EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2022
EMA/893684/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VidPrevtyn Beta

Common name: COVID-19 Vaccine (recombinant, adjuvanted)

Procedure No. EMEA/H/C/005754/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Ad-vector	adenovirus-vector
AKM	Advanced Kinetic Modelling
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ATCC	American Type Culture Collection
ACE2	angiotensin-converting enzyme 2
Ab	antibody
APHP	Assistance Publique – Hôpitaux de Paris
AcNPV	*Autographa californica* Nuclear Polyhedrosis Virus
AS	Active Substance
B.1.351	Beta variant
BCA	Bicinchoninic Acid Assay
BV	bivalent
BL	blood sample
BSE	Bovine spongiform encephalopathy
CRF	Case Report Form
CMIAS	cellular immunity and mucosal analysis set
CMI	cellular-mediated immunity
CBER	Center for Biologics Evaluation and Research
CT	Characterization Testing
CMC	Chemistry Manufacturing and Controls
DRCI	Clinical Research and Innovation Department
CSR	Clinical Study Report
Com	Commercial
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CPV	Continuous process verification
COVID-19	coronavirus disease 2019
CLI	COVID 19-like illness
CUMI	cumulative incidence
CPE	Cytopathic effect
D	day
DOM	Day of Manufacture
B.1.617.2	Delta variant
DNA	deoxyribonucleic acid
DC	diary card
DO	Dissolved oxygen
DSP	Downstream Process
EUA	Emergency Use Authorization
ELISA	Enzyme-linked Immunosorbent Assay
ELISpot	enzyme-linked immunospot
EMA	European Medicines Agency
Ph. Eur.	European Pharmacopoeia

EU	European Union
FDA	Food and Drug Administration
FAS	full analysis set
GMFRs	geometric mean fold ratios
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GCP	Good Clinical Practice
HCP	host cell protein
HCS	human convalescent sera
IEDB	Immune Epitope Database
IgG	immunoglobulin G
IPT	In Process Test
IRR	incidence rate ratio
IPV	Initial Process Verification
ITT	Intent To Treat population
IFN	interferon
IL	interleukin
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN	International Non-Proprietary Name
IM	intramuscular
kDa	Kilodalton
LB	lower bound
LLOQ	lower limit of quantitation
MLE	Mary l'Etoile
MCB	Master Cell Bank
MVB	Master Virus Bank
MAAE	medically-attended adverse event
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	messenger ribonucleic acid
mS	Millisievert
mFAS-PD	Modified Full Analysis Set post-dose
MV	monovalent
NICD	National Institute of Communicable Diseases
NIST	National Institute of Standards and Technologies
NRJ	Non Risk Evaluation and Mitigation Strategies justification
NMT	Not More Than
NAAT	nucleic acid amplification test
NP	nucleocapsid protein
B.1.1.529	Omicron variant
OOT	Out Of Trend
PIP	Pediatric Investigation Plan
PP	Per Protocol
PP	Process Parameter
PPAS	Per-Protocol Analysis Set
PYR	person-years at risk

PRNT	plaque reduction neutralisation test
PD	post-dose
pIMD	potential immune-mediated disease
psi	Pound-force per square inch
PPQ	Process Performance Qualification
PDB	Protein Data Bank
RDT	rapid diagnostic test
RSafAS	Reactogenicity Safety Analysis Set
RBD	receptor-binding domain
RLU	relative luminescence units
RR	Relative risk
RSD	Relative standard deviation
RT	Release Test
SafAS	Safety Analysis Set
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
S	spike
S protein	spike glycoprotein
SD	standard deviation
SOP	Standard Operating Procedure
SAP	statistical analysis plan
SOC	system organ class
TC	telephone call
Th	T-helper
TSE	Transmissible spongiform encephalopathy
UK	United Kingdom
US	United States of America
USP	Upstream Process
VAC	vaccination
VAED	Vaccine Associated Enhanced Disease
VE	vaccine efficacy
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VTAS	Variant Testing Analysis Set
VOC	Variants of concern
WFI	Water for Injection
WCB	Working Cell Bank
WVB	Working Virus Bank
WVS	Working Virus Stocks
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi Pasteur submitted on 29 March 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Vidprevtyn Beta, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

During the procedure, the applicant changed the application from VidPrevtyn to VidPrevtyn Beta (see below). The applicant applied initially for VidPrevtyn (Wuhan strain) for the following indication:

10 µg primary series

"Vidprevtyn is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 through 59 years of age.

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

5 µg booster

"Vidprevtyn is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older previously vaccinated against COVID-19.

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

During the procedure, the applicant changed the application from VidPrevtyn to VidPrevtyn Beta (Beta strain, 5 µg booster). For VidPrevtyn Beta, the applicant applied for the following indication:

"VidPrevtyn Beta is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV- 2, in individuals 18 years of age and older previously vaccinated against COVID-19.

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

The applicant's strategy was initially to seek a marketing authorisation for VidPrevtyn (Wuhan based) as a vaccine to be used for primary series and as a booster, then followed by the addition of the beta variant booster vaccine (VidPrevtyn Beta). In view of the epidemiological evolution and needs to support the choice of a booster with broad protection against Variants of Concern (including Omicron) for a population already primed, the application was updated to seek only a marketing authorisation for VidPrevtyn Beta.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0201/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0046/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance SARS-CoV-2 prefusion Spike delta TM protein, recombinant (B.1.351 strain) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development in the context of the present application:

Date	**Reference**	**SAWP co-ordinators**
5 June 2020	EMEA/SA/4562/1/2020/III	*Ms Blanca García-Ochoa Martín and Dr Andreas Kirisits*
23 October 2020	EMEA/H/SA/4688/1/2020/PED/II	*Dr Andreas Kirisits and Dr Rune Kjeken*
10 November 2020	EMEA/SA/4562/1/FU/1/2020/II	*Dr Mair Powell and Dr Ewa Balkowiec-Iskra*
30 November 2020	EMA/SA/0000050371	*Dr Walter Janssens and Dr Mário Miguel Coelho da Silva Rosa*
16 February 2021	EMA/SA/0000053386	*Dr Hrefna Gudmundsdottir, Dr Walter Janssens, Dr Mair Powell and Dr Ingrid Schellens*
18 June 2021	EMA/SA/0000061686	*Dr Charlotta Bergquist*
18 June 2021	EMA/SA/0000063817	*Dr Koen Brusselmans, Dr Heidi Meyer*
10 November 2021	EMA/SA/0000073025	*Dr Jens Reinhardt*
26 January 2022	EMA/SA/0000078093	*Dr Ingrid Schellens*
13 July 2022	EMA/SA/0000096498	*Dr Sol Ruiz, Dr Manuela Mura*

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- *CMC, non-clinical and clinical strategy to support MAA of the D614 monovalent vaccine*
- *CMC package to support the MAA of the B.1.351 monovalent vaccine*
- *Comparability approach for the COVID-19 vaccine Active Substance (DS) and Drug Product (DP) produced at the different sites to support authorisation*
- *DS process validation approach for demonstrating manufacturing consistency of the B1.351 monovalent variant vaccine at manufacturing sites already qualified for Sanofi-Pasteur's parental Covid-19 vaccine D614*
- *Risk assessment discussing the implementation of B1.351 strain specific changes in terms of viral clearance impact*
- *Non-clinical programme to support the MAA of the B.1.351 monovalent vaccine*
- *Adequacy of study VAT00008 and VAT00002 and amendment cohorts to support approval of the B.1.351 monovalent variant vaccine in different priming and boosting indications*
- *Agreement on the post-hoc analyses on immunogenicity data from VAT00013 (COVIBOOST) to demonstrate superiority of the monovalent B.1.351 vaccine compared to licensed mRNA booster vaccine and to support approval*
- *Agreement that the totality of immunogenicity and safety database to support MAA of the monovalent B.1.351 vaccine*

Scientific advice compliance

There is no major non-compliance with the given scientific advice that precludes the approval.

1.7. COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application: The ETF endorsed the Scientific Advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure. Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP. For the exact steps taken at ETF, please refer to section 1.8.

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Ingrid Wang

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Jana Lukacisinova

The CHMP confirmed eligibility to the centralised procedure on	04 September 2020
ETF recommendation on a request for appointment of Rapporteurs for a potential rolling review procedure on	15 July 2021

Applicant submitted documentation as part of a rolling review to support the marketing authorisation application on	20 July 2021
The procedure (Rolling Review 1) started on	20 July 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 September 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP members on	21 September 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	21 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	24 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2021
ETF discussion on Rolling Review 1 took place on	28 September 2021
CHMP discussion on Rolling Review 1 took place on	04 October 2021
Applicant submitted documentation as part of a rolling review to support the marketing authorisation application on	17 September 2021
The procedure (Rolling Review 2) started on	17 September 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP members on	26 October 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	27 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	04 November 2021
ETF discussion on Rolling Review 2 took place on	04 November 2021
CHMP discussion on Rolling Review 2 took place on	10 November 2021
Applicant submitted documentation as part of a rolling review to support the marketing authorisation application on	17 November 2021
The procedure (Rolling Review 3) started on	17 November 2021
The CHMP assessment report was circulated to all CHMP and PRAC members on	26 January 2022
BWP plennary discussion	01 February 2022
ETF discussion on Rolling Review 3 took place on	10 February 2022
CHMP discussion on Rolling Review 3 took place on	14 February 2022
The MAA application was received by the EMA on	29 March 2022
The MAA procedure started on	30 March 2022

The CHMP Rapporteurs' first Assessment Report was circulated to all CHMP and PRAC members on	29 April 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 June 2022
The ETF discussion on the application took place on	13 June 2022
BWP plenary discussion	15 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 June 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
ETF discussion	06 October 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	13 October 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 October 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	26 October 2022
The ETF discussion on the application took place on	3 November 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vidprevtyn Beta on	10 November 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	10 November 2022

VidPrevtyn Beta was evaluated as part of 'OPEN', an initiative started in December 2020 with the aim of increasing international collaboration in the EU review of COVID-19 vaccines and therapeutics. More information can be found on the EMA website.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

In December 2019, the World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020, the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally. On 30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

2.1.2. Epidemiology and risk factors

As of 7 November 2022, there have been over 629 million confirmed cases of SARS-CoV-2 infection globally with approximately 6.58 million deaths resulting from infection and subsequent coronavirus disease (COVID-19) as registered by WHO (https://covid19.who.int/). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

As for all viruses, the SARS-CoV-2 virus will constantly change through mutation and, indeed, many variants of the SARS-CoV-2 virus with different sets of mutations have been observed worldwide. While most emerging SARS-CoV-2 variants will not have a significant impact on the spread of the virus, some mutations or combinations of mutations may provide the virus with a selective advantage,

such as increased transmissibility or the ability to evade the host immune response. These variants could increase the risk posed by SARS-CoV-2 to human health and are considered variants of concern (VoC). End of 2020, one year after the emergence of SARS-CoV-2 Wuhan ancestral strain late 2019, various variants of concern (VOC) were identified, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28). In spring 2021, Delta (B.1.617.2) became the dominant variant worldwide, and end of 2021, Omicron BA.1 replaced Delta. Currently BA.5 is dominating in the EU.

According to European Centre for Disease Prevention and Control (ECDC), histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

2.1.4. Clinical presentation, diagnosis

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

The severity of COVID-19 disease varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical disease may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

Studies among hospitalised patients have found that high SARS-CoV-2 viral load is associated with worse outcomes, including increased mortality rates (Magleby, 2020) (Westblade, 2020). Community-based studies in non-hospitalised patients show symptomatic patients have higher viral load across both adults and children compared to asymptomatic individuals (Chung, 2021).

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed since the start of the pandemic, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy such as Veklury (remdesivir, EMEA/H/C/005622) or Paxlovid, that can be used in the outpatient setting (PF-07321332/ritonavir, EMEA/H/C/005973).

Monoclonal antibodies and notably bi-therapies to overcome potential escape by VOC with mutations on spike are perceived as of potential value. This was particularly true for immunocompromised individuals especially where vaccines might not induce adequate immune response in those patients of particular medical need. Thus, recently, four monoclonal antibodies Ronapreve (casirivimab/imdevimab, EMEA/H/C/005814), Regkirona (regdanvimab, EMEA/H/C/005854), Xevudy (sotrovimab, EMEA/H/C/005676) and Evusheld (tixagevimab /cilgavimab, EMEA/H/C/005788) have been authorised for the treatment of COVID-19 disease in individuals who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. In the case of Ronapreve, it is also authorised for prevention of COVID-19, and Evusheld also for pre-exposure prophylaxis of COVID-19.

Other products have been repurposed to be used for the treatment of COVID-19, such as Kineret (anakinra, EMEA/H/C/000363) in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR)≥6 ng/ml; and RoActemra (tocilizumab, EMEA/H/C/000955) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Additionally, there are 6 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease: Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Vaxzevria (EMEA/H/C/005675), Jcovden (EMEA/H/C/005737), Nuvaxovid (EMEA/H/C/005808) and COVID-19 Vaccine (inactivated, adjuvanted) Valneva (EMEA/H/C/006019). The mRNA vaccine include in their marketing authorisation adapted Omicron vaccines.

2.2. About the product

VidPrevtyn Beta vaccine (SARS-CoV-2 prefusion Spike delta TM recombinant protein vaccine candidate from the strain B.1.351 and adjuvanted with AS03) is intended as a booster for the active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in individuals 18 years of age and older previously vaccinated against COVID-19. A single injection of 5 µg dosage of the vaccine is intended to be used. The vaccine contains a version of the spike protein found on the surface of SARS-CoV-2 Beta variant.

The adjuvant AS03 is an oil-in-water emulsion containing squalene and α tocopherol. This adjuvant may enhance the quality and quantity of the immune response by promoting a more balanced T-helper (Th)1/Th2 response. The combination of antigen and adjuvant enhances the magnitude of immune response, which may contribute to protection against COVID-19.

A booster dose of VidPrevtyn Beta is administered intramuscularly. It is recommended to administer VidPrevtyn Beta at least 4 months after the completion of primary vaccination with authorised COVID-19 vaccine.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a solution and emulsion for emulsion for injection containing 5 micrograms of SARS-CoV-2 prefusion Spike delta-transmembrane protein (B.1.351 strain) [SARS-CoV2 preS dTM (B.1.351)] produced by recombinant DNA technology using a baculovirus expression system in an insect cell line that is derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda* as active substance (AS).

These are two multidose vials (antigen vial and adjuvant vial) that must be mixed before use. After mixing, the vaccine vial contains 10 doses of 0.5 mL.

The adjuvant, AS03, is composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).

Other ingredients are:

- Antigen vial: Sodium dihydrogen phosphate monohydrate, Disodium phosphate dodecahydrate, Sodium chloride, Polysorbate 20, Water for injections,
- Adjuvant vial: Sodium chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium chloride, Water for injections.

The product is available as one pack containing:

- 2.5 mL antigen solution in a multidose vial (type 1 glass) with a stopper (chlorobutyl) and an aluminium seal with a green plastic flip-off cap
- 2.5 mL adjuvant emulsion in a multidose vial (type 1 glass) with a stopper (chlorobutyl) and an aluminium seal with a yellow plastic flip-off cap.

The volume after mixing 1 vial of solution (2.5 mL) with 1 vial of emulsion (2.5 mL) corresponds to 10 doses of vaccine (5 mL).

2.3.2. Active substance

2.3.2.1. General information

The active substance, CoV2 preS dTM (B.1.351) contains the recombinant SARS-CoV2 prefusion Spike deleted (also referred as delta or d)-transmembrane protein whose sequence is based on the South African variant (B.1.351; GISAID Accession EPI_ISL_1048524) as the COVID-19 vaccine antigen.

The gene sequence was derived by modifying the gene encoding the CoV2 preS dTM (D614) protein, which was an earlier vaccine candidate with a sequence based on the native genome isolate Wuhan-Hu-1. Additional modifications were made to the native SARS-CoV2 S protein gene coding (GenBank Accession NC045512) to enable the expression and secretion of the prefusion-stabilized soluble S protein of the beta variant from strain B.1.351, as trimer. This protein is expressed in expresSF+ (Lepidopteran) insect cell line using a baculovirus expression vector.

These modifications include: i) the substitution of the native S protein secretion signal peptide with a baculovirus specific secretion signal peptide, ii) amino acid substitutions at the polybasic protease cleavage site to prevent S1-S2 subunit cleavage and maintain the spike protein in a pre-fusion state, iii) adding two stabilizing proline mutations in the S2 fusion region (2), iv) removal of the C-terminal

transmembrane domain and adjacent cytoplasmic domain to enable secretion from the expressing cell, and v) addition of a T4 bacteriophage fibritin foldon domain to the C-terminus to enable S protein trimerization in the absence of the transmembrane domain.

The active substance of the recombinant CoV2 preS dTM (B.1.351) protein has a purity higher than 90% and to have a molecular mass of approximately 170 kDa.

2.3.2.2. Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured at two different sites (Genzyme Corporation, Framingham, USA and Sanofi-Chimie, Vitry, France). Good Manufacturing Practice (GMP) compliance has been documented for sites involved.

Description of manufacturing process and process controls

The manufacture of the CoV2 preS dTM active substance is divided into Upstream Process (USP) and Downstream Process (DSP).

The Upstream Process for production of the CoV2 preS dTM active substance includes expansion of expreSF+ (SF+) cells from Working Cell Bank (WCB), expansion of the Working Virus Bank (WVB) to Working Virus Stocks (WVS) and infection of SF+ cells with WVS allowing the production of the CoV2 preS dTM protein in the production bioreactor.

The Downstream Process for purification of the CoV2 preS dTM active substance includes a clarification step followed by several chromatography steps to further purify the CoV2 preS dTM protein and contribute to viral clearance. An ultrafiltration / diafiltration step is used to concentrate the CoV2 preS dTM protein. Additionally, a detergent treatment contributes to viral clearance and a filtration step ensures a low bioburden content.

