up form for COVID-19 like illness to document any vaccination failure/lack of efficacy including VAED and VAERD **Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study, Final CSR: 31-Dec-2023 • VAT00008 Open Label Extension, Final CSR: 30-Sep-2024 • VBA00003 Post-Licensure Effectiveness Study, Final study report: 31-Mar-2025
Myocarditis and Pericarditis	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Adverse event follow-up form Myocarditis and Perimyocarditis **Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study, Final CSR: 31-Dec-2023 • VAT00008 Open Label Extension, Final CSR: 30-Sep-2024 • VAT00006 Clinical Study, Final CSR: 31-Mar-2025 • VAT00007 Post-Authorization Safety Study, Final study report: 31-Dec-2025
Use in Pregnancy and while breast-feeding	**Routine risk minimization measures:** • EU-SmPC section 4.6 (Fertility, pregnancy and lactation) • PL section 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • VAT00006 Clinical Study, Final CSR: 31-Mar-2025 • VAT00012 Post-Authorization Safety Study, Final study report: 16-May-2028[a] • VAT00007 Post-Authorization Safety Study, Final study report: 31-Dec-2025

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in Immunocompromised subjects	**Routine risk minimization measures:** EU-SmPC section 4.4 (Special warning and precautions for use) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study, Final CSR: 31-Dec-2023 • VAT00008 Open Label Extension, Final CSR: 30-Sep-2024 • VAT00007 Post-Authorization Safety Study, Final study report: 31-Dec-2025
Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study, Final CSR: 31-Dec-2023 • VAT00008 Open Label Extension, Final CSR: 30-Sep-2024 • VAT00007 Post-Authorization Safety Study, Final study report: 31-Dec-2025
Use in subjects with autoimmune or inflammatory disorders	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study, Final CSR: 31-Dec-2023 • VAT00008 Open Label Extension, Final CSR: 30-Sep-2024 • VAT00007 Post-Authorization Safety Study, Final study report: 31-Dec-2025
Interaction with other vaccines	**Routine risk minimization measures:** • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • PL section 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study, Final CSR: 31-Dec-2023 • VAT00008 Open Label Extension, Final CSR: 30-Sep-2024 • VAT00007 Post-Authorization Safety Study, Final study report: 31-Dec-2025

Safety concern	Risk minimization measures	Pharmacovigilance activities
Long-term Safety	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study, Final CSR: 31-Dec-2023 • VAT00008 Open Label Extension, Final CSR 30-Sep-2024 • VAT00006 Clinical Study, Final CSR 31-Mar-2025 • VAT00007 Post-Authorization Safety Study, Final study report: 31-Dec-2025

a VAT00012 only addresses use in pregnancy.

COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease-2019; CSR: Clinical Study Report; EU: European Union; PL: Package Leaflet; SmPC: Summary of Product Characteristics; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine-Associated Enhanced Respiratory Disease.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for VidPrevtyn Beta (CoV2 preS dTM-AS03 [B.1.351])

This is a summary of the RMP for VidPrevtyn Beta. The RMP details important risks of VidPrevtyn Beta, how these risks can be minimized, and how more information will be obtained about VidPrevtyn Beta's risks and uncertainties (missing information).

VidPrevtyn Beta SmPC and its PL give essential information to HCPs and patients on how VidPrevtyn Beta should be used.

This summary of the RMP for VidPrevtyn Beta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of VidPrevtyn Beta's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

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

It contains CoV2 preS dTM (B.1.351 strain) as the active substance and it is given by IM route.

Further information about the evaluation of VidPrevtyn Beta's benefits can be found in VidPrevtyn Beta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/vidprevtyn-beta

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of VidPrevtyn Beta, together with measures to minimize such risks and the proposed studies for learning more about VidPrevtyn Beta's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of VidPrevtyn Beta is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of VidPrevtyn Beta are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VidPrevtyn Beta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the vaccine).

Table 44 - List of important risks and missing information

Important identified risk	None
Important potential risks	Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
	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 [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in subjects with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety

COPD: Chronic Obstructive Pulmonary Disease; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine-Associated Enhanced Respiratory Disease.

II.B Summary of important risks

Table 45 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	
Evidence for linking the risk to the medicine	A theoretical concern with coronavirus vaccines is VAED. [117,118,119,120] This is the potential (hypothetical) increased disease severity in naive vaccinees [120] upon exposure to wild-type virus. [121] This disease enhancement of viral infection is also not fully understood. Mostly in the context of non-clinical beta coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the Th cell response. [96,122,123] Animal models of SARS-CoV-2 infection have not shown evidence of VAED disease after immunization. [94] Available data for other COVID-19 vaccines from different platforms do not indicate a risk of vaccine enhanced disease. [94,124,125,126] However, considering limited long-term safety data and in the absence of effectiveness data, the available evidence is not yet fully sufficient to rule out VAED including VAERD as a safety concern. Thus, it remains an important potential risk.
Risk factors and risk groups	Individuals with lower neutralizing antibodies titers or those with waning immunity. [119,120,134]
Risk minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study • VAT00008 Open Label Extension • VBA00003 Post-Licensure Effectiveness Study See Section II.C of this summary for an overview of the post-authorization development plan.

COVID-19: Coronavirus Disease-2019; Fc: Fragment Crystallizable; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; Th: T-helper; VAED: Vaccine-Associated Enhanced Disease; VAERD: Vaccine-Associated Enhanced Respiratory Disease.

Table 46 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Myocarditis and Pericarditis

Myocarditis and Pericarditis	
Evidence for linking the risk to the medicine	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. [127]

Myocarditis and Pericarditis	
	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. [128,129] 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. [130] 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 adjuvant system than the CoV2 preS dTM vaccine. [131] 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.
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk. [138,139]
Risk minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study • VAT00008 Open Label Extension • VAT00006 Clinical Study • VAT00007 Post-Authorization Safety Study See Section II.C of this summary for an overview of the post-authorization development plan.

CI: Confidence Interval; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; IRR: Incidence Rate Ratio; mRNA: Messenger Ribonucleic Acid; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2.

Table 47 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in Pregnancy and while breast-feeding

Use in Pregnancy and while breast-feeding	
Risk minimization measures	**Routine risk minimization measures:** • EU-SmPC section 4.6 (Fertility, pregnancy and lactation) • PL section 2 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • VAT00006 Clinical Study • VAT00012 Post-Authorization Safety Study[a] • VAT00007 Post-Authorization Safety Study

Use in Pregnancy and while breast-feeding	
	See Section II.C of this summary for an overview of the post-authorization development plan.

a VAT00012 only addresses use in pregnancy.
EU: European Union; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 48 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in Immunocompromised Subjects

Use in Immunocompromised Subjects	
Risk minimization measures	**Routine risk minimization measures:** EU-SmPC section 4.4 (Special warning and precautions for use) **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study • VAT00008 Open Label Extension • VAT00007 Post-Authorization Safety Study See Section II.C of this summary for an overview of the post-authorization development plan.

EU: European Union; SmPC: Summary of Product Characteristics.

Table 49 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)

Use in frail subjects with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	
Risk minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study • VAT00008 Open Label Extension • VAT00007 Post-Authorization Safety Study See Section II.C of this summary for an overview of the post-authorization development plan.

COPD: Chronic Obstructive Pulmonary Disease.

Table 50 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in subjects with autoimmune or inflammatory disorders

Use in subjects with autoimmune or inflammatory disorders	
Risk minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study • VAT00008 Open Label Extension • VAT00007 Post-Authorization Safety Study See Section II.C of this summary for an overview of the post-authorization development plan.

Table 51 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Interaction with other vaccines

Interaction with other vaccines	
Risk minimization measures	**Routine risk minimization measures:** • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • PL section 2 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study • VAT00008 Open Label Extension • VAT00007 Post-Authorization Safety Study See Section II.C of this summary for an overview of the post-authorization development plan.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 52 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Long-term safety

Long-term safety	
Risk minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • VAT00002 Supplemental Cohort 2 Clinical Study • VAT00008 Open Label Extension • VAT00006 Clinical Study • VAT00007 Post-Authorization Safety Study

Long-term safety	
	See Section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-authorization development plan

II.C.I *Studies which are conditions of the marketing authorization*

There are no studies which are conditions of the marketing authorization or specific obligation of VidPrevtyn Beta.