The CoV2 preS dTM active substance manufacturing process does not include reprocessing. The manufacturing process has been sufficiently described and it is similar between the two active substance manufacturing sites. The batch numbering system has been described in the dossier.

Control of materials

Cell banks

The source, history and generation of the *expres*SF+ cell line is described in sufficient detail. The applicant is using a two-tiered cell bank system. The master cell bank (MCB) and the two working cell banks (WCB) lots derived thereof have been characterised in line with ICH Q5D requirements. Cell banks have been sufficiently qualified using an adequate testing panel which is in line with Ph. Eur. 5.2.3.

Virus Banks

The baculovirus strain used for recombinant protein manufacturing is *Autographa californica* nuclear polyhedrosis virus (AcNPV), which is the prototype virus of the Baculoviridae family and was originally isolated from a single field collected alfalfa looper larva. Generation of the parental linear baculovirus master bank has been described. The generation of the parental transfer vector has been sufficiently described. The choice of the transgene sequence and the cloning of the CoV2 preS dTM gene into the parental transfer vector has been sufficiently described.

The master virus bank (MVB) has been adequately qualified. The master virus bank without the gene encoding the active substance is used to generate a working virus bank (WVB) containing the gene. The cloning strategy is described in sufficient detail. The qualification tests and acceptance criteria have been described and batch analysis results have been provided to ensure identity, titer, sterility, viral safety and correct assembly of the WVB.

Raw materials

Both, compendial and non-compendial raw materials have been listed by the applicant. Compendial materials are proposed to be tested against the relevant Ph. Eur. specifications, whereas non-compendial materials are proposed to be tested against in-house specifications. Data has been presented to give reassurance on viral/ Transmissible spongiform encephalopathy (TSE) safety.

Control of critical steps and intermediates

During the manufacture of the active substance, process parameters (PPs) and in-process tests (IPTs) and specification / release tests have been implemented to ensure that the manufacturing process steps remain under control and meet their operating range and specifications. The defined PPs and IPTs has been justified. There are no intermediates in the manufacturing process.

Process Validation

Process validation/process performance qualification (PPQ) has been performed for both active substance manufacturing sites individually. The applicant's approach of performing a continuous process verification (CPV) for B.1.351 at the sites that have already performed PPQ for D614 has been agreed during scientific advice procedures for this product.

The PPQ campaign with the D614 strain has been performed at Framingham and Vitry using three consistency lots, respectively. The Initial Process Verification (IPV) studies for the B.1.351 strain was conducted after the initial PPQ and consisted of three consistency lots at each manufacturing site (Framingham, USA and Vitry, France). Release test results have been provided and all results met the respective acceptance criteria, which is also applicable to the PPs investigated. Process hold time investigations; resin lifetime studies and microbial control studies have been provided. Small scale resin lifetime studies were performed with the D614 strain. At scale resin lifetime continuous process verification report studies for B.1.351 process batches will be provided by Q1 2023 (Recommendation 1). In addition, a transport validation report for the active substance should be provided (Recommendation 7).

Manufacturing process development

The present B.1.351 strain application is based on the initial development of the applicant's D614 vaccine candidate. Therefore, most of the manufacturing process development is based on the D614 vaccine development. When designing the B.1.351 active substance manufacturing process, process adjustments compared to D614 strain have been limited to the strict minimum to adapt to the new strain characteristics. Consequently, the additional manufacturing process development and industrial work for the implementation of the B.1.351 active substance strain has been leveraging significantly the D614 prior knowledge and qualification/validation.

The development of the specifications has been sufficiently described. Some critical tests have been changed during the clinical development, but the evolution of these tests has been adequately described and justified.

Manufacturing process development from phase I/II over phase II to phase III/commercial has been sufficiently described and changes are justified. Major changes have been introduced in the manufacturing process from Phase I/II to Phase II in order to improve the purity. Therefore, differences found in the characterisation comparability are expected. Comparability data demonstrate that the Spike Protein is folded correctly in all active substance vaccine preparations and the antigen used in clinical Phase I/II and Phase II process demonstrated physical and antigenic characteristics as expected. Comparability analyses between phase II and phase III/commercial batches demonstrate good comparability.

A comparability evaluation has been performed to demonstrate comparability between clinical batches manufactured at the clinical manufacturing site and each of the two commercial active substance manufacturing sites Framingham and Vitry. The comparability approach is acceptable, and the choice of characterization tests is endorsed. The comparability analysis demonstrates for both commercial active substance manufacturing sites that characterization and release test results are consistent within three PPQ batches. These differences have been assessed and the comparability exercise as a whole is considered acceptable. The applicant committed to implement final active substance (B.1.351) process monitoring limits when data for a minimum of 30 batches are available at each manufacturing site (Recommendation 3).

Additionally, a process comparison between the initial D614 spike protein and the B.1.351 spike protein has been presented and the impact has been evaluated. In general, the same process control strategy in terms of PPs, IPTs and release tests is applied for both D614 and B.1.351. Following the procedure for the D614 strain, a comparability assessment was performed with three commercial B.1.351 active substance batches manufactured at each site. However, no comparability between the D614 and the B.1.351 strains has been conducted as the characterization features are strain specific, which makes a comparison difficult.

There are some characteristics identified, which are specific to the B.1.351 S protein and were not observed for the initial D614 Spike protein, i.e. maturation of the protein and conformational changes. The maturation phenomenon has been characterised intensively and results have been presented for the three sites. In summary, the applicant concluded that the maturation phenomenon has no impact on product quality.

Characterisation

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of CoV2 preS dTM B.1.351.

Phase III/commercial process CoV2 preS dTM B.1.351 active substance batches have been used for characterization. The overall characterisation approach remains the same as for D614, though new data for B.1.351 is provided. The active substance has been characterised using glycopeptide mapping, disulfide bond mapping, thermal analysis and Infrared Spectroscopy to analyse secondary structures. Besides that, additional characterization tests to assess HCP (host cell protein) identity, purity, potency and biological activity have been provided. Overall, the results for B.1.351 are similar to the results for D614 and are consistent with the proposed structure. In summary, the provided information on characterization is deemed sufficient and considered acceptable.

Potential process-related and product-related impurities have been discussed and have been shown to be reduced to acceptable levels by the manufacturing process. Additionally, the applicant commits to provide additional data regarding impurity clearance by end of Q4 2022 (Recommendation 2). So far, no protein aggregates have been observed.

2.3.2.3. Specification

Release tests include tests performed at the active substance and tests performed at other stages (pre-harvest or pre-infection). Overall, release tests have been chosen adequately. The active substance specifications include physico-chemical and safety tests, adventitious agents tests, Identity, Potency, Protein content, Potency to total protein content ratio and process-related impurities tests.

Analytical methods

All methods have been described in the dossier. Method validation has been described for all non-compendial methods and for the different active substance sites separately.

Batch analysis

B.1.351 Batch data from three Initial Process Verification (IPV) batches manufactured at the Framingham and the Vitry site have been provided. In addition, batch analysis data from the clinical manufacturing site are included in the dossier. All results for the batches manufactured at the three sites are consistent and within the specifications.

Justification of specifications

The proposed active substance acceptance criteria have been justified in detail. Overall, the justifications are considered sufficient. During the procedure, questions have been raised regarding the release specifications. Some specifications have been amended, further justified or included as an additional release test as requested. The Relative Antigen Content determination will only be performed in stability studies. The applicant committed to implement limits when further real-time stability data are available from at least three commercial batches from each active substance site (Recommendation 5). The applicant is requested to revise the 'Potency to total protein content ratio' specification when data from 30 B.1.351 batches are available (Recommendation 6). Impurities have been studied in nonclinical and clinical studies as relevant.

Reference materials

Two representative lots of frozen CoV2 preS dTM material for variant B.1.351 were qualified for use as reference standard and positive control in potency and/or identity tests. The reference standard has been qualified and stability has been addressed. The new B.1.351 reference standard lots are the same for active substance and finished product.

Container-Closure system

Single-use bags are used for storage and transport of the active substance. The bags are received from the supplier pre-sterilized via gamma irradiation. The bags comply with Ph. Eur. requirements and are therefore deemed suitable for the intended use.

Both leachable and extractable studies have been performed, showing the suitability of the container closure system of the active substance for up to 6 months. The applicant committed to perform a new small-scale leachable study, which should support the intended storage of the B.1.351 active substance (Recommendation 4).

2.3.2.4. Stability

Active substance (B.1.351) stability data have been provided for three manufacturing sites (clinical manufacturing site, Framingham and Vitry) for three batches each. Stability has been analysed at the intended storage conditions and under accelerated conditions. For all batches manufactured at the different sites data are available. In the course of the current procedure, the applicant has revised the acceptance criterion applied in stability studies. The accelerated conditions show a decrease of the potency over time. However, they were still within the specification applied for the long-term storage conditions.

The determination of the Relative Antigen Content is a newly introduced method. The applicant committed to implement limits when further real-time stability data is available from at least three commercial batches from each active substance site (Recommendation 5).

Stability data at long term conditions and accelerated conditions from the batches of the clinical site were used to build a kinetic model. The kinetic model allows for an extrapolation of shelf life for the active substance. The applicant committed to immediately report any results of the on-going stability studies that may imply a significant risk to not comply with the end of shelf-life specification. The stability data and supportive kinetic stability model supports the active substance shelf life at the storage conditions.

2.3.3. Finished medicinal product

2.3.3.1. Description of the finished product and Pharmaceutical development

The CoV2 preS dTM (B.1.351) finished product is composed of a modified recombinant SARS-CoV-2 prefusion Spike delta TM protein as the COVID-19 vaccine antigen. The recombinant CoV2 preS dTM (B.1.351) protein is formulated in phosphate buffered saline with polysorbate 20 without preservatives or antibiotics. The CoV2 preS dTM finished product (B.1.351) is supplied in multi-dose vials. One dose of finished product (non adjuvanted) corresponds to 0.25 mL.

The non-adjuvanted finished product is a sterile, colourless clear liquid solution to be mixed with adjuvant AS03 (GlaxoSmithKline Biologicals) for intramuscular injection. The primary container closure system used for the CoV2 preS dTM (B.1.351) finished product consists of a multi-dose glass vial, a rubber stopper and an aluminium seal with a plastic flip-off cap. The finished product composition includes the following ingredients: the active substance, sodium dihydrogen phosphate monohydrate, disodium phosphate dodecahydrate, sodium chloride, polysorbate 20 and water for injections.

The adjuvant AS03 (GlaxoSmithKline Biologicals) is already authorised in various vaccine products (e.g. Adjupanrix) and therefore assessed as known excipients. The adjuvant composition includes squalene, D,L-α-tocopherol, polysorbate 80, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride and water for injections. The liquid AS03 formulation is filled in glass vials, sealed with rubber stoppers for liquid formulations and secured with flip-off caps.

The CoV2 preS dTM (B.1.351) active substance consists of a recombinant SARS-CoV2 Spike (S) protein manufactured by recombinant DNA technology in a qualified expresSF+ (Lepidopteran) insect cell line using baculovirus expression system technology and it is compatible with the excipients, i.e. sodium phosphate, sodium chloride and polysorbate 20. Sodium phosphate is included in the CoV2 preS dTM finished product formulation as a buffer. Sodium chloride is added to maintain osmolality of the finished product. Polysorbate 20 is included in the formulation as a stabilizer.

Several formulations have been developed and used in clinical studies during vaccine development, including D614 strain monovalent formulations, B.1.351 strain monovalent formulations and D614 strain/B.1.351 strain bivalent formulations.

During clinical development three different targeted amounts of CoV2 preS dTM (D614) active substance were investigated, i.e. either 5 µg, 10 µg or 15 µg of the antigen per dose. One multi-stage Phase III efficacy study was initiated to support the formulation intended for commercial production of CoV2 preS dTM (D614) non-adjuvanted finished product priming dose (10 µg). In parallel, a booster study was initiated to support the formulation intended for commercial production of CoV2 preS dTM (D614) non-adjuvanted finished product booster dose (5 µg) to assess the ability of the vaccine to generate a booster response regardless of the initial primary vaccine platform received.

Two formulations containing CoV2 preS dTM (B.1.351) were prepared with targeted amounts of 2.5 µg and 5 µg of the antigen per dose and were implemented for the clinical study to assess the ability of the vaccine to generate a booster response regardless of the initial primary vaccine platform. The same manufacturing process was used as for the D614 DP phase III clinical batches.

Sanofi Pasteur has also developed two bivalent formulations, a 2.5 µg (D614) + 2.5 µg (B.1.351) per dose bivalent formulation and a 5 µg (D614) + 5 µg (B.1.351) per dose bivalent formulation, to be used in several clinical studies.

Total protein content has been used to formulate the clinical materials and will be used to formulate the commercial vaccine.

The commercial presentation is a 5 µg/dose CoV2 preS dTM (B.1.351) booster monovalent vaccine. The B.1.351 strain formulation has fully leveraged development work previously conducted with the D614 strain. Except for the strain change, the formulation and the filling processes remain the same as for the D614 booster vaccine. The D614 vaccines are not in scope of this marketing authorization but data generated during formulation development and manufacturing development are considered supportive for the B.1.351 strain booster vaccine marketing authorization application.

With regards to the commercial supply needs, the manufacturing process has been transferred from clinical manufacturing site to Sanofi S.r.l Anagni site (Italy), associated with scale-up. At the finished product stage, the manufacturing process consists of active substance formulation and filling into vials.

A comparability study was performed to demonstrate that the transfer and scale up of the CoV2 preS dTM finished product formulation and filling processes do not adversely affect the CoV2 preS dTM finished product in terms of Quality, Safety and Efficacy. Initially the presented data was not considered sufficient to conclude on comparability between the clinical manufacturing site and Anagni (major objection). To resolve the major objection, the applicant presented an updated comparability analysis, for the D614 variant, including Equivalence Testing of both sites, which confirmed the comparability of the two finished product manufacturing sites. To strengthen the original comparability study, the applicant will provide the final report of the comparability assessment including the final D614 stability data by Q2 2023 (Recommendation 8). Final finished product process monitoring limits will be implemented when data for a minimum of 30 B.1.351 batches are available at the Anagni site, by Q2 2023 (Recommendation 9).

An in-use stability study was performed with the purpose of providing data to assess the in-use shelf-life for the mix and shoot formulation of CoV2 preS dTM finished product when combined with AS03. Review of the study results demonstrates consistency from the initial mixing stage at T0 through the final testing time points. After mixing, the vaccine should be administered immediately or stored at 2 °C to 8 °C, protected from light, and used within 6 hours as reflected in the SmPC.

2.3.3.2. Manufacture of the product and process controls

Finished product is manufactured, tested and released at Sanofi S.r.l. Anagni, Italy. Batch release will be performed by Sanofi Pasteur, Marcy l'Etoile, France. Compliance with GMP has been appropriately documented for all sites.

Manufacture of CoV2 preS dTM (B.1.351) finished product described in eCTD is based on supportive data generated with the previously developed manufacturing process of CoV2 preS dTM (D614) finished product.

Production of the Final Bulk Product involves combining CoV2 preS dTM active substance with the formulation buffer and blending. Pooling of active substance batches has been conducted and will be applied to the commercial processes. Final Bulk Product is filtered to reduce the bioburden, followed by sterilizing filtration, vial filling, stopper insertion and capping. There is no intermediate in the CoV2 preS dTM finished product manufacturing process. The finished product batch numbering system has been described.

The manufacturing process, process parameters and in-process tests have been described in sufficient detail.

Validation studies were performed to assess the mixing at Final Bulk Product stage, the sterile filtration and vial filling steps at Filled Product stage. The sterility assurance of the aseptic processing conditions is demonstrated during Aseptic Process Simulations.

It is considered that sufficient information is provided for authorisation and remaining requests for the final reports (e.g. transport validation) can be resolved as a recommendation (Recommendation 7). Re-filtration is not performed and therefore not validated.

For the initial scale validation, three PPQ batches of Filled Product of CoV2 preS dTM finished product have been produced at Sanofi S.r.l., Anagni site, Italy, at different dosages using a bracketing approach. Given the current pandemic, this approach is considered acceptable as it allowed to accelerate approval.

For the additional scale validation, three PPQ batches of filled booster dose CoV2 preS dTM finished product have been produced at the Sanofi S.r.l., Anagni site, Italy. Commercial scales are considered suitably validated at the at the Sanofi S.r.l., Anagni site, Italy.

2.3.3.3. Product specification

The CoV2 preS dTM Final Bulk Product is formulated into a stainless-steel tank and is not stored. Therefore, release specifications for the filled product and end of shelf-life have been provided. The finished product specifications include general tests, total protein content, relative antigen content, identity, potency, safety tests, fill volume and container closure integrity.

A number of concerns were raised on the proposed specifications. A major objection was raised requesting adjustment of the specifications for potency to ensure sufficient potency throughout shelf life and further describe the approach to apply test variability correction for setting the proposed limits. During the review, the applicant provided additional information on the potency assay, assay validation and justification for the proposed specifications.

The potency lower specification limit has been adjusted. The lower end of shelf-life potency specification is considered clinically justified and is considered acceptable. The applicant commits to re-evaluate tightening of the potency release specification limit once data from a minimum of 30 batches are available. In addition, in a re-evaluation exercise of the potency specification, the applicant is

recommended to optimise the method to reduce its variability and to include robust stability data on the B.1.351 strain to determine the decrease in potency over time. Finally, the applicant should implement three significant numbers for the potency specification (Recommendation 10).

The total protein content lower specification limit is considered acceptable for both release and end of shelf-life specifications since total protein content is not considered stability indicating as shown by supportive data provided for the D614 vaccine. Regarding the consistency approach, the applicant commits to re-evaluate tightening of the total protein lower release specification limit based on a minimum of 30 batches (B.1.351) based on release data (Recommendation 10).

At the present time there is data from a limited number of finished product batches available which hampers any meaningful statistical analysis to define a relevant upper limit based on process performance and consistency. Therefore, the applicant commits to establish an upper limit for the potency and total protein content release specifications starting with a minimum of 15 batches and will be finalized and submitted with a minimum of 30 B.1.351 batches (Recommendation 11). This is considered acceptable.

Further, the applicant has also committed to implement a testing procedure for polysorbate 20 for release of commercial product after finalizing the development of a polysorbate 20 quantitation test without matrix interference to be performed on the finished product. An appropriate acceptance criterion for the specification will be identified after testing of a sufficient number of commercial B.1.351batches (Recommendation 12).

A risk assessment for elemental impurities according to ICH Q3D has been performed. The safety risk associated with the presence of elemental impurities has been considered as negligible by the company. This is agreed.

The nitrosamine risk assessment reports have been provided with this submission and have been included in section 3.2.R. The presence of nitrosamines in SARS-CoV 2 S protein monovalent bulks manufactured at Framingham and Vitry has been evaluated as unlikely. There is no risk of nitrosamines impurities in the finished product.

Analytical methods

Testing procedures and their validation are described in sufficient detail. Method validation has been described for all non-compendial methods. All excipients used to prepare the formulation buffer of the CoV2 preS dTM finished product are compendial. Therefore, no method validation is needed, and the information provided is considered acceptable.

Reference materials

Relevant information on the in-house reference standard(s) for potency estimation is provided in the dossier. The reference standards used for potency and identity testing of finished product are also used for active substance and are considered adequately qualified for routine release testing. The qualification of a new reference standard or/and a new positive control will follow the protocol as already described for the current standards.

Batch analysis

For the Anagni manufacturing site, a description of three commercial batches of the CoV2 preS dTM (B.1.351) Filled Product with corresponding batch analysis data has been provided. The release results for the clinical CoV2 preS dTM (B.1.351) finished product batch are available in eCTD section 3.2.P.2.3

Manufacturing Process Development and in Section 3.2.P.5.4 Batch analyses. All release results presented are within the defined acceptance criteria.

Container closure system

The primary container closure system used for the CoV2 preS dTM finished product consists of a multi-dose type I borosilicate glass vial, a chlorobutyl rubber stopper and an aluminium seal with a plastic flip-off cap. The summary of the extractables study done has been provided. Sanofi commits to provide the results of the ongoing leachables study done on three batches of B.1.351 CoV2 preS dTM Filled Product by Q1 2023 (Recommendation 14).

The container closure systems for the CoV2 preS dTM non-adjuvanted finished product is considered suitable for use.

Adjuvant (AS03)

AS03 is a well-known and already approved adjuvant manufactured by GSK. Relevant information has been provided in the dossier, including on composition, manufacturing and testing sites, specifications and information on the manufacturing authorisation. Considering that AS03 is a known excipient the information provided is adequate. AS03 contains squalene as an excipient of animal origin. The adventitious agents risk assessment for AS03 has been provided with this submission and is considered acceptable. Further, relevant information with regard to specifications and testing were provided for AS03. There is no risk of nitrosamines impurities in AS03. The AS03 liquid formulation is filled in vial containers, sealed with rubber stoppers for liquid formulations and secured with flip-off caps. The container closure systems for the AS03 adjuvant is considered suitable for use.

2.3.3.4. Stability of the product

Sanofi Pasteur proposes a 12-month shelf-life for the Filled Product when stored at +2°C to +8°C.

Stability evaluation is based the completed stability study of 1 clinical CoV2 preS dTM B.1.351 Filled Product batch and on-going stability studies of three commercial batches under real-time long-term storage conditions and accelerated conditions.

As indicated before, comparability of clinical and commercial lots has been shown, therefore stability data from the clinical lot are considered relevant. For the clinical batch long term stability study, data are available. The stability study conducted on the clinical batch is completed and fulfils the specifications in Section 3.2.P.5.1. For the three commercial batches, the current long term B.1.351 database is very limited. However, the proposed shelf-life claim is justified by applying a kinetic stability model. The approach is supported. The applicant committed to immediately report any results of the on-going stability studies that may imply a significant risk to not comply with the end of shelf-life specification.

The tests performed for stability are general tests, total protein content, potency, purity, safety tests and container closure identity. 'Purity by Relative Antigen Content' stability acceptance criteria for the B.1.351 strain finished product will be implemented when at least 12 months of real-time stability data is available from at least 3 commercial B.1.351 batches with a total of 10 batches minimum (Recommendation 13).

A photostability study on the finished product was performed as per ICH Guideline Q1B, leading to the conclusion that naked finished product vials are sensitive to visible and UV light, but secondary packaging guarantees sufficient protection from visible and UV light as per ICH. Sanofi Pasteur has

included in its clinical documentation and in the SmPC, the recommendation to protect the product from light.

An in-use stability study was performed with the purpose of providing data to assess the in-use shelf-life for the mix and shoot formulation of CoV2 preS dTM finished product when combined with AS03. After mixing, the vaccine should be administered immediately or stored at 2 °C to 8 °C, protected from light, and used within 6 hours as reflected in the SmPC.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable. The proposed 12 months shelf-life for the Filled Product, when stored at +2°C to +8°C, is considered acceptable.

The VidPrevtyn Beta overall shelf life is based on the shorter shelf life between AS03 and antigens vials. For the finished product batches already available, the shorter shelf life was associated to the antigen vials and therefore was based on antigen stability data only.

2.3.3.5. Post approval change management protocol(s)

The submitted post-approval change management protocol (PACMP) provides for the introduction of an additional manufacturing and testing site for the active substance. The site is covered by an EU GMP certificate. The strategy includes a process comparison and a product comparability assessment for VidPrevtyn Beta. The starting materials (WCB and WVB) are identical for all manufacturing sites.

A high-level process comparison strategy between sending and receiving sites was provided and a potential impact of the change was evaluated. Similarly, process parameters were compared. The PPQ at receiving site includes three full-scale production batches. The approach used for testing product comparability has also been presented. Overall, the general approach is deemed acceptable.

2.3.3.6. Adventitious agents

Cell substrates, virus seeds and raw materials used during manufacture of VidPrevtyn Beta are qualified by adequate testing to provide high confidence that extraneous agents are not present in the final product. The master and working virus seeds and the cell bank system were principally adequately tested.

No materials of porcine origin have been used for generation and maintenance of SF+ cells, or during recombinant protein production in SF+cells. Bovine-derived serum was used prior to the establishment of the MCB. Therefore, the risk of bovine spongiform encephalopathy (BSE) contamination is negligible.

During the manufacturing, sufficient routine testing is performed to guarantee the absence of adventitious agents. Viral clearance studies have been performed. The calculated safety margin for baculovirus clearance has been justified according to ICH Q5A Appendix 5.

2.3.3.7. GMO

Not applicable

2.3.4. Discussion on chemical, and pharmaceutical aspects

During the assessment the applicant changed the active substance from the D614 strain to the B.1.351 strain, spike protein. Much of the B.1.351 dossier content remains the same as for D614 which had undergone assessment. The applicant has provided B.1.351 specific data and supportive D614 data

where applicable. However, the final marketing authorisation application only concerns VidPrevtyn Beta (B.1.351 variant).

Sufficient information regarding the manufacturing process, process controls and control of materials for the active substance and finished product part have been provided.

Finished product process validation confirms consistent production of active substance and finished product of the required quality. Data have been provided for D614, which is considered supportive and sufficient. At the finished product stage, the manufacturing process is kept identical between the two strains and is therefore strain independent. Consequently, all finished product process development and process validation, and comparability investigations have been conducted with the D614 strain and are not reperformed for the B.1.351 strain. This approach is widely applied for implementation of influenza annual strain changes and was supported during a scientific advice for this B.1.351 strain vaccine.

The comparability of the three active substance manufacturing sites was shown. PPQs were provided for the initial D614 strain, and Initial Process Verification (IPV) studies were provided for the current B.1.351 strain. Release test results have been provided and all results met the respective acceptance criteria.

The active substance shelf life claim is supported by sufficient data and therefore considered acceptable.

During the procedure, two major objections were raised, in relation to comparability between clinical site and Anagni finished product manufacture, and specifications. Data have been submitted by the applicant during the procedure in response to the major objections and other concerns raised. Further information on the resolution of major objections, other concerns and the rationale for accepting some open issues to be addressed post-authorisation as Recommendations is provided below. These cover various aspects of the active substance and finished product.

During the procedure, a number of issues were raised concerning demonstration of comparability between active substance commercial (Framingham and Vitry) and phase III sites. The applicant provided additional data to address the questions. The comparability analysis demonstrates for both commercial active substance manufacturing sites that characterization and release test results are consistent between three PPQ batches, but for some tests, are slightly different. These differences have already been assessed within the scope of the initial D614 application. B.1.351 data were also provided, and the comparability exercise as a whole is considered acceptable. However, due to differences observed between the active substance manufacturing sites, final active substance process monitoring limits will be implemented when data for a minimum of 30 B.1.351 batches are available at each manufacturing site (Recommendation 3).

The major objection on comparability affected the finished product manufacturing sites. Comparability is based on D614 batch release data together with process validation data; however, the initial analysis was hampered by limited batch data and the fact that the interim release criteria used for comparability assessment had a broader range based on lot-to-lot consistency. The provision of additional data during the evaluation procedure and further analysis by Equivalence Testing supported the comparability analysis between the sites, demonstrating the equivalence between the processes. To strengthen the original comparability study, the applicant committed to include the final D614 stability data and provide the final report of the comparability assessment (Recommendation 8). In addition, final finished product process monitoring limits will be implemented when data for a minimum of 30 B.1.351 batches are available at the Anagni site (Recommendation 9).

The major objection on specifications requested to adjust the specifications for potency to ensure sufficient potency throughout shelf life and to describe the approach to apply test variability correction

used for setting protein content limits. During the review, the applicant adjusted the (D614) potency specification and provided additional information on the potency assay, assay validation and justification for the proposed specifications. The approach to determine potency test variability has been described and is accepted. The revised lower end of shelf-life potency specification is considered clinically justified. However, since the proposed specification is based on limited manufacturing experience, the applicant commits to re-evaluate tightening of the potency and total protein release specification limits once data from a minimum of 30 B.1.351 batches is available, and to optimise the method to reduce its variability (Recommendation 10).

In addition, the applicant commits to establish an upper limit for potency and total protein content release specifications, starting with a minimum of 15 batches, and will be finalized with a minimum of 30 B.1.351 batches (Recommendation 11).

During the procedure, questions have been raised regarding the active substance release specifications. The specification for Appearance has been changed, and 'Potency to Total Protein Content Ratio' has been included as an additional release test as requested. In addition, specifications for potency, purity and host cell protein have been further justified. The Relative Antigen Content determination has been added to the active substance and finished product stability specifications and the current acceptance criterion is "for information only" due to limited batch data, where an acceptance criterion will be implemented when further real-time stability data are available (Recommendation 5 and 13). In addition, the applicant will review the total protein content ratio specification when data from 30 batches measured with the specific potency test are available (Recommendation 6).

At the time of the CHMP opinion, there were a number of minor additional unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These points are put forward and agreed as recommendations for future quality development. Some recommendations derive from the D614 submission but are still applicable for the current B.1.351 submission and therefore the data should be obtained with the B.1.351 strain, where applicable.

The proposed 12 months shelf life for the filled product is considered acceptable based on (limited) stability data supported by applying a kinetic stability model describing the loss of potency as function of time and temperature. The AS03 adjuvant is already approved in the EU. The information provided is considered adequate for a known excipient.

The finished product should be protected from light and after mixing with AS03, the vaccine should be administered immediately or stored at 2 °C to 8 °C, protected from light, and used within 6 hours.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points* for investigation:

Active substance

1. To provide an at scale resin lifetime continuous process verification report for B.1.351 process (by Q1 2023).
2. To provide the full analysis demonstrating clearance of impurities (by Q4 2022).
3. To implement final active substance process monitoring limits when data from a minimum of 30 B.1.351 active substance batches are available at each manufacturing site (by Q2 2023).
4. To provide a small-scale leachable study supporting the intended storage of the B.1.351 active substance (by Q1 2024).
5. To implement an acceptance criterion for the Relative Antigen Content determination in the active substance stability studies when real-time stability data are available from at least three commercial B.1.351 batches from each active substance manufacturing site (by Q1 2024).
6. To revise the Potency to Total Protein Content Ratio specification for active substance when data from 30 B.1.351 batches are available (by Q1 2023).

Finished product

7. To provide the transport validation report for active substance and finished product (by Q1 2023).
8. To provide the final report of the comparability assessment between the finished product manufacturing sites including the final D614 stability data (by Q2 2023)
9. To implement final finished product process monitoring limits when data for a minimum of 30 B.1.351 finished product batches are available at the Anagni manufacturing site (by Q2 2023).
10. To re-evaluate tightening of the potency and total protein release specifications limits based on release data of a minimum of 30 finished product batches (B.1.351) to reflect consistency of the manufacturing process. During the re-evaluation exercise of the potency specification, the applicant is recommended to optimise the method to reduce its variability and to include robust stability data on the B.1.351 strain to determine the decrease in potency over time. Finally, the applicant should implement three significant numbers for the potency specification (by Q2 2023).
11. To establish upper limits for potency and total protein content starting with a minimum of 15 batches and will be finalized and submitted with a minimum of 30 B.1.351 batches (by Q2 2023).
12. To implement a testing procedure for polysorbate 20 for release of commercial finished product. An appropriate acceptance criterion specification should be identified after testing of a sufficient number of commercial B.1.351 batches (Q1 2023).
13. To implement Relative Antigen Content stability acceptance criteria for B.1.351 strain finished product when at least 12 months of real-time stability data is available from at least 3 commercial B.1.351 batches from the Anagni finished product manufacturing site with a total of 10 batches minimum (by Q1 2024).
14. To provide the results of the leachables study conducted on three batches of B.1.351 CoV2 preS dTM Filled Product (Q1 2023).

*Some recommendations derive from the D614 submission but are still applicable for the current B.1.351 submission and therefore the data should be obtained with the B.1.351 strain, where applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Vidprevtyn Beta (B.1.351) is a recombinant protein subunit vaccine to SARS-CoV-2 Beta variant virus and is built on prefusion-stabilized Spike (S) delta TM of SARS-CoV-2 as active substance. The vaccine formulation includes the AS03 adjuvant.

The non-clinical studies conducted refer also to vaccine VidPrevtyn CoV2 preS dTM-AS03 (D614). This relates to the applicant's initial strategy to seek a marketing authorisation for VidPrevtyn (Wuhan based) as a vaccine to be used for primary series and as a booster.

In the non-clinical studies, effective doses were re-calculated based on new assays which differentiate structurally correct CoV2 preS dTM trimers from host cell proteins (HCP) impurities. When appropriate, the non-clinical studies will refer to targeted and effective doses. The differences between the targeted and the effective dose levels correspond to an excess HCP content.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The primary pharmacodynamic studies for VidPrevtyn CoV2 preS dTM-AS03 (D614) was characterized through studies conducted in mice, non-human primates and hamsters.

CoV2 preS dTM-AS03 (D614) in mice

Immunogenicity of CoV2 preS dTM-AS03 (D614) was assessed in two studies in mice: Swiss Webster mice (CoV2-02_Ms study) and BALB/c mice (CoV2-03_Ms study).

In the first study, groups of 10 outbred mice (Swiss Webster) were administered twice (day 0 and day 21) at varying dose levels from targeted 0.167 µg to 4.5 µg/dose (recalculated to effective 0.04 µg to 1.8 µg/dose), in the absence or presence of AS03 or AF03 at 1/10 of the intended human dose. No or very low IgG and PRNT50 responses were induced by the non-adjuvanted vaccine, whereas the AF03-, AS03-adjuvanted CoV2 preS dTM vaccines elicited high IgG responses after 1 injection across all dose levels tested. The IgG responses were further increased by the second injection (8-fold- difference between D21 and D36). Moreover, a slight dose-effect was observed on the S-specific IgG responses and on the neutralising antibody responses across the targeted antigen dose range tested from 0.167 to 4.5 µg. The CoV2 preS dTM-AS03 (D614) vaccine elicited both S-specific IgG1 and IgG2a responses indicating presence of Th2- and Th1-associated Ab responses with a Th2 bias as previously documented in published literature for oil-in-water emulsion adjuvants in mice. No or low cellular responses were detected.

In the second study, groups of 5 Balb/c mice were immunized twice (D0 and D14) with adjuvanted AF03 or AS03 vaccines with a targeted dose of 4.5 µg (effective dose of 1.8 µg). Control groups received AF03 alone of a mRNA/LNP vaccine (Th1-inducing vaccine control). Ten days after the second immunization, S-specific T cells secreting Th1 (IFN-γ, TNF-α, IL-2) and Th2 (IL-4 and IL-5) cytokines were determined. S-specific CD4 T cells were detected at low levels in the CoV2 preS dTM-AS03 vaccine immunized mice, with a predominance of TNF-α secreting cells (Th1) (around 0.1%), and some IL-5 secreting cells (Th2) (around 0.05%, above levels in naïve controls). The cytokine profile suggests a mixed Th1/Th2 response induced by the CoV2 preS dTM-AS03 vaccine in BALB/c mice. No S-specific CD8 T cell responses were detected.

CoV2 preS dTM-AS03 (D614) in non-human primates

Immunogenicity and efficacy of CoV2 preS dTM-AS03 (D614) were assessed in two non-human primate studies: CoV2-01_NHP and CoV2-04_NHP.

In the first study (CoV2-01_NHP), groups of 6 rhesus macaques (3-7 years-old, males and females) received twice (on D0 and D22) the CoV2 preS dTM-AS03 vaccine through intramuscular route, either 5 or 15 µg targeted dose (1.3-2 µg and 3.9-6.1 µg effective doses), the CoV2 preS dTM alone (15 µg targeted dose), or were left unvaccinated (as control with PBS). The rhesus macaques were challenged 28 days post-dose 2 with 10^6 PFU of SARS-CoV-2 (USA-WA1/2020 strain) by both, intranasal and intratracheal routes.

This study included passive transfer studies to hamsters. Golden Syrian hamsters were randomized into five groups (4M and 4F). Total IgG were isolated from plasma collected three weeks post-dose 2 in the AS03-high dose group or naïve NHP, and passively transferred to naïve hamsters intraperitoneally one day prior to challenge.