II.C.II *Other studies in post-authorization development plan*

Table 53 - Other studies in post-authorization development plan

VAT00002 Supplemental Cohort 2 Clinical Study (Cat. 3)
Purpose of the study: The purpose of this Phase III Supplemental Cohort 2 Clinical study is: • To assess the safety profile of all participants in each study intervention group. • To demonstrate that a booster dose of Monovalent (B.1.351) vaccine SARS-CoV-2 vaccine given to adults previously vaccinated with the Pfizer/BioNTech mRNA COVID-19 vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with the Monovalent (D614) vaccine, and superior to that observed immediately before booster.
VAT00008 - Open Label Extension (Cat. 3)
Purpose of the study: The purpose of this study is to assess the safety of a monovalent booster dose (B.1.351) of SARS-CoV-2 adjuvanted recombinant protein vaccine in adults 18 years of age and older. Secondary safety objectives: • To describe the frequency and spectrum of disease in episodes of symptomatic COVID-19 in SARS-CoV-2 non-naive adults after the booster vaccination. • To assess the safety of the CoV2 preS dTM-AS03 vaccine after booster vaccination.
VAT00007 - Post-Authorization Safety Study (Cat. 3)
Purpose of the study: To assess the occurrence of pre-specified AESIs and safety concerns following administration of VidPrevtyn Beta as a booster dose in a real-world setting. Primary objective: To determine whether there is an increased risk of AESIs and safety concerns following vaccination with VidPrevtyn Beta, as a booster dose. Secondary objective: To assess whether there is an increased risk of AESIs and safety concerns following vaccination with VidPrevtyn Beta as a booster dose stratified by characteristics including age, sex, comorbidities, previous SARS-CoV-2 vaccination or infections, concomitant vaccinations, concomitant medications, immunocompromised status, autoimmune or inflammatory disorder status, frailty (with unstable conditions or co-morbidities), if feasible. Exploratory objective: To describe the safety profile of VidPrevtyn Beta in pregnant or breast-feeding women, if feasible.

VAT00006 - Clinical Study (Cat. 3)

Purpose of the study:

- To describe the safety profile of all healthy pregnant participants aged 18 to 35 years.
- To assess immunogenicity 21 days following booster dose of SARS-CoV-2 recombinant protein (B.1.351) vaccine with AS03 adjuvant vaccine in pregnant participants.

Exploratory objective:

To describe the safety of a monovalent booster dose (B.1.351) of SARS-CoV-2 adjuvanted recombinant protein vaccine for study participants and their infants in the period following delivery and during the breast-feeding period.

VAT00012 - Post-Authorization Safety Study (Cat. 3)

Purpose of the study:

To evaluate the occurrence of obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with VidPrevtyn Beta. Specifically, the C-VIPER will estimate the risk of common obstetric outcomes, neonatal outcomes, and infant outcomes among pregnant women exposed to VidPrevtyn Beta CoV2 preS dTM-AS03 vaccine from 30 days prior to the first day of the LMP to end of pregnancy and their offspring from birth and up to the first 12 months of life relative to a matched reference group who received no COVID-19 vaccines during pregnancy.

VBA00003 Post-Licensure Effectiveness Study (Cat. 3)

Purpose of the study:

As part of its European regulatory obligations, benefit of VidPrevtyn Beta will be monitored in real-life setting using the COVIDRIVE platform and partnership (https://covidrive.eu/) [153,154].

Master protocol coprimary objectives:

To estimate CVE of VidPrevtyn Beta against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed a primary series with any COVID-19 vaccine and have received at least one additional dose of VidPrevtyn Beta as last dose, compared to unvaccinated patients or patients who previously completed at least a primary series with any COVID-19 vaccine but did not receive the last additional dose of interest.

AESI: Adverse Event of Special Interest; CoV2 preS dTM: CoV-2 prefusion Spike delta TM; COVID-19: Coronavirus Disease-2019; CVE: COVID Vaccine Effectiveness; C-VIPER: COVID-19 Vaccines International Pregnancy Exposure Registry; LMP: Last Menstrual Period; mRNA: Messenger Ribonucleic Acid; SARI: Severe Acute Respiratory Infection; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

FOLLOW-UP FORMS

COVID-19 Like Illness

Targeted Follow-up Form (coversheet)

Please provide the below requested information in the dedicated sections of the support used to provide the data (i.e., safety collection form or Sanofi Portal)

- **Suspect Product(s):**

  Number of doses of COVID-19 vaccine with dates of vaccination, batch number, tradenames

- **Medical History/Risk Factors:**

  Personal history of smoking (current or former smoker), obesity, respiratory and Gastro-Intestinal Tract [GIT] infections, lymphoma, Human Immunodeficiency Virus [HIV] positive, Systemic Lupus Erythematosus [SLE], vasculitis, other autoimmune disorders, Hypertension [HT], Diabetes Mellitus [DM], heart disease, lung disease, kidney disease, liver disease, coagulation disorders