In immunized macaques, no significant dose effect was observed for the tested dose range, but the second dose effect and the AS03 adjuvanting effect were clearly demonstrated by a significant increase in humoral (IgG binding, virus-neutralising antibodies) and CD4 T cell responses to the vaccine antigen, including prefusion S protein and specific subdomains such as receptor binding domain (RBD). The neutralising antibody titres against 614D strain were found generally higher than those measured for a panel of human convalescent sera. Titres of neutralisation against variants of concern B.1.351 and P.1 (B.1.1.28) significantly declined (around 5-fold reduction), which could be expected. High level of cross-neutralising activity against the B.1.1.7 and B.1.429 variants was observed. S-specific CD8 T cell responses were undetectable in most NHPs.

With respect to protection, both antigen doses of CoV2 preS dTM-AS03 vaccine showed protection in NHPs against a moderate SARS-CoV-2 viral challenge (Wuhan, D614 strain), four weeks post-dose 2. No viral replication was detected in the lungs on D2 and D4 post-challenge and no viral N protein was detected in the lungs at necropsy (D7 to D9 post-challenge). Moreover, neither increase in lung inflammation, nor any clinical signs linked to the SARS-CoV-2 infection were observed in the CoV2 preS dTM-AS03 vaccine groups compared to naïve control and unadjuvanted vaccine groups. However, the virus used for the challenge was characterized as attenuated (post-study finding). The PBS control group of animals showed only partial infection post-challenge. Therefore, evaluation of efficacy of CoV2 preS dTM-AS03 vaccine was repeated at VRC (CoV2-04_NHP study) against a wild type, non-mutated, highly virulent viral stock (NR-53780). In relation to the transfer study to hamsters, adoptive transfer of pooled IgGs, purified from NHPs to hamsters, strongly protected hamsters from body weight loss after IN challenge with $3x10^4$ PFU of a highly virulent SARS-CoV-2 stock (viral stock: NR-53780). Histopathology examination of the hamster lungs was not performed, and only measurements of viral load in the upper respiratory tract (URT) were conducted and reported, which is not relevant to assess vaccine protection in this animal model.

In the second study (CoV2-04_NHP), two groups of 8 macaques (4-14 years) previously immunised with measles, were IM immunized on D0 and D21 with a target dose of CoV2 preS dTM of either 5 or 15 µg (4 and 12 µg effective doses respectively) per animal with AS03 as adjuvant, or diluent (placebo). All rhesus macaques were challenged 21 days post-dose 2 with 3 x 10^6 PFU of SARS-CoV-2 (USA-WA1/2020 strain, qualified stock) by both IN and IT routes.

Both effective dose levels elicited high systemic antibody responses against S protein, RBD and NTD subdomains. The post-dose 1 S-specific IgG were improved by dose 2, with an increase in titres and avidity. In addition, mucosal S-specific IgG responses were detected post-dose 2 in the lungs and nares of vaccinated animals. 2 IM injections elicited high titres of functional antibodies measured in

various assays, and these titres were significantly higher than those measured for two panels of human convalescent sera. There was high level of cross-neutralisation of the B.1.1.7 (Alpha) variant, but neutralisation of B.1.351 (Beta) variant was lower compared to titres against D614G parental virus (5 to 10-fold drop). A mixed Th1/Th2 profile of S-specific CD4 T cell responses and S-specific CD4 Tfh cells were also evidenced. CD8 T cell responses were not detected.

In terms of efficacy, the study showed that two immunizations with low or high dose CoV2 preS dTM-AS03 vaccine conferred robust protection against viral replication in the lower and upper airways after a virulent challenge with the parental SARS-CoV-2 strain (qualified stock). A strong reduction of the viral replication was demonstrated on D2 and D4 in the two vaccine groups and no viral replication was detected 4 days post-challenge in the lungs and nares from the high dose group indicating a stronger and faster viral clearance in this group.

7 days post-challenge, lung pathology and inflammation were reduced in vaccinated macaques compared to naïve macaques. No histopathological changes of the lungs nor increase in inflammatory cytokines or chemokines (Th1/Th2) were observed 7 and 14 days post-challenge, which indicate no increased risk of Vaccine Associated Enhanced Respiratory Disease (VAERD).

<u>CoV2 preS dTM-AS03 (D614) in hamsters</u>

Immunogenicity and efficacy of CoV2 preS dTM-AS03 (D614) were also assessed in one study in hamsters (CoV2-02_Hm study). Groups of 8 Golden Syrian hamsters were immunized once or twice (three weeks apart) with a target dose of CoV2 preS dTM of either targeted 0.75 or 2.25 µg/dose (effective dose 0.2 or 0.6 µg/dose at D0, and 0.1 or 0.3 µg/dose at D21) with or without adjuvants (AF03 or AS03). A group of eight animals received PBS only to serve as a non-vaccinated control (placebo). On D56 (five weeks post last injection), all hamsters were inoculated intranasally with 2.3 10^4 PFU of SARS CoV-2 with same attenuated viral strain as used in the NHP challenge study (CoV2-01_NHP).

Results from hamster model are generally consistent with those from mice and NHPs, demonstrating high immunogenicity of the CoV2 preS dTM-aduvanted vaccine formulation. All CoV2 preS dTM vaccine formulations produced Spike-specific IgG responses after one injection, but low or no pseudovirus neutralising Ab titres. After the second dose, all vaccine treated groups showed increases in S-specific IgG titres and pseudoviral neutralising antibodies. The adjuvant effect was observed on neutralising titres after 2 injections.

Following challenge, two injections of CoV2 preS dTM, unadjuvanted or formulated with AF03 or AS03, provided protection against viral challenge with SARS-CoV-2 (clade 19, D614), carried out 5 weeks after the last immunization. A minor but significant reduction of body weight loss was detected for the high dose CoV2 preS dTM-AF03 group. In contrast to the PBS control group, protection was demonstrated in all vaccine groups after two injections as the viral replication was controlled by D7 and reduced on D4 post-challenge in nares and lungs. Also, all vaccine formulations were able to reduce lung lesions regardless of the antigen dose in the 2-dose cohort, while high pathology scores were observed in the lungs of the PBS control group. No sign of vaccine-associated enhanced disease was observed for the CoV2 preS dTM-AS03 candidate.

<u>CoV2 preS dTM-AS03 (D614, B.1.351 and D614+B.1.351) in hamsters</u>

Immunogenicity and efficacy were studied in hamsters (CoV2-03_Hm). In this study, the monovalent CoV2 preS dTM-AS03 (D614) and (B.1.351) vaccines and the bivalent CoV2 preS dTM-AS03 vaccine (D614+B.1.351) were analysed in SARS-CoV-2 in naïve female Golden Syrian hamsters (n=8/group), 6-8 weeks old. The animals were injected via the intramuscular route two doses (D0 and D21). 1 µg monovalent CoV2 preS dTM-AS03 or 2 µg bivalent CoV2 preS dTM-AS03 in 100 µl/dose were administered into the animals. Three weeks after the 1st dose and two weeks after the 2nd dose, the

vaccine immunogenicity of the vaccines was analysed by measuring serum SARS-CoV-2 S-specific IgG antibody titres. After the 2nd vaccine dose on D35, neutralising antibody titres against D614G, Alpha (B.1.1.7), Beta (B.1.351) and Delta (B.1.617.2) variants were analysed. On Day 49, hamsters were challenged via the intranasal route with SARS-CoV-2 B.1.351 strain at $5x10^2$ $TCID_{50}$ for cohort A (groups 1 to 4) or NY D614G strain at $9.8x10^3$ $TCID_{50}$ for cohort B (groups 5 to 8) or B.1.1.7 strain at 1.58×10^6 $TCID_{50}$ for cohort C (groups 9 to 12). All the cohorts included a buffer control group.

In general, all three vaccine formulations showed high wild type S-protein specific IgG antibody titres and high neutralising antibody titres against several SARS-CoV-2 variants after two vaccine doses. More precisely, the bivalent vaccine induced high neutralising antibody titres against D614G, Alpha, Delta and Beta variants; the monovalent D614 vaccine induced high neutralising antibody titres against D614G, Alpha and Delta variants, but low Beta-specific titres; and the monovalent B.1.351 vaccine induced high neutralising antibody titres against Beta variant, slightly lower D614G and Alpha titre and low Delta titre. All vaccine formulation seems to be well tolerated as indicated by the stable body weight during the study. Furthermore, the viral load after challenge with D614G, Alpha or Beta variants was reduced compared to the buffer-treated control animals. In histopathological analysis of the lung, lower inflammation than in buffer-control animals, and no nucleocapsid protein expression were observed in the vaccinated animals after challenge.

<u>CoV2 preS dTM-AS03 (D614, B.1.351 and D614+B.1.351) in non-human primates</u>

Immunogenicity from the beta variant CoV2 preS dTM-AS03 monovalent (B.1.351) and bivalent (D614 + B.1.351) vaccines were studied in in naïve (CoV2-06_NHP study) and non-naïve non-human primates (CoV2-07_NHP and CoV2-08_NHP)

In the first study (CoV2-06_NHP), fifty-four adults cynomolgus macaques (males and females) from 2 to 8 years of age were randomized in nine groups of six macaques. The macaques were immunized with the three vaccine formulations (D614, B.1.351 or bivalent) at doses of 2.5, 5 and 10 µg per antigen, adjuvanted with AS03. The immunizations were performed by two IM injections three weeks apart in a volume of 0.5 mL/injection.

After two doses, all vaccine formulations induced high S- and RBD-specific IgG binding antibody titres against different SARS-CoV-2 VoC (D614, Alpha, Beta, Gamma, Delta, Omicron) independent of the dose level. Even low SARS-CoV-1 RBD-specific IgG binding antibody titres were measured in the different vaccine formulations. However, the IgG binding antibody titres declined relative fast over time in all vaccine formulations as demonstrated for the wt S-specific IgG antibody response. In addition, the applicant could show that the different vaccine formulations induce strong, dose-independent neutralising antibody titres against different VoC after two vaccine doses. The different vaccine formulations showed different response patterns. However, all tested vaccine formulations showed low neutralising antibody responses against Omicron BA.1. In line with the IgG binding antibody titres, the neutralising antibody titres declined also over time. All vaccine formulations showed comparable memory B-cell responses in PBMCs.

In the second study (CoV2-07_NHP), four groups of four (2/sex) cynomolgus macaques (4-10 years of age), previously immunized twice (21 days apart) with various COVID-19 mRNA-LNP vaccine were randomized according to sex, age, weight, mRNA vaccine construct used for the primary immunization, and their SARS-CoV-2 (D614) neutralising antibody (Nab) titres on D35 (they had positive nAb titres) to receive the booster injection of 5µg (non-adjuvanted monovalent (B.1.351) CoV2 preS dTM, AS03-adjuvanted monovalent (D614 or B.1.351) or bivalent (D614+B.1.351) CoV2 preS dTM) administered by IM route into the right deltoid was performed seven months after the first mRNA immunization.

The results from the booster study showed that one booster dose of AS03-adjuvanted CoV2 preS dTM, D614 (parental) or B.1.351 (Beta), in monovalent or bivalent (D614 + B.1.351) formulations,

significantly boosted pre-existing neutralising antibodies to levels higher than post-primary immunization. Furthermore, the booster elicited high and stable cross-neutralising antibodies covering the four SARS-CoV-2 variants of concern (Alpha, Beta, Gamma and Delta) and SARS-CoV-1 in all animals as soon as D7 whatever the vaccine formulation. Notably, the non-adjuvanted CoV2 preS dTM B.1.351 vaccine formulation also boosted and broadened the neutralising antibody responses, though at lower levels compared to the AS03-adjuvanted CoV2 preS dTM B.1.351 vaccine candidate.

In the third study (CoV2-08_NHP), five groups of 4-5 male rhesus macaques (4-10 years old) previously immunized twice (21 days apart, 7 months earlier with different CoV2 preS dTM-AS03 (D614) vaccine candidates) received a 5µg booster dose of monovalent adjuvanted vaccines D614 and B.1.351, non-adjuvanted B.1.351, and a bivalent adjuvanted vaccine (total booster dose of 5 µg or 10 µg).

The results showed that a booster injection with any of the tested vaccine formulations induced strong memory Spike-specific IgG and neutralising antibody responses against the parental D614 strain. The booster injections also extended the neutralisation to the B.1.351 variant and other tested SARS-CoV-2 variants of concern (VoC) (B.1.1.7, B.1.1.28 and B.1.617.2) and SARS-CoV-1. The non-adjuvanted CoV2 preS dTM B.1.351 vaccine formulation significantly boosted and broadened the neutralising antibody responses, although at lower levels compared to the AS03-adjuvanted CoV2 preS dTM B.1.351 vaccine candidate.

2.4.2.2. Secondary pharmacodynamic studies

No studies on the secondary pharmacodynamics have been performed, which is in accordance with applicable guidelines.

2.4.2.3. Safety pharmacology programme

No studies on the safety pharmacology have been performed, which is in accordance with applicable guidelines.

2.4.2.4. Pharmacodynamic drug interactions

No studies on the pharmacodynamic drug interactions have been performed, which is in accordance with applicable guidelines.

2.4.3. Pharmacokinetics

In accordance with WHO guidelines on non-clinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), traditional absorption, distribution, metabolism, and excretion (ADME) evaluations are not generally needed for vaccines. The safety concerns associated with vaccines are generally not related to the pharmacokinetics but are related to the potential induction of immune response.

2.4.4. Toxicology

The non-clinical toxicology program was conducted only for the parental vaccine Vidprevtyn (D614) due to the high similarity between Vidprevtyn parental D614 and Vidprevtyn Beta-specific B.1.351.

The non-clinical toxicology program consists of two repeat-dose toxicity studies and one developmental and reproductive toxicity study. All three studies were conducted in New Zealand White rabbits and in compliance with GLP.

Regarding AS03, toxicity data have previously been generated after administration alone or in combination with vaccine antigens, such as the H1N1 pandemic influenza vaccines Pandemrix and Arepanrix which contain AS03 at the same dose-level as the CoV2 preS dTM AS03 vaccine.

2.4.4.1. Single dose toxicity

No single dose toxicity studies were performed by the applicant, which was agreed.

2.4.4.2. Repeat dose toxicity

Data from two repeat dose toxicity studies were provided: 5003471 and 5003591. The first study (5003471) was performed with a Ph I/II vaccine batch, whereas the second study (5003591) used an antigen batch derived from an intermediate Ph III manufacturing process. There are two main considerations with the vaccine batches: first, the host cell proteins (HCP) impurity level is higher than in the clinical production batches. This is acceptable since a high HCP impurity level represent a worst-case scenario. The second issue, similarly as in some of the primary pharmacodynamic studies, the actual antigen concentration was considerably lower than targeted (effective concentration for the first and second studies was only 26% and 48% of target, respectively).

The four-week repeat-dose toxicity in rabbits with 2-week recovery (5003471) was a study that consisted of two phases: a single dose and a repeat-dose (3 doses) phase where animals were vaccinated every two weeks (D1, D15 and D29). Each of the phases included a control group (physiological saline), a group receiving only the antigen (CoV-2 preS dTM) and two groups consisting of antigen and one of the two adjuvants (AF03 or AS03). The target and effective intramuscular vaccine dose were 15 µg and 3.9 µg CoV-2 preS dTM per dose, respectively. Except for the low antigen dose, the design of the toxicity study is considered to follow the recommendations provided in relevant non-clinical WHO vaccine guidelines.

Overall, the vaccine antigen alone or with adjuvants AF03 or AS03 were well tolerated in rabbits. There were no unscheduled mortality, vaccine related effects to clinical observations, body weight, food consumption, body temperature or ocular changes. At Day 15, all animals vaccinated with antigen and adjuvant were positive for S-specific IgG antibodies while some of the animals in the unadjuvanted group were still negative. However, at Day 31 and 45, all vaccine treated animals (with or without adjuvant) were positive for S-specific IgG antibodies. Animals treated with antigen and adjuvant generally had significantly higher ELISA titres than those vaccinated without adjuvant. The only toxicological effects considered related to the vaccine were transient and non-adverse changes in haematology, coagulation, and clinical chemistry parameters indicative of a transient acute phase response/inflammation. These changes correlated with non-adverse histopathological 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 CoV-2 preS dTM with either adjuvant. In both phases, increases in spleen weights were observed. This correlated with increased lymphoid cellularity in both the interim (recovery only) and repeat-dose phases. Increased lymphoid cellularity was also observed in the iliac, inguinal, and sacral lymph nodes.

The two-week repeat-dose toxicity study in rabbits with 2-week recovery (5003591) was aimed to evaluate the local tolerance and systemic toxicity of two doses two weeks apart (D1 and D15) with CoV-2 preS dTM-AS03. The target and effective intramuscular vaccine dose were 5 µg and 2.4 µg CoV-

2 preS dTM per dose, respectively. Except for the low antigen dose, the design of the toxicity study and measured parameters are considered to follow the recommendations provided in relevant non-clinical WHO vaccine guidelines.

Overall, the vaccine with adjuvant AS03 was well tolerated in rabbits. There was no unscheduled mortality, or vaccine-related effects to clinical observations, body weights, food consumption or ocular changes. Only slight increases in mean body temperature were noted for both sexes of vaccine-treated animals 24 hours after the first and second dose. It was a slight increase with general overlap of individual values with the range of the control and pre-study values. This effect may be related to the vaccine since vaccine-induced increases in body temperature are not uncommon.

A higher incidence of very slight to slight erythema and/or oedema on Days 1 and 15 was observed at the injection sites in vaccinated animals. These changes were transient and had generally resolved by 4 days following injection. Toxicological effects detected were transient and consisted of non-adverse changes in haematology, coagulation, and clinical chemistry parameters indicative of a transient acute phase response/inflammation. These changes correlated with non-adverse histopathological findings of increased severity of mixed cell inflammation (subacute/chronic) and presence of fibrosis/fibroplasia at the injection site and in the overlying skin of animals administered the test item. In the main and recovery group of vaccinated animals, increases in spleen weights (~50%) were observed in males. This correlated with increased lymphoid cellularity only in the recovery group (Day 29). An increase in adrenal weights (~40%) in vaccinated males was reported in the main group (D17). However, this finding was not correlated with any histopathological changes. Similar adrenal weight changes were not observed at the end of recovery (Day 29), nor in the previous repeat dose toxicity study. Increased lymphoid cellularity and/or mixed cell infiltration was also observed in the iliac, inguinal, and sacral lymph nodes in both main and recovery groups.

2.4.4.3. Genotoxicity

The adjuvant AS03 is already an approved adjuvant in the EU. Based on the data provided, AS03 did not show any genotoxic potential.

2.4.4.4. Carcinogenicity

No carcinogenicity studies have been performed in accordance with the WHO Guidelines on Non-clinical Evaluation of Vaccines (2005) and Guidelines on the Non-clinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines (2014). The absence of these studies is considered acceptable.

2.4.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity (DART) study was carried out in rabbits (20288238). This was a GLP compliant study. Female NZW rabbits were administered intramuscularly with the CoV-2 preS dTM adjuvanted with AS03 (formulation equivalent to the phase 3 manufacturing process material) in 0.5 mL volume (dosage at 10 and 15 µg CoV-2 preS dTM antigen, respectively), at 24 and 10 days pre-mating and on gestation days (GD) 6, 12 and 27. Control female animals received placebo on the same occasions.

The repeated administrations of CoV-2 preS dTM-AS03 at dosages indicated above did not adversely affect reproductive or developmental parameters, with no vaccine-related adverse effects identified on the mating performance, female fertility, embryonic and foetal development and growth, parturition, and survival and development of the offspring through postnatal day 35.

Furthermore, in all CoV-2 preS dTM-AS03 vaccinated dams, high S-specific IgG response was detected with no dose-response observed. Similar high anti-S IgG titres were also detected in F1 generation foetuses and offspring from the vaccinated dam groups, thus confirming the transfer of maternal antibodies during the gestational period and also in the postnatal stages of development.

2.4.4.6. Local Tolerance

No stand-alone local tolerance study was conducted. This is acceptable and in line with relevant guidance on non-clinical vaccine development since local tolerance was evaluated in repeated dose toxicity studies.

2.4.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100), due to their nature vaccines are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this application for Marketing Authorisation, which is considered acceptable.

2.4.6. Discussion on non-clinical aspects

The pharmacology of Vidprevtyn (D614 and B.1.351 vaccine variants) has been adequately addressed in mice, hamsters and NHP, including extensive characterization of immunogenicity profile and the clear demonstration of protective activity of the vaccine following primary dose series. In each animal model, the beneficial effects of the second dose administration and AS03 adjuvant were shown, supporting choice of 2-doses regimen for primary vaccination and inclusion of AS03 in vaccine formulation. A slight dose effect was shown on the parental D614 vaccine immunogenicity in outbred mice, but no significant dose effect observed in NHP in dose ranges tested. However, the protection data in NHPs revealed a trend for a stronger and faster viral clearance in the high dose group (12 µg) compared to low dose group (4 µg).

Intramuscular administration of a single dose of various vaccine formulations (non-adjuvanted monovalent B.1.351, AS03-adjuvanted monovalent D614 & B.1.351 or bivalent), 7 months after completion of the primary vaccination in the vaccine-primed macaques, induced a strong recall of the initial neutralising antibody responses against the parental D614G strain, and extended the neutralisation to B.1.351 (Beta) variant and all other known variants of concerns (B.1.1.7/Alpha, B.1.1.28/Gamma, B.1.617.2/Delta and Omicron), as well as to SARS-CoV-1. The high IgG titres were stable between D7 and D28 post-boost, and then declined slowly until 6 months, the final timepoint analysed.

Of importance, animal challenge studies in hamsters and NHP showed protection when compared to control groups. No sign of the potential risk of vaccine-associated enhanced lung pathology was observed.

There are no studies performed with Vidprevtyn D614, B.1.351 for the secondary pharmacodynamics, the safety pharmacology, and the pharmacodynamic drug interactions. Similarly, no pharmacokinetic studies were carried out with Vidprevtyn. The omission of these studies is in accordance with the applicable regulatory guidelines and is thus acceptable.

The non-clinical toxicology program was conducted only for the parental vaccine Vidprevtyn (D614) due to the high similarity between Vidprevtyn parental D614 and Vidprevtyn Beta-specific B.1.351. This is acceptable.

In the two pivotal repeat-dose toxicity study, Vidprevtyn D614 was overall well tolerated and safe in young rabbits. The test article itself as well as the adjuvant AS03 and AF03 did not show adverse toxicity in the animals after intramuscular injection.

Both toxicity studies were GLP-compliant, and their study designs were in general in agreement with the applicable guidelines. However, some limitation of both repeat-dose toxicity studies is the antigen contents/dose administered to animals (3.9 µg and 2.4 µg respectively), which were lower than the intended human dose (10 µg). This was due to unintended calculation mistake. The impact of antigen content on vaccine-induced immune responses is assumed to be much smaller than did the AS03 adjuvant and the dosing regimen, as clearly revealed by the results of pharmacodynamics studies in mice and NHPs. On the µg antigen/body weight basis, the administered antigen amount to rabbits was 6.5-fold higher compared to human. The interpretation of the study results and the following conclusions were not affected by the lower antigen amount.

The clinical pathology findings in both repeat-dose toxicity studies are similar. After injecting of the test article, the rabbits showed overall mild toxicity. In general, the observed findings were more severe in animals injected with the adjuvanted vaccine (AF03 or AS03) than injected with the non-adjuvanted vaccine. Most of the clinical blood parameters were minimal to mild, except for the CRP concentrations, which showed a marked increase in the vaccinated animals. These changes were of transient nature except for white blood cells, which were still slightly increased in rabbits treated with adjuvanted vaccine after the 2-week recovery period.

The microscopic and macroscopic pathology of the rabbits revealed findings in the spleen (increased spleen weight, mixed cell inflammation), lymph nodes (enlargement, mixed cell inflammation) and injection site/overlying skin (mixed cell inflammation, swelling, haemorrhage, fibrosis). As expected, the severity of the findings was higher in adjuvanted vaccine groups than in the non-adjuvanted vaccine group. Most of the pathology findings were still observed after the 2-week recovery period, indicating a chronicity of the results and an ongoing immune reaction. However, the observed findings were in general slightly milder than shortly after the last dose.

In a GLP-compliant DART study, vaccination of rabbits with parental CoV-2 preS dTM-AS03 D614 did not adversely affect the mating performance, female pregnancy, embryonic and foetal development, parturition or post-natal development.

In conclusion, the VidPrevtyn was overall well tolerated and safe in rabbits. Both adjuvanted vaccine formulations inducted higher immunogenicity compared to the non-adjuvanted vaccine and thus, more severe reactions were seen. The observed findings were expected and common for adjuvanted vaccines injected by the intramuscular route.

2.4.7. Conclusion on the non-clinical aspects

No major non-clinical issues are identified in this application. Several concerns were identified and have been properly addressed by the applicant. The CHMP is of the view that non-clinical data reveal no special hazard for humans based on appropriate studies of repeat dose toxicity and reproductive and developmental toxicity. SARS-CoV-2 prefusion Spike delta TM protein, recombinant (B.1.351 strain) is not expected to pose a risk to the environment.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Identifiers	Study Design and Type of Control	Number of Study participants	Study Status; Type of Report
VAT00013 Eudra CT**:** 2021-004550-33	Multicenter, single-blind, randomized, 3-arm parallel-group trial stratified by age	Total participants: 247 Arm 1 (BNT162b2): 82 Arm 2 (Sanofi D614): 85 Sanofi B.1.351: 80	Ongoing; [VAT00013 D28 Interim CSR, v1.0]
VAT00001 BB-IND: 23143 WHO UTN: U1111-1250-4757	Phase 1/2, first-in-human, randomized, parallel group, placebo-controlled, modified double-blind (observer-blind), dose-ranging, multi-center study with a Sentinel Safety Cohort and Early Safety Data Review (ESDR)	441 participants (299 aged 18 to 49 years, and 142 participants aged 50 years or older; 378 randomized to a vaccine group and 63 to placebo). Cohort 1: 170 participants (34 each in Group 1 [Low Dose+AF03], Group 2 [Low Dose+AS03], Group 3 [High Dose+AF03], Group 4 [High Dose+AS03] and Group 5 [Placebo]). Cohort 2: 271 participants (28 in Group 6 [Low Dose+AF03];84 in Group 7 [Low Dose+AS03]; 27 in Group 8 [High Dose+AF03]; 85 in Group 9 [High Dose+AS03]; 18 in Group 10 [High Dose]; 29 in Group 11 [Placebo]).	Ongoing; [VAT00001 Interim CSR v1.0, dated 17 February 2021]
VAT00002 Primary series (Phase 2) BB-IND: 23143 WHO UTN: U1111-1251-4616 EudraCT: 2020-003370-41	Phase 2, randomized, modified double-blind (observer-blind), multi-center, dose-finding	722 participants (360 aged 18 to 59 years and 362 aged 60 years and older; 241 in Group 1, 239 in Group 2, and 242 in Group 3).	Ongoing; [VAT00002 Interim CSR, v1.0, dated 20 August 2021] [VAT00002 Original Cohort long-term safety follow-up

			Section 8 tables, v1.0 dated 01 March 2022]
VAT00002 Booster (Phase 3) BB-IND: 23143 WHO UTN: U1111-1251-4616 EudraCT: 2020-003370-41	Phase 3, randomized, non-randomized open-label and modified double-blind (observer-blind), multi-center	Total participants for Supplemental Cohort 1 Brief CSR: 1285 participants Supplemental Cohort 1: 674 participants primed with non-Sponsor COVID-19 vaccines to receive a single booster dose of CoV2 preS dTM-AS03 (D614). Supplemental Cohort 2: - 705 participants primed with the Sponsor and non-Sponsor COVID-19 vaccines to receive a single booster dose of CoV2 preS dTM-AS03 (B.1.351); - 621 participants primed with non-Sponsor COVID-19 vaccines to receive a single booster dose of CoV2 preS dTM-AS03 (D614 + B.1.351); - 78 participants primed with the Sponsor vaccine to receive a single booster dose of CoV2 preS dTM-AS03 (B.1.351). Supplemental Cohorts 1 and 2 Comparator Group: 479 participants (18-55 years of age only) SARS-CoV-2 naïve, unvaccinated, participants to receive 2 doses of CoV2 preS dTM-AS03 (D614) for primary immunisation.	Ongoing; [VAT00002 Supplemental Cohort 1 Brief Interim CSR v1.0, dated 15 March 2022] [VAT00002 Supplemental Cohort 1 Addendum to the Brief Interim CSR v1.0, dated 14 June 2022] [VAT00002 Supplemental Cohort 2 Brief Interim CSR, v1.0, dated 08 June 2022] [VAT00002 Cohort 2 Additional Analysis, v1.0, dated 13 July 2022]
VAT00008 (Stage 1 and Stage 2) BB-IND: 23143 WHO UTN: U1111-1264-3238	Phase 3, randomized, modified double-blind, placebo-controlled, multi-stage, multi-center, multi-country	Stage 1: Total: 10 139 participants CoV2 preS dTM-AS03: 5061 participants Placebo group: 5078 participants Stage 2: Total: 13 002 participants	Ongoing; [VAT00008 Interim Brief CSR (Stage 1) v1.0, dated 11 March 2022] [VAT00008 Addendum

		CoV2 preS dTM-AS03: 6512 participants Placebo group: 6490 participants	Report (Stage 1) v1.0, dated 11 July 2022] [VAT00008 Interim Brief CSR (Stage 2) v1.0, dated 21 July 2022]

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

No pharmacokinetics studies have been conducted for VidPrevtyn Beta. This is because pharmacokinetics studies are generally not needed for vaccines, consistent with current Guidelines on clinical evaluation of vaccines.

2.5.2.2. Pharmacodynamics

The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005). As immunogenicity data of this vaccine are used to support the authorisation of this vaccine, immunogenicity data are included under the clinical efficacy section.

Assays

In study VAT00013, the study samples were verified by the CRB APHP SU (central biological resources center) and tested by Unité des Virus Emergents, UMR190, IHU Méditerranée Infection.

Neutralising antibodies against European strain of SARS-CoV-2 and variants of interest (Pr X. De Lamballerie, IHU Méditerrannée, Marseille, France) to support primary immunogenicity endpoints

The microneutralisation test is performed according to the published protocol (Gallian P. et al, 2002). The test uses a clinical strain of SARS-CoV-2 (100 TCID50/well), Vero E6 cells and a readout by the reading of the cytopathic effect (CPE) at 5 days post-infection. It is a VNT100 (100% of wells lysed in quadruplicate format). According to the Applicant, its performance is very close to a PRNT90 test. The test is automated in the NSB3 laboratory for all dilution and distribution steps and for the reading of the CPE. The dilutions tested are 20, 40, 80, 160, 320, 640, 1280. The range is extended if a titre of 1280 is observed at first intension. This assay was not validated and therefore not suitable for intended purpose. As a result, samples tested with this assay were subject to a re-test using the validated Monogram Psv assay.

Anti SARS-CoV-2 antibodies anti-Spike (Pr X. De Lamballerie, IHU Méditerrannée, Marseille, France) to support secondary immunogenicity endpoints

The CE-marked ELISA kit from Euroimmun (Luebeck, Germany) targets anti-SARS-CoV-2 IgG antibodies directed against the S1 domain of the virus' Spike protein is used according to the recommendations given by the manufacturer. As justified by the Applicant, this method is frequently cited in peer-reviewed primary literature and exhibits diagnostic sensitivity, specificity, and correlation to plaque reduction neutralisation test (PRNT50) and the « First WHO International Standard for anti-SARS-CoV-2 immunoglobulin » (NIBSC Code: 20/136), demonstrating suitability for its intended use

for the quantitative detection of antibodies against the S1 antigen of SARS-CoV-2 to support a secondary endpoint.

ELISpot IFN CD4 and CD8 (Pr E. Tartour, laboratoire d'immunologie biologique, Hôpital Européen Georges Pompidou, APHP, Paris, France) to support secondary endpoints / ancillary subgroup analysis

This test was performed in a subset of participants from each booster group. ELISpot uses a commercially available kit from Mabtech or C.T.L. The peptides are purchased from JPT technologies. This technique has been accredited by the French accreditation agency Cofrac.

In study VAT00002, immunogenicity assessments for D614G variant and for Beta (B.1.351) variant used the validated SARS-CoV-2 pseudovirus neutralising assay performed at Monogram laboratory.

Immunogenicity assessment for the Delta (B.1.617.2) variant in Study VAT00002 – Supplemental Phase III Cohort 2 used the SARS-CoV-2 pseudovirus neutralisation assay performed at Nexelis laboratory. The Applicant confirmed that the status of the Nexelis assay used to measure neutralising antibodies against the Delta strain was exploratory at the time when testing of blood samples in clinical trials was carried out. Since then, the Nexelis assay has been validated.

The following three different assays in 3 different laboratories were used to perform immunogenicity assessment for the Omicron strains BA.1, BA.2, and BA.4. The Monogram assay for the assessment of the immune response against BA.1 is qualified, whereas the assays for BA.2 and BA.4 immune response assessment are explorative.

- Monogram: Lentivirus-based pseudovirus neutralisation assay (qualified assay), Omicron BA.1
- Institut Pasteur (Olivier Schwartz Lab): S-fuse rapid live-virus neutralisation assay (exploratory assay), Omicron BA.1 and BA.2
- National Institute of Communicable Diseases (NICD), South Africa (Penny Moore Lab): Lentivirus-based pseudovirus neutralisation assay (exploratory assay), Omicron BA.1 and BA.4.

2.5.3. Discussion on clinical pharmacology

In the context of vaccines, PK studies are not required because the PK is not considered informative towards the determination of an optimal dose and the metabolic pathways of vaccines are generally understood.

The applicant has performed several assays to characterise the vaccine-induced immune response. At the present time, there is no established immunological correlate of protection against SARS-CoV-2 infection. The evaluation of the protective effect of VidPrevtyn Beta is based on bridging clinical immunogenicity results to Pfizer/BioNTech vaccine which has been shown to be protective against COVID-19. No efficacy studies with VidPrevtyn Beta have been performed.

In pivotal study VAT00013, the applicant confirmed that the microneutralisation assay used to support the primary endpoints is lacking an official validation which is considered critical for assessment of the pivotal study results. The applicant provided a re-analysis based on re-tested samples using the validated Monogram assay. A validated Monogram laboratory SARS-CoV-2 pseudovirus neutralisation (PsVN) assay against D614G, Omicron BA.1 and BA.4/5 variant strains was used. The primary and secondary objectives of the VAT00013 post-hoc analyses were assessed using the results generated following Monogram PsVN assay testing. This was acceptable.

In VAT00002, the bioanalytical method used were acceptable for their intended purposes.

2.5.4. Conclusions on clinical pharmacology

The pivotal evidence for this MAA is based on induction of neutralising antibodies by VidPrevtyn Beta vaccination compared to vaccination with the authorised mRNA vaccine with known efficacy. This is acceptable. The immunogenicity results used to infer efficacy are presented in the clinical efficacy.

2.5.5. Clinical efficacy

The clinical development plan of CoV2 preS dTM-AS03 vaccine is based on the evolution of SARS-CoV-2 global pandemic. The vaccine was firstly developed with the global spreading of the original D614 strain. The CoV2 preS dTM-AS03 (D614) vaccine was administered as a 2-dose primary series and as a single booster dose in clinical studies. Following the emergence and global spread of new variants, the Beta (B.1.351) variant strain was also introduced in the clinical development of the vaccine either as a monovalent (MV) vaccine (CoV2 preS dTM-AS03 [B.1.351] vaccine) or as a bivalent (BV) vaccine (CoV2 preS dTM-AS03 [D614 + B.1.351] vaccine). As part of an amendment to the VAT00002 Original Phase II Cohort, Supplemental Phase III Cohorts were incorporated into the study to evaluate the potential use of CoV2 preS dTM-AS03 vaccine to boost responses in individuals previously vaccinated with other platforms (2 mRNA-and 2 adenovirus-vectored COVID-19 vaccines).