  Please provide details on start date (DD/MM/YY), Stop date (DD/MM/YY) and if the patient is treated for the specified condition

- **Description of the Reported Event(s)/Clinical Course:**
  Please consider all the following Event(s)/Symptoms and if relevant, enter it/them as Reported Event(s)/Clinical course in safety collection form or Sanofi Portal

  - General symptoms/disorders
    - Fever
      - Temperature ≥ 38°C or ≥ 100,4 °F during ≥ 24h
    - Chills
    - Cough
    - Myalgia
    - Pharyngitis
    - Anosmia
    - Ageusia
    - Rhabdomyolysis
    - Multisystem inflammatory syndrome
    - Multiorgan failure (Please specify which organ systems were affected)
    - Signs of severe systemic illness
      - FDA definition: Respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg
    - Others: Please provide details

  - Respiratory symptoms/disorders
    - Rhinorrhea
    - Pneumonia
    - Dyspnea
    - Tachypnea
    - Hypoxemia
    - Acute respiratory failure
    - Acute Respiratory Distress Syndrome (ARDS)

    - FDA definition: Needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or Extra Corporeal membrane Oxygenation (ECMO)
  - Others: Please provide details

- Cardiac symptoms/disorders
  - Chest pain
  - New onset arrhythmia
  - Pericarditis
  - Myocarditis
  - Myocardial Infarction
  - Acute coronary artery disease
  - Heart failure
  - Cardiogenic shock
    - Systolic Blood Pressure < 90 mm Hg, Diastolic Blood Pressure < 60 mm Hg, or requiring vasopressors
  - Others: Please provide details

- Hepato-gastrologic symptoms/disorders
  - Abdominal pain
  - Nausea
  - Diarrhea
  - Vomiting
  - Acute hepatic dysfunction
  - Others: Please provide details

- Renal symptoms/disorders
  - Acute renal dysfunction
  - Acute renal failure
  - Others: Please provide details

- Neurologic symptoms/disorders
  - Headache
  - Stroke
  - Guillain-Barré syndrome
  - Encephalitis
  - Meningitis
  - Convulsions
  - Altered consciousness
  - Another significant acute neurologic dysfunction
  - Others: Please provide details

- Coagulation symptoms/disorders
  - Coagulopathy
  - Thrombocytopenia
  - Disseminated intravascular coagulation symptoms/disorders
  - Vasculitis
  - Hemorrhage
  - Thromboembolic events:
    - Deep vein thrombosis
    - Pulmonary embolism
  - Purpura fulminans
  - Others: Please provide details

- Dermatologic symptoms/disorders
  - Rash
  - Erythema multiforme
  - Chilblains
  - Others: Please provide details

- Endocrine system symptoms/disorders
    - Subacute thyroiditis
    - Acute pancreatitis
    - Others: Please provide details

- Ophthalmologic symptoms/disorders
    - Conjunctivitis
    - Others: Please provide details

- **<u>Complementary Investigations (including lab tests):</u>**

    - Investigations in research of SARS-CoV-2 infection (providing details, dates, results with units and normal ranges, and clinical interpretation)
        - SARS-CoV-2 viral test on a respiratory sample (e.g., Polymerase Chain Reaction [PCR])
        - SARS-CoV-2 Serology (IgM, IgG, Specificity: spike-proteins, non-spike protein or unknown)
        - SARS-CoV-2 Variant to be specified if available (Alpha, Beta, Delta, Gamma, ...)
        - Other SARS-CoV-2 test to be specified
        - Chest imaging (e.g., X-ray, Computed Tomography [CT])
        - Hematology (e.g., leucocyte count [including neutrophil and lymphocyte counts], hemoglobin, platelet count, coagulation parameters [Prothrombin Time [PT], Partial Thromboplastin Time [PTT], D-Dimer, International Normalized Ratio [INR], fibrinogen, B and T cell function, assays)
        - Clinical chemistry (e.g., serum creatinine, glomerular filtration rate [GFR], liver enzymes, bilirubin, albumin, B-type natriuretic peptide [BNP], troponin)
        - Inflammatory markers (e.g., C- Reactive Protein [CRP], Erythrocyte Sedimentation Rate [ESR], procalcitonin, ferritin, Lactate Dehydrogenase [LDH], cytokines [including IL-6], others, please specify)
        - Urinalysis
        - Evidence of hypoxemia (e.g., PaO2/FiO2 [P/F ratio], SpO2/FiO2 [S/F ratio]), hypercapnia (PaCO2) or acidosis (pH)
        - Other, please specify

    - Have alternative etiologies and differential diagnoses been ruled out (e.g., flu, bacterial or non-COVID viral pneumonia, other infections …)?
        - Other investigations performed to be specified, including pertinent positive and negative results with dates / units / normal ranges (as applicable)

Discharge summary should be attached if needed/applicable.