The clinical efficacy of VidPrevtyn Beta is intended to be inferred by immunobridging of immune responses to an authorised COVID-19 vaccine, for which vaccine efficacy has been established.

2.5.5.1. Dose response study(ies)

VAT00001 is a Phase I/II, randomized, modified double-blind, placebo-controlled, parallel group, first-in-human, dose-ranging, multi-center study with a Sentinel Safety Cohort and Early Safety Data Review (ESDR) evaluating the safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations (with or without adjuvant) conducted in the United States in healthy seronegative adults 18 years of age and older.

This study was used as the basis of the selection of a 2-dose schedule, and the selection of the AS03 adjuvant to proceed to the phase 3 efficacy trial for VidPrevtyn (D614) primary series. The dose of the vaccine was approximately 4-6 fold lower than planned. Intended doses were 5µg for the low dose and 15µg for the high dose, while effective doses were 1.3µg and 2.6µg respectively. Study VAT00002 - Original Phase II Cohort was used to decide on progression to the Phase III efficacy study VAT00008 and to select an antigen dose formulation for further clinical development of the primary series and booster.

VAT00002, Phase II, randomized, modified double-blind, multi-center, dose-finding study conducted in adults 18 years of age and older to evaluate the safety, reactogenicity, and immunogenicity of 2 injections of 3 different antigen doses (effective doses of 5 µg, 10 µg, and 15 µg) of CoV2 preS dTM-AS03 vaccine administered 21 days apart by intramuscular (IM) route.

The primary immunogenicity objective was to assess the neutralising Ab profile 14 days after the last vaccination (up to D36) in SARS-CoV-2-naïve (hereafter referred to as "naïve") participants from each study intervention group. The secondary immunogenicity objective was to assess the neutralising Ab profile of the vaccine at D22 in naïve and non-naïve participants.

A total of 722 participants 18 years of age and older were randomized to one of the 3 dose groups in a 1:1:1 ratio.

Approximately 81% of the participants were from the US and 19% of participants were from Honduras. The racial origin of participants was mostly "White" (63.9% of participants), followed by "American Indian or Alaska Native" (9.2% of participants), "Black or African American" (7.8% of participants), and "Asian" (4.6% of participants). The study population was predominantly comprised of those of "Not Hispanic or Latino ethnicity" (71.4% of participants).

Overall, the baseline demographics were similar across treatment groups, between age groups, and across the analysis populations.

The number of participants included in each analysis population is provided below. Among the 721 randomized participants from the FAS, 611 participants were included in the PPAS (295 participants aged 18-59 years and 361 participants aged ≥ 60 years): 201 participants in Group 1, 207 in Group 2, and 203 in Group 3. Of the PPAS, 521 participants were included in the PPAS Naïve-D01+D22 since they tested negative by the anti-S immunoassay on D01 serum sample, by the anti-N immunoassay on D01 and D22 serum samples, and by nucleic acid amplification test (NAAT) on D01 and D22 respiratory samples.

Table 1: VAT00002 - Original Phase II Cohort: Analysis sets by randomized group, age group, prior SARS-CoV-2 infection at baseline and high-risk medical condition group - Randomized participants

		Group 1 (5 µg)	Group 2 (10 µg)	Group 3 (15 µg)	All
Age group		**n/M (%)**	**n/M (%)**	**n/M (%)**	**n/M (%)**
All	**FAS**	240/241 (99.6)	239/239 (100)	242/242 (100)	721/722 (99.9)
	PPAS	201/241 (83.4)	207/239 (86.6)	203/242 (83.9)	611/722 (84.6)
18-59 years	**FAS**	121/121 (100)	119/119 (100)	120/120 (100)	360/360 (100)
	PPAS	98/121 (81.0)	99/119 (83.2)	98/120 (81.7)	295/360 (81.9)
>= 60 years	**FAS**	119/120 (99.2)	120/120 (100)	122/122 (100)	361/362 (99.7)
	PPAS	103/120 (85.8)	108/120 (90.0)	105/122 (86.1)	316/362 (87.3)
Prior SARS-CoV-2 infection at baseline					
Naïve-D01	**FAS**	211/211 (100)	210/210 (100)	207/207 (100)	628/628 (100)
	PPAS	175/211 (82.9)	185/210 (88.1)	180/207 (87.0)	540/628 (86.0)
Non-Naïve-D01	**FAS**	26/27 (96.3)	27/27 (100)	32/32 (100)	85/86 (98.8)
	PPAS	23/27 (85.2)	22/27 (81.5)	20/32 (62.5)	65/86 (75.6)
Prior SARS-CoV-2 infection at second injection					
Naïve-D01+D22	**FAS**	198/198 (100)	198/198 (100)	198/198 (100)	594/594 (100)
	PPAS	168/198 (84.8)	177/198 (89.4)	176/198 (88.9)	521/594 (87.7)
Non-Naïve-D01/D22	**FAS**	33/34 (97.1)	31/31 (100)	36/36 (100)	100/101 (99.0)
	PPAS	28/34 (82.4)	26/31 (83.9)	23/36 (63.9)	77/101 (76.2)
High-risk medical condition group					
YES	**FAS**	151/152 (99.3)	143/143 (100)	143/143 (100)	437/438 (99.8)
	PPAS	124/152 (81.6)	126/143 (88.1)	119/143 (83.2)	369/438 (84.2)
High-risk medical condition group					
NO	**FAS**	89/89 (100)	96/96 (100)	99/99 (100)	284/284 (100)
	PPAS	77/89 (86.5)	81/96 (84.4)	84/99 (84.8)	242/284 (85.2)

n: number of participants fulfilling the item listed.
M (for FAS and PPAS): number of participants randomized in each vaccine and subgroup
Note: a participant may be associated with more than one criterion.
Source: Modified from 5.3.5.1 VAT00002 Interim CSR, Section 8, Table 8.9

Table 2: Criteria for SARS-CoV-2 Naïve and Non-Naïve at D01 or both D01 and D22 timepoints in VAT00002 study - Original Phase II Cohort

Participant Analysis Sets	Description
SARS-CoV-2 Naïve at baseline (Naïve-D01)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by the anti-N immunoassay on D01 serum sample AND • Negative NAAT for SARS-CoV-2 on respiratory sample collected on D01
SARS-CoV-2 Non-Naïve at baseline (Non-Naïve-D01)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 serum sample OR • Positive NAAT for SARS-CoV-2 on respiratory sample collected on D01
SARS-CoV-2 Naïve at second injection (Naïve- D01+D22)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by anti-N immunoassay on D01 and D22 serum sample AND • Negative NAAT for SARS-CoV-2 on respiratory sample collected on D01 and D22
SARS-CoV-2 Non-Naïve at second injection (Non-Naïve - D01/D22)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 or D22 serum sample OR • Positive NAAT for SARS-CoV-2 on respiratory sample collected on D01 or D22

Abbreviations: D, Day; NAAT, nucleic acid amplification test
Source: Modified from 5.3.5.1 VAT00002 Interim CSR, Appendix 1 Clinical study protocol

Primary and secondary immunogenicity objectives were determined from 521 participants included in the PPAS Naïve-D01+D22 analysis set (i.e., naïve participants) and 77 participants included in the PPAS Non-Naïve-D01/D22 analysis set (i.e., non-naïve participants) across the 3 dosages.

The primary objective was to determine the neutralising Ab profile against the D614G variant at D36 in SARS-CoV-2 naïve participants.

A summary of the neutralising Ab profile by dose group at D01 (pre-injection) and at D36 (14 days post-injection 2) is presented below. At baseline, geometric mean titres (GMTs) were below the LLOQ for all groups. At D36, the proportion of participants with ≥ 2 and 4-fold-rise in neutralising Ab titres were > 90% in both younger and older adult age groups (18 to 59 years and ≥ 60 years) and similar across treatment groups. The proportion of responders (defined as participants who had baseline values below LLOQ with quantifiable neutralising titre above assay LLOQ at D36) was equal to the participants with ≥ 2-fold-rise in neutralising Ab titres.

Table 3: VAT00002 - Original Phase II Cohort: Summary of Neutralising Ab Profile at D36 – PPAS Naïve D01+D22

		Group 1 (5 µg) (N=168)			Group 2 (10 µg) (N=177)			Group 3 (15 µg) (N=176)		
Summary of GMT and GMTR for neutralizing Ab titers										
Age group (years)	**Time point / ratio**	**M**	**GMT/ GMTR**	**(95% CI)**	**M**	**GMT/ GMTR**	**(95% CI)**	**M**	**GMT/ GMTR**	**(95% CI)**
All	**D01**	163	20.0	(NC;NC)	171	20.0	(NC;NC)	167	20.0	(NC;NC)
	D36	165	2189	(1744;2746)	173	2269	(1792;2873)	172	2895	(2294;3654)
	D36/D01	162	107	(85.1;135)	168	110	(86.6;140)	166	141	(111;179)
18-59	**D01**	81	20.0	(NC;NC)	78	20.0	(NC;NC)	80	20.0	(NC;NC)
	D36	82	2954	(2272;3840)	81	3951	(2851;5474)	81	5142	(3800;6958)
	D36/D01	80	146	(112;190)	78	192	(137;269)	80	261	(192;354)
>= 60	**D01**	82	20.0	(NC;NC)	93	20.0	(NC;NC)	87	20.0	(NC;NC)
	D36	83	1628	(1132;2341)	92	1393	(1021;1899)	91	1736	(1264;2385)
	D36/D01	82	79.2	(55.0;114)	90	68.1	(49.7;93.2)	86	79.9	(57.9;110)
Number of participants with ≥ 2-fold-rise and ≥ 4-fold-rise of neutralizing Ab titers										
Age group (years)	**Time point**	**Fold-rise**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
All	**D36**	**≥ 2**	158/162	97.5	(93.8;99.3)	166/168	98.8	(95.8;99.9)	163/166	98.2	(94.8;99.6)
		≥ 4	157/162	96.9	(92.9;99.0)	163/168	97.0	(93.2;99.0)	162/166	97.6	(93.9;99.3)
18-59	**D36**	**≥ 2**	80/80	100	(95.5;100)	76/78	97.4	(91.0;99.7)	80/80	100	(95.5;100)
		≥ 4	80/80	100	(95.5;100)	76/78	97.4	(91.0;99.7)	80/80	100	(95.5;100)
>= 60	**D36**	**≥ 2**	78/82	95.1	(88.0;98.7)	90/90	100	(96.0;100)	83/86	96.5	(90.1;99.3)
		≥ 4	77/82	93.9	(86.5;98.0)	87/90	96.7	(90.6;99.3)	82/86	95.3	(88.5;98.7)

n: number of participants experiencing the endpoint.
M: number of participants with available data for the relevant endpoint.
NC: not calculable.
GMTR (geometric mean titer ratio): geometric mean of individual titer ratios (post-vaccination/pre-vaccination).
For this analysis, n: number of participants fulfilling the item listed; M: number of participants with available data and had baseline value below LLOQ.
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant D614G.
Source: Modified from 5.3.5.1 VAT00002 Interim CSR Section 8, Table 8.80 and Table 8.92

The GMTs were similar across treatment groups in the older age group (≥ 60 years) while in participants aged 18 to 59 years, GMTs increased across treatment groups with higher GMTs observed in the treatment groups with higher antigen dose (i.e., Group 3 presented the highest neutralising Ab levels).

Higher neutralising Ab titres were observed in participants aged 18 to 59 years compared to older individuals (≥ 60 years).

The secondary objective #1 was to determine the neutralising Ab profile against the D614G variant at D22 in naïve participants. At D22 (21 days post-injection 1), for each treatment group, minimal increase in neutralising Ab titres from baseline were observed in naïve participants.

The secondary objective #2 was to determine the neutralising Ab profile against the D614G variant at D01, D22, and D36 in non-naïve participants.

At baseline, a comparable level of neutralising Abs was observed across treatment groups. At D22, high levels of neutralising Abs were observed after a single injection for each of the 3 antigen dose

levels. At this timepoint, the percentage of participants with titres ≥ 2-fold-rise ranged between approximately 59% and 74% and the percentage of participants with ≥ 4-fold-rise, which was also similar to the percentage of responders, ranged between approximately 55% and 70% across the 3 treatment groups.

At D36, there was a general pattern of increase in the magnitude of the neutralising Ab titres from post injection 1 in the overall (18 years of age and older) non naïve population. The percentage of participants with titres ≥2-fold-rise ranged between approximately 91% and 100%. The proportion of responders, as well as the percentage of participants with ≥4-fold-rise, ranged between approximately 86% and 96% across the 3 treatment groups.

Table 4: VAT00002 - Original Phase II Cohort - Summary of Neutralising Ab Profile – PPAS Non Naïve-D01/D22

			Group 1 (5 µg) (N=28)			Group 2 (10 µg) (N=26)			Group 3 (15 µg) (N=23)		
Summary of GMT and GMTR for neutralizing Ab titers											
Age group	**Time point / ratio**		**M**	**GMT/ GMTR**	**(95% CI)**	**M**	**GMT/ GMTR**	**(95% CI)**	**M**	**GMT/ GMTR**	**(95% CI)**
All	**D01**		28	180	(87.3;373)	23	218	(82.4;578)	23	192	(77.8;475)
	D22		27	3143	(836;11815)	25	2338	(593;9226)	23	7069	(1361;36725)
	D36		28	13637	(8187;22717)	25	10216	(4610;22641)	23	26647	(12318;57643)
	D22/D01		27	16.1	(6.84;37.7)	22	9.32	(3.27;26.6)	23	36.8	(11.5;118)
	D36/D01		28	75.6	(41.7;137)	22	47.8	(19.0;121)	23	139	(66.6;288)
18-59	**D01**		13	167	(51.9;537)	14	245	(63.3;950)	14	156	(49.3;495)
	D22		12	6082	(733;50437)	15	4070	(714;23200)	14	9094	(834;99150)
	D36		13	15444	(6271;38036)	15	17973	(7274;44408)	14	29417	(8365;1.03E+05)
	D22/D01		12	30.5	(6.94;134)	13	16.9	(3.96;71.7)	14	58.2	(10.7;316)
	D36/D01		13	92.5	(38.8;221)	13	84.5	(23.2;308)	14	188	(77.8;456)
>= 60	**D01**		15	193	(68.0;548)	9	182	(33.0;1004)	9	265	(44.8;1571)
	D22		15	1853	(285;12051)	10	1018	(78.4;13219)	9	4777	(340;67165)
	D36		15	12244	(6349;23611)	10	4378	(971;19736)	9	22848	(10576;49361)
	D22/D01		15	9.61	(3.30;28.0)	9	3.96	(0.749;21.0)	9	18.0	(3.21;101)
	D36/D01		15	63.5	(25.6;157)	9	21.0	(5.23;84.6)	9	86.1	(19.8;374)
Number of participants with ≥ 2-fold-rise and ≥ 4-fold-rise of neutralizing Ab titers											
Age group	**Time point**	**Fold-rise**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
All	**D22**	**≥ 2**	20/27	74.1	(53.7;88.9)	13/22	59.1	(36.4;79.3)	17/23	73.9	(51.6;89.8)
		≥ 4	18/27	66.7	(46.0;83.5)	12/22	54.5	(32.2;75.6)	16/23	69.6	(47.1;86.8)
	D36	**≥ 2**	28/28	100	(87.7;100)	20/22	90.9	(70.8;98.9)	23/23	100	(85.2;100)
		≥ 4	27/28	96.4	(81.7;99.9)	19/22	86.4	(65.1;97.1)	22/23	95.7	(78.1;99.9)
Number and percentage of responders post injection for neutralizing Ab titers											
Age group	**Time point**	**Endpoint**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
All	**D01**	**> LLOQ**	18/28	64.3	(44.1;81.4)	15/23	65.2	(42.7;83.6)	15/23	65.2	(42.7;83.6)
	D22	**Responders**	19/27	70.4	(49.8;86.2)	12/22	54.5	(32.2;75.6)	16/23	69.6	(47.1;86.8)
	D36	**Responders**	27/28	96.4	(81.7;99.9)	19/22	86.4	(65.1;97.1)	22/23	95.7	(78.1;99.9)

For booster vaccine, the magnitude of differences in cross-neutralising antibody responses to Beta (B.1.351) variant strain compared to homologous D614G strain was lower in non-naïve individuals compared to naïve individuals, suggesting that a booster vaccination may provide improved immune coverage against variants of concern. A lower antigen dose than proposed for naïve populations was considered appropriate for non-naïve individuals. The data suggested that a single injection of an antigen dose of 5 µg with AS03 adjuvant may be sufficient for boosting previously primed individuals.

2.5.5.2. Main study(ies)

VAT00013 – COVIBOOST

Immunogenicity and reactogenicity following a booster dose of COVID-19 mRNA vaccine (Pfizer-BioNtech) and two adjuvanted subunit vaccines administered as a booster dose in adults who received two doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: a randomized, multicentre, single-blind trial.

Methods

- **Study Participants**

Adults aged 18 years and older previously primed with 2 doses of Pfizer/BioNTech vaccine 3 to ≤ 7 months prior the booster injection.

Inclusion criteria:

1. Age ≥ 18 years
2. Adult in a healthy condition or with a stable health status if pre-existing medical history. Stable health status is defined as an existing disease that has not required a significant change in treatment or hospitalization for worsening in the 3 months before enrolment, and for which neither a significant change in treatment or hospitalization for worsening is expected in the near future
3. For women of childbearing age: a negative highly sensitive pregnancy urinary test during the inclusion visit AND use of an effective contraceptive method at least 4 weeks prior to vaccination and until at least 12 weeks after the vaccination
4. Who has received 2 doses of mRNA vaccine (Pfizer-BioNTech) with an interval of 3 to 6 weeks
5. Second dose of mRNA vaccine (Pfizer-BioNTech) administered between 3 months and 7 months before the booster dose
6. Understands and agrees to comply with the study procedures
7. Written informed consent signed by both the participant and the investigator
8. Subject affiliated to the French Social Security System

Exclusion criteria:

1. Acute febrile infection (body temperature ≥ 38.0°C) within the previous 72 hours and/or presenting symptoms suggestive of COVID-19 within the previous 28 days or having been in contact with an infected individual for the last 14 days before the inclusion visit;
2. Virologically documented history of COVID-19 (PCR or serology);
3. Immunosuppressive therapy such as corticosteroids > 10 mg prednisone equivalent/day (excluding topical preparations and inhalers) within 3 months prior to inclusion or within 6 months for chemotherapies;
4. Treatment with immunoglobulins or other blood derivatives within 3 months prior to inclusion or scheduled administration of immunoglobulins or blood derivatives before the end of the study;

5. Known HIV, HCV or HBV infection;
6. Any medical condition, such as cancer, that might impair the immune response;
7. Use of experimental immunoglobulins, experimental monoclonal antibodies or convalescent plasma is not permitted during the study;
8. Pregnancy or breastfeeding currently ongoing, or positive pregnancy test at enrolment visit;
9. History of severe adverse events following vaccine administration including anaphylactic reaction and associated symptoms such as rash, breathing problems, angioedema, and abdominal pain, or a history of allergic reaction that could be triggered by a component of the SARS-COV-2 vaccine at the time of the first vaccine injection;
10. Participant who has received BCG (tuberculosis) vaccine within the previous year
11. Has received a vaccine within 2 weeks prior to the boost injection or is scheduled to receive a registered vaccine 2 weeks after the boost injection
12. Any bleeding disorder considered as a contraindication to an intramuscular injection, previous phlebotomy or receipt of anticoagulants
13. Participation in other research involving humans (French classification Jardé 1 or Jardé 2) within 4 weeks prior to the inclusion visit, or participation in any other vaccine trial
14. Subject under legal protection (e.g. guardianship, tutorship)

- **Treatments**

Participants stratified by age group (18-64 years of age and 65 years and older) were randomly assigned to receive a booster dose of either:

- an approved COVID-19 mRNA vaccine (Pfizer/BioNTech vaccine) at 30 µg of antigen dose. The nucleoside-modified messenger RNA is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation.
- the adjuvanted protein recombinant vaccine CoV2 preS dTM-AS03 from D614 strain at 5 µg of antigen dose, or;
- the adjuvanted protein recombinant vaccine CoV2 preS dTM-AS03 from B.1.351 strain at 5 µg of antigen dose.

- **Objectives and endpoints**

Only immunogenicity variables are listed here. The studies included safety endpoints. Study objectives have been protocol version 5.0. Only endpoints relevant to the booster indication for VidPrevtyn Beta initial marketing authorisation application are shown below.

Table 5: Immunogenicity objectives and endpoints of Study VAT000013

Objectives	Endpoints
Post-hoc Analyses	
Primary objective: 1) To compare the neutralising antibody titres against Omicron BA.1 strain 28 days after booster vaccination between the groups receiving the CoV2 preS dTM-AS03 (B.1.351) and Pfizer/BioNTech vaccines	GMT ratio between CoV2 preS dTM-AS03 (B.1.351) and Pfizer/BioNTech vaccines against Omicron BA.1
Secondary objectives are conditional on the success of the primary objective: 1) To compare the seroresponse rate against Omicron BA.1 strain 28 days after booster vaccination between the groups receiving the CoV2 preS dTM-AS03 (B.1.351) and Pfizer/BioNTech vaccines 2) To compare the post-boosting neutralising antibody titres and seroresponse rate against the wild-type D614G strain 28 days after booster vaccination between the groups receiving the CoV2 preS dTM-AS03 (B.1.351) and Pfizer/BioNTech vaccines	Endpoints for secondary objectives #2 and #3: • Difference of seroresponse rate (defined as the percentage of participants with a 4-fold or greater rise in serum neutralisation titre at D28 relative to baseline) between CoV2 preS dTM-AS03 (B.1.351) and Pfizer/BioNTech vaccines against Omicron BA.1 strain • GMT ratio between CoV2 preS dTM-AS03 (B.1.351) and Pfizer/BioNTech vaccines against D614 strain • Difference of seroresponse rate between CoV2 preS dTM-AS03 (B.1.351) and Pfizer/BioNTech vaccines against D614 strain
Exploratory objectives (descriptive): 3) To assess post-booster neutralising antibody GMT ratios between the 3 pairs of boosters vaccines by variant (Omicron BA.1, Omicron BA.4/BA.5†, D614G, Beta, Delta) 4) To assess post-booster differences of seroresponse rates between the 3 pairs of booster vaccines by variant (Omicron BA.1, Omicron BA.4/BA.5, D614G, Beta, Delta)	Endpoints for secondary objectives #4: • GMT with log10 transformation within a booster group at D15 and D28. • GMT ratio and confidence interval between 2 booster groups of the 3 pairs specified above at D15 and D28 Endpoints for secondary objectives #5: • Seroresponse rate of each booster group at D15 and D28 • Difference of seroresponse rate and confidence interval between 2 booster groups of the 3 pairs specified above at D15 and D28
Primary Immunogenicity	
To assess the immunogenicity of a booster dose of an adjuvanted subunit vaccine (Sanofi vaccine) as between D614 or B.1.351 and a mRNA vaccine (Pfizer/BioNTech) in adults who were primarily vaccinated with 2 doses of mRNA vaccine (Pfizer/BioNTech) and received the 2nd dose of vaccine between 3 months and 7 months before the booster dose	Increased rate of at least 10-fold between D0 and D15 after the booster dose in neutralising antibody titres against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique in each group
Secondary Immunogenicity*	

Note: *The numbering, description, and associated endpoints of secondary immunogenicity objectives are as introduced in the study protocol.*	
1) To compare the increase in neutralising antibody titres with regard to age groups (18-64 years old and >65 years or older) 3) To assess the humoral immune response by ELISA of a booster dose of mRNA vaccine or adjuvanted subunit vaccine at 15 and 28 days 5) To evaluate the immunogenicity of the 3 vaccines on variants of interest 8) To assess the early humoral response by ELISA of a booster dose of mRNA vaccine or subunit adjuvanted vaccine at 3 days (ancillary analysis) 9) To explore CD4 and CD8 cellular response induced by a booster dose of mRNA vaccine or adjuvanted subunit vaccine (ancillary analysis)	1) Rate of increase in neutralising antibody titres against SARS-CoV-2 D614 and B.1.351 viral strains, measured by a microneutralisation technique between 0 and 28 days after the booster dose in each group 3) Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations D15 and D28 after the booster dose mRNA or adjuvanted subunit vaccine 5) Neutralising antibody titres against variants of interest at 28 days, 3 months and 12 months† 8) Anti-Spike (D614) and anti-RBD (D614 and B.1.351) IgG levels, expressed in BAU/ml, according to WHO recommendations, on D3 after the booster dose of mRNA or adjuvanted subunit vaccine (ancillary analysis) 9) ELISpot IFN CD4 and CD8 response at 28 days, 3 months and 12 months (ancillary analysis)‡

Abbreviations: BAU, binding antibody units; D, Day; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immunospot; IFN, interferon; M, mRNA, messenger ribonucleic acid; PRNT, plaque reduction neutralisation test; RBD, receptor-binding domain; WHO, World Health Organization
*Note: Immunogenicity data up to D28 are available and presented for this application.
†Neutralising Ab titres for Omicron BA.4/BA.5 were not available at the time of the analysis.
‡ For this endpoint, results at D15 and D28 are available.
Source: Modified from 5.3.5.1 VAT00013 Interim CSR, Exhibit 1 Clinical study protocol

- **Sample size**

The study was powered to estimate the proportion of participants (expected: 80%) with a given increase in the neutralising antibody titres (expected: 10 times) and its 95% CI with a given precision (set: half width of 7.8%). From these assumptions, 100 participants per group were planned, thus a total of 300 volunteers was to be randomised.

- **Randomisation and Blinding (masking)**

Proc PLAN from SAS was used to generate the randomization list 1:1:1 using block balanced and stratified by age ([18-64] years or ≥65 years) and site.

An independent statistician was in charge to generate the randomization list and to store it in a secure location.

Randomization was planned to be performed by the site staff using the centralized tool in the e-CRF just prior to the vaccine injection on D0 visit.

The participants, investigating physician, the central laboratories performing antibodies analysis and the sponsor staff monitoring the trial at the study sites were not to be aware of the treatment received.

The healthcare professional administrating the vaccine was planned to be aware of the treatment arm, as the vaccines required different preparation, therefore the injection was planned to be carried out by

a person external to the study.

- **Statistical methods**

The Statistical analysis plan (SAP) by the investigator was finalised prior to the database lock. A post-hoc analysis plan was created by the Sponsor on the 14th of July 2022 as the basis of the analysis to support regulatory approval of the B.1.351 variant containing booster vaccine. The assessment below will mainly refer to the prespecified SAP; references to the post-hoc analysis plan are explicitly mentioned.

Analysis Populations/Sets

Intention to treat (ITT) population: all patients as randomised, regardless of the strategy received by the patient, except patient with positive or doubtful or missing nucleocapsid antibodies at baseline.

Safety population: all patients as randomised who have received the boost dose of vaccine.

Per protocol (PP) population: all patients randomised, treated without major protocol violations/deviations.

Original protocol and Post-hoc analysis: All analyses will be performed in the Per-Protocol Analysis Set (PPAS).

Primary Endpoint(s) / Primary Estimand(s)

Original protocol/SAP: The main analysis was planned to be performed on the per protocol population. For each viral strains (D614 and B.1.351), proportion of participants with an increase rate in neutralising antibody titres against SARS-CoV-2 of at least 10 fold between D0 and D15 was planned to be calculated with it 2-sided 95% confidence interval (95%CI) using the exact Clopper-Pearson method.

CSR: The primary endpoint was compared between the 3 groups by a Pearson Chi2 test.

Post-hoc analysis: Geometric mean of neutralising antibody titre (GMT) ratio against Omicron BA.1 strain 28 days after booster vaccination between Sanofi B.1.351 and BNT162b2. Superiority will be demonstrated if the lower bound of the 95% CI > 1.2 for the ratio of the GMTs between B.1.351 vaccine and BNT162b2 vaccine at D28 against the Omicron BA.1 strain. Two-sample t-test will be used to assess the superiority of GMT ratio of Sanofi B.1.351 and BNT162b2.

Supplementary Analysis for Primary Endpoint

The primary analysis was repeated in several subsets of the ITT population (ITT, ITT with available data, ITT with multiple imputation).

Secondary Endpoints / Secondary Estimand(s) and Subgroup Analyses

Post-hoc analysis: three secondary endpoints, conditional on the success of the primary objective:

- Difference of seroresponse rate between Sanofi B.1.351 and BNT162b2 against Omicron BA.1 strain.
- GMT ratio between Sanofi B.1.351 and BNT162b2 against D614 strain.
- Difference of seroresponse rate between Sanofi B.1.351 and BNT162b2 against D614 strain.

The seroresponse rate is defined as the percentage of participants with a 4-fold or greater rise in serum neutralisation titre at D28 relative to Baseline (D0).

The same success criteria of superiority test will be applied for GMT difference of secondary endpoint with the lower bound of the 95% CI > 1.2. To declare the success of secondary endpoints of non-

inferiority, the lower bound of confidence interval of the seroresponse rate difference need to be >-10%, the non-inferiority margin.

Multiplicity

All tests will be two-sided, and a p-value of <0.05 will be considered significant. No adjustment will be planned for multiplicity except for comparisons between groups in pairs for which a Bonferroni correction will be used.

Post-hoc analysis: A significance level of 0.025 one-sided will be used for hypothesis testing defined above for primary and secondary objectives. To control the family-wise type-I-error rate, the hypothesis testing of secondary endpoints is conditional on the success of the primary objective. The testing of secondary endpoints will be sequentially based on above listed.

Results

- **Participant flow**

A total of 247 participants were enrolled, randomised and received the vaccine allocated: 85 participants were allocated in the Sanofi D614 group, 80 in the Sanofi B.1.351 group and 82 in the BNT162b2 group.

Six participants were randomized in the age stratum ≥65 years (2.4%): 2 participants in CoV2 preS dTM-AS03 (D614) booster group, 1 participant in CoV2 preS dTM-AS03 (B.1.351) booster group, and 3 participants in Pfizer/BioNTech booster group.

A total of 67 participants (27.1%) participated in the ancillary study (to assess humoral and cellular responses): 25 participants in CoV2 preS dTM-AS03 (D614) booster group, 23 participants in CoV2 preS dTM-AS03 (B.1.351) booster group, and 19 participants in Pfizer/BioNTech booster group.

Figure 1: Participant flow

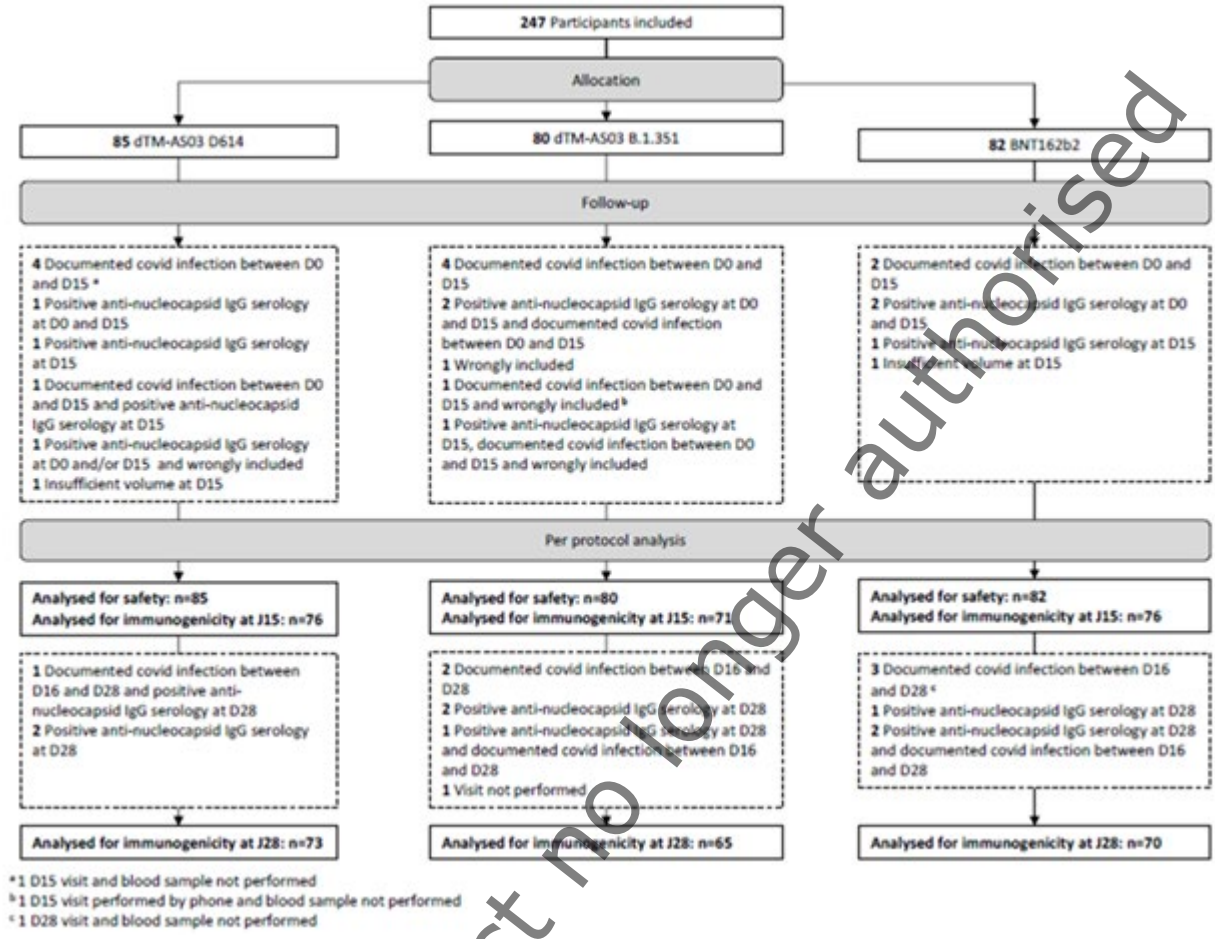
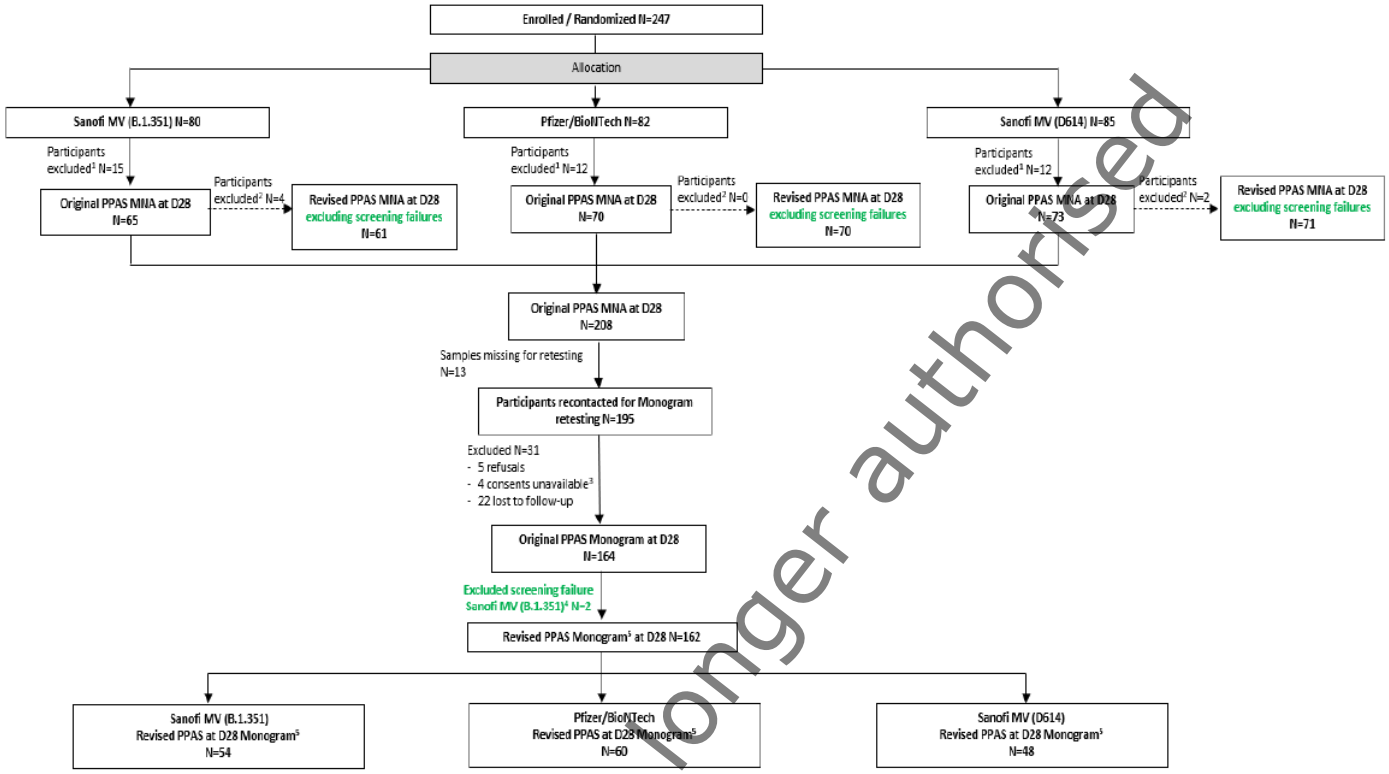


Figure 2: VAT00013 – Summary of the per protocol sets at D28 (including re-analysis with validated monogram assay)



Abbreviation: MNA, microneutralisation assay; Sanofi MV (B.1.351), CoV2 preS dTM-AS03 (B.1.351); Sanofi MV (D614), CoV2 preS dTM-AS03 (D614)
Note: Original PPAS=PPAS including screening failures; Revised PPAS=PPAS that excludes screening failure following EMA requirement
1 Participants with major protocol deviations leading to per protocol exclusion (see Figure 3 with details of exclusion from Original PPAS)
2 Participants excluded due to screening failures
3 Consent unavailable by 30 August 2022
4 No screening failure in Sanofi MV (D614) and Pfizer/BioNTech
5 Participants:
• Who reconsent to have samples sent to Monogram laboratory for retesting
• With available samples at D0 and D28

- **Recruitment**

247 volunteers were included between 8 December 2021 and 14 January 2022, including 85 in the Sanofi D614 group, 80 in the Sanofi B.1.351 group and 82 in the BNT162b2 group.

The study was conducted in France.

Date of last follow-up of last patient included: Follow-up in progress

Date of the interim (D28) report: 23 June 2022

- **Conduct of the study**

According to the Applicant, VAT00013 was conducted according to GCP Guidelines and current version of the Declaration of Helsinki.

The protocol was amended several times. Protocol version 6.0 was valid on 10th May 2022. The current

Interim CSR is based on protocol version 5.0 (dated 3rd January 2021). All protocol versions have been provided together with an overview of the major protocol changes.

- **Baseline data**

The mean age (SD) of participants was similar between vaccine groups and in both the ITT and PP analysis sets: 40.4 (± 13.1) years and 40.6 (± 13.0) years, respectively. The overall proportion of females was lower than the one of males in the 2 analysis sets (about 40% of female participants) as well as in Group 2 and 3 (CoV2 preS dTM-AS03 [D614] and [B.1.351] booster vaccine groups). In Group 1 (Pfizer/BioNTech booster vaccine group), the proportion of females and males was balanced. The interval between the second dose of the primary series and the booster dose was 174 days (approximately 5.8 months) and was comparable across groups. The most common high-risk medical conditions associated with increased risk of severe COVID-19 were smoking, obesity, and hypertension. Those were equally distributed across treatment arms.

The baseline demographics of participants' whose samples were retested with the validated Monogram PsVN assay are comparable to those tested with the MNA (Revised PPAS MNA at D28). The mean age was comparable across groups with 41.4 and 40.4 years for VidPrevtyn Beta and COVID-19 mRNA vaccine (tozinameran), respectively. Age ranged from 20.0 to 69.0 years. The mean duration between the second dose of the primary series and the booster dose was comparable across groups, being 171.0 and 174.5 days for VidPrevtyn Beta and COVID-19 mRNA vaccine (tozinameran), respectively

- **Numbers analysed**

The safety population included 247 randomized and vaccinated participants. The ITT population comprises 242 randomized participants: 84 participants in CoV2 preS dTM-AS03 (D614) booster group, 78 participants in CoV2 preS dTM-AS03 (B.1.351) booster group, and 80 participants in Pfizer/BioNTech booster group. Among them, 65 participants (26.9%) participated in the ancillary study (i.e. to assess the humoral and cellular responses): 24 participants in CoV2 preS dTM-AS03 (D614) booster group, 23 participants in CoV2 preS dTMAS03 (B.1.351) booster group, and 18 participants in Pfizer/BioNTech booster group.

Overall, 223 participants were included in the PP population at D15: 76 participants in CoV2 preS dTM-AS03 (D614) booster group, 71 participants in CoV2 preS dTM-AS03 (B.1.351) booster group, and 76 participants in Pfizer/BioNTech booster group. Of these, 61 participants (27.4%) participated in the ancillary study: 23 participants in CoV2 preS dTM-AS03 (D614) booster group, 20 participants in CoV2 preS dTM-AS03 (B.1.351) booster group, and 18 participants in Pfizer/BioNTech booster group.

At D28, 208 participants were included in the PP population: 73 participants in CoV2 preS dTM-AS03 (D614) booster group, 65 participants in CoV2 preS dTM-AS03 (B.1.351) booster group, and 70 participants in Pfizer/BioNTech booster group.

Samples were re-tested with the validated monogram PsVN assay. The per-protocol analysis population included 143 participants receiving VidPrevtyn Beta (N=67) or COVID-19 mRNA vaccine (tozinameran) (N=76).

- **Outcomes and estimation**

Post-hoc analysis - Validated Monogram PsVN assay results

The below outcomes and estimations are presented based on the validated monograph PsVN assay in the revised PPAS.

For the primary endpoint, the neutralising Ab geometric mean titre ratio (GMTR) against Omicron BA.1 variant strain of CoV2 preS dTM-AS03 (B.1.351) vaccine relative to Pfizer/BioNTech vaccine was 2.53 (95% confidence interval [CI]: 1.80; 3.57) which meets the superiority criterion of lower limit of the 2-sided 95% CI of GMTR > 1.2 as shown in the below table.

Table 6: Superiority of post-booster GMT ratio against Omicron BA.1 at D28 for CoV2 preS dTM-AS03 (B.1.351) vs Pfizer/BioNTech vaccine demonstrated – Revised PPAS Monogram at D28

	CoV2 preS dTM-AS03 (B.1.351) booster (N=54)			Pfizer/BioNTech booster (N=60)			CoV2 preS dTM-AS03 (B.1.351) / Pfizer/BioNTech booster		
Strain Readout	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)***	**GMT ratio**	**(95% CI)***	**Superiority†**
B.1.1.529 (Omicron BA.1)	54	1327.5	(1005.0 ; 1753.4)	58	524.0	(423.3 ; 648.6)	2.53	(1.80 ; 3.57)	Yes

N: number of participants in Revised PPAS Monogram at D28
M: number of participants available for the endpoint
* 2-sided 95% CI is based on the student t-distribution of logarithmic transformation of the individual titers.
† Superiority is concluded if the lower limit of the 2-sided 95% CI of the GMT ratio > 1.2
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram
Source: Appendix 1, Table 1

For the secondary endpoints, the difference of neutralising seroresponse rate against Omicron BA.1 variant strain between CoV2 preS dTM-AS03 (B.1.351) vaccine and Pfizer/BioNTech vaccine was 3.8 (95% CI: -3.9; 12.8) which meets the non-inferiority criterion of lower limit of the 2-sided 95% CI of the difference > -10%, as shown in the table below.

Table 7: VAT00013 - Non-inferiority of seroresponse rate against Omicron BA.1 at D28 for CoV2 preS dTM-AS03 (B.1.351) vs Pfizer/BioNTech vaccine demonstrated - Revised PPAS Monogram at D28

	CoV2 preS dTM-AS03 (B.1.351) booster (N=54)		Pfizer/BioNTech booster (N=60)		CoV2 preS dTM-AS03 (B.1.351) booster - Pfizer/BioNTech booster		
Strain Readout	**n/M**	**Seroresponse rate (%) (95% CI)***	**n/M**	**Seroresponse rate (%) (95% CI)***	**Difference (%)**	**(95% CI)‡**	**Non-inferiority§**
B.1.1.529 (Omicron BA.1)	50/50	100.0 (92.9 ; 100.0)	51/53	96.2 (87.0 ; 99.5)	3.8	(-3.9;12.8)	Yes

N: number participants in Revised PPAS Monogram at D28
M: number of participants available for the endpoint
n: Number of participants who achieve seroresponse.
*95% CI of the single proportion calculated from the exact binomial method.
‡95% CI of the difference calculated from the Wilson Score method without continuity correction.
§Non-inferiority is concluded if the lower limit of the 2-sided 95% CI of the difference in seroresponse rate between groups is > -10%.
Seroresponse: defined as a 4-fold or greater rise in serum neutralization titer [D28/D0]
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram
Source: Appendix 1, Table 2

The neutralising Ab GMTR against D614G strain of CoV2 preS dTM-AS03 (B.1.351) vaccine relative to Pfizer/BioNTech vaccine was 1.43 (95% CI: 1.06; 1.94) which does not meet the superiority criterion of lower limit of the 2-sided 95% CI of GMTR > 1.2. The difference of neutralising seroresponse rate against D614G strain between CoV2 preS dTMAS03(B.1.351) vaccine and Pfizer/BioNTech vaccine was 3.0 (95% CI: -6.9; 12.8) which meets the non-inferiority criterion of lower limit of the 2-sided 95% CI of the difference > -10%, as shown in the below table.

Table 8: VAT00013 - Superiority of post-booster GMT ratio and non-inferiority of seroresponse rate against D614G at D28 for CoV2 preS dTM-AS03 (B.1.351) vs Pfizer/BioNTech vaccine - Revised PPAS Monogram at D28

Superiority based on GMTs									
	CoV2 preS dTM-AS03 (B.1.351) booster (N=54)			**Pfizer/BioNTech booster (N=60)**			**CoV2 preS dTM-AS03 (B.1.351) booster / Pfizer/BioNTech booster**		
Strain Readout	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)***	**GMT ratio**	**(95% CI)***	**Superiority†**
D614G	54	6458.5	(5103.1 ; 8174.0)	60	4507.5	(3695.4 ; 5498.1)	1.43	(1.06 ; 1.94)	No
Non-inferiority based on seroresponse									
	CoV2 preS dTM-AS03 (B.1.351) booster (N=54)			**Pfizer/BioNTech booster (N=60)**			**CoV2 preS dTM-AS03 (B.1.351) booster - Pfizer/BioNTech booster**		
Strain Readout	**n/M**	**Seroresponse rate (%) (95% CI)‡**		**n/M**	**Seroresponse rate (%) (95% CI)‡**		**Difference (%)**	**(95% CI)§**	**Non-inferiority****
D614G	51/53	96.2 (87.0 ; 99.5)		55/59	93.2 (83.5 ; 98.1)		3.0	(-6.9;12.8)	Yes

N: number of participants in Revised PPAS Monogram at D28
M: number of participants available for the endpoint
n: Number of participants who achieve seroresponse.
* 2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers.
† Superiority is concluded if the lower limit of the 2-sided 95% CI of the GMT ratio > 1.2
‡ 95% CI of the single proportion calculated from the exact binomial method.
§ 95% CI of the difference calculated from the Wilson Score method without continuity correction.
**Non-inferiority is concluded if the lower limit of the 2-sided 95% CI of the difference in seroresponse rate between groups is > -10%.
Seroresponse: defined as a 4-fold or greater rise in serum neutralization titer [D28/D0]
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram
Source: Appendix 1, Table 3 and Table 4

In addition to the VAT00013 study samples retesting for D614G and Omicron BA.1 variant strains, VAT00013 samples were tested for the Omicron BA.4/BA.5 variant strain using the validated Monogram PsVN assay.

The Sanofi CoV2 preS dTM-AS03 (B.1.351) booster vaccine induced 2.5-fold higher neutralising antibody titres against Omicron BA.4/5 than those induced by the Pfizer/BioNTech booster prototype vaccine in the fully validated Monogram PsVN assay, GMT ratio 2.5 (95% ci: 1.7; 3.67).

Furthermore, the neutralising seroresponse rates observed with the Sanofi CoV2 preS dTM-AS03 (B.1.351) vaccine at D28 was higher than those observed with Pfizer/BioNTech vaccine irrespective of the variant tested as shown in the below table.

Table 9: VAT00013 - Summary of seroresponse rate and associated 95% CI between CoV2 preS dTM-AS03 (B.1.351) vs Pfizer/BioNTech vaccine by variant - Revised PPAS Monogram at D28

			CoV2 preS dTM-AS03 (B.1.351) (N=54)			Pfizer/BioNTech (N=60)			CoV2 preS dTM-AS03 (B.1.351) - Pfizer/BioNTech	
Age group	**Strain**	**Time point**	**n/M**	**SR**	**(95% CI)**	**n/M**	**SR**	**(95% CI)**	**SR Difference**	**(95% CI)**
Overall	**Omicron BA.1**	**D28**	50/50	100	(92.9 ; 100)	51/53	96.2	(87.0 ; 99.5)	3.8	(-3.9 ; 12.8)
	Omicron BA.4/5	**D28**	48/49	**98.0**	**(89.1 ; 99.9)**	47/55	**85.5**	**(73.3 ; 93.5)**	**12.5**	**(1.4 ; 24.2)**
	D614G	**D28**	51/53	96.2	(87.0 ; 99.5)	55/59	93.2	(83.5 ; 98.1)	3.0	(-6.9 ; 12.8)
18-55 years	**Omicron BA.1**	**D28**	42/42	100	(91.6 ; 100)	44/46	95.7	(85.2 ; 99.5)	4.3	(-4.6 ; 14.5)
	Omicron BA.4/5	**D28**	40/41	97.6	(87.1 ; 99.9)	41/48	85.4	(72.2 ; 93.9)	12.1	(-0.4 ; 24.9)
	D614G	**D28**	43/45	95.6	(84.9 ; 99.5)	49/51	96.1	(86.5 ; 99.5)	-0.5	(-11.3 ; 9.3)
>=56 years	**Omicron BA.1**	**D28**	8/8	100	(63.1 ; 100)	7/7	100	(59.0 ; 100)	0	(-32.4 ; 35.4)
	Omicron BA.4/5	**D28**	8/8	100	(63.1 ; 100)	6/7	85.7	(42.1 ; 99.6)	14.3	(-20.2 ; 51.3)
	D614G	**D28**	8/8	100	(63.1 ; 100)	6/8	75.0	(34.9 ; 96.8)	25.0	(-12.0 ; 59.1)
18-59 years	**Omicron BA.1**	**D28**	47/47	100	(92.5 ; 100)	46/48	95.8	(85.7 ; 99.5)	4.2	(-4.0 ; 14.0)
	Omicron BA.4/5	**D28**	45/46	97.8	(88.5 ; 99.9)	43/50	86.0	(73.3 ; 94.2)	11.8	(0.3 ; 24.1)
	D614G	**D28**	48/50	96.0	(86.3 ; 99.5)	51/54	94.4	(84.6 ; 98.8)	1.6	(-8.6 ; 11.5)
>=60 years	**Omicron BA.1**	**D28**	3/3	100	(29.2 ; 100)	5/5	100	(47.8 ; 100)	0	(-56.1 ; 43.4)
	Omicron BA.4/5	**D28**	3/3	100	(29.2 ; 100)	4/5	80.0	(28.4 ; 99.5)	20.0	(-38.5 ; 62.4)
	D614G	**D28**	3/3	100	(29.2 ; 100)	4/5	80.0	(28.4 ; 99.5)	20.0	(-38.5 ; 62.4)

N: number of participants in Revised PPAS Monogram at D28
M: number of participants available for the endpoint
n: number of participants who achieve seroresponse
SR: Seroresponse Rate
Seroresponse rate at a post-dose visit (eg, D28) is defined as the percentage of participants with a 4-fold or greater rise in serum neutralization titer at the corresponding post-dose visit relative to Baseline
95% CI of the single proportion calculated from the exact binomial method.
2-sided 95% CI for the difference between proportions is based on the Wilson score method without continuity correction
Source: Appendix 1, Table 8

Post-hoc analyses - non-validated microneutralisation assay results

The below outcomes and estimations are presented based on the non-validated MNA in the PPAS.

The primary objective of the post-hoc analyses was to compare neutralising Ab titres against the Omicron BA.1 strain 28 days after booster vaccination between the groups that received the CoV2 preS dTM-AS03 (B.1.351) and the Pfizer/BioNTech booster vaccine. In the PPAS-D28, the superiority of a booster dose of the CoV2 preS dTM-AS03 (B.1.351) vaccine compared with the Pfizer/BioNTech vaccine was demonstrated using GMTs at D28. The neutralising Ab GMT ratio against the Omicron BA.1 variant was 1.9 (95% CI: 1.4; 2.6), which meets the superiority criterion of the lower bound of the two-sided 95% CI of GMTR > 1.2, as shown in table below.

Table 10: AT00013: Superiority of post-booster GMT