Myocarditis, Perimyocarditis

Targeted Follow-up Form (coversheet)

Please provide the below requested information in the dedicated sections of the support used to provide the data (i.e., safety collection form or Sanofi Portal).

- **Medical History/Risk Factors:**

  - Pertinent medical history of risk factors (if yes, please provide details)
    - Recent history of or flu-like symptoms, pharyngitis, upper respiratory tract infection, diarrhea within 2-3 weeks preceding myocarditis
    - History of systemic inflammatory disease (i.e., Systemic Lupus Erythematosus (SLE), Crohn's disease, sarcoidosis, rheumatoid arthritis), familial history of myocarditis
    - Myocarditis, pericarditis, hypertension, venous thromboembolism, cardiac arrythmias, myocardial infarction, coronary artery disease
    - COVID-19 infection
    - Cancer
    - Radiation therapy
    - Hypothyroidism
    - Renal failure
    - Recent history of pregnancy
    - Alcohol intake, exposure to toxic (carbon monoxide, arsenic, lead, phosphorus, mercury, cobalt)
    - Other: please provide details

- **Concomitant Medicines (e.g., drugs, devices, vaccines)**

  - Concomitant treatment with e.g., antibiotics, sulfonamides, antihypertensive, anti-seizure, amphetamines, cocaine. If other, please provide details.
  - Previously administrated COVID-19 and other vaccines

- **Description of the Reported Event(s)/Clinical Course:**

  - Signs, symptoms, diagnosis (if applicable, please add start date and duration)
    - Chest pain
    - Arrhythmia
    - Palpitations
    - Dyspnea
    - Cough
    - Peripheral edema
    - Fever, sweats, chills
    - Stomach pain
    - Nausea
    - Vomiting
    - Fatigue
    - Syncope
    - Near-syncope
    - Other: please provide details

- Final diagnosis: myocarditis or myopericarditis
- Have differential diagnoses been ruled out?

  e.g., coronary artery vasospasm, myocardial infarction, pulmonary edema, interstitial pulmonary fibrosis, sudden cardiac death, unstable angina, ventricular tachycardia, cardiac tamponade, cardiomyopathy. If other, please provide details.
- Corrective treatment for reported events (drug name, start/stop date, route, daily dose)

- **<u>Complementary Investigations (including lab tests):</u>**

  - Infectious check-up [Provide detailed pertinent Positive (+) / Negative (-) or Normal / Abnormal; Results with units, normal range, date (NA= not available) and details (IgG, IgM, blood, CSF PCR, serology, culture, value)]
    - Coxsackievirus group B
    - Enterovirus
    - Adenovirus
    - Cytomegalovirus
    - Epstein-Barr virus
    - Hepatitis viruses
    - Influenza viruses
    - HIV
    - Rubeola, Mumps, Varicella
    - Bacterial culture
    - Fungal culture
    - Parvovirus B-19
    - SARS-CoV-2
    - Borrelia burgdorferi
    - Mycoplasma
    - Legionella
    - Other: please provide details

  - Blood tests (for each test, please provide date, results and normal reference range)
    - Blood count
    - White blood cell formula
    - Erythrocyte sedimentation rate
    - C-reactive protein
    - Creatine Kinase MB
    - Troponin I and/or Troponin T
    - Rheumatoid factor, cryoglobulins
    - Autoimmune antibodies
    - Lactate dehydrogenase
    - Aspartate aminotransferase
    - Alanine aminotransferase
    - D-dimer
    - Others (please provide details)

  - Other investigations performed (for each investigation, please provide the date and the result)
    - Echocardiography
    - ECG
    - Scintigraphy, PET scan, MRI, angiography
    - Chest X Ray
    - CT scan

- Endomyocardial biopsy (EMB)
- Other: please provide details

Discharge summary should be attached if needed/applicable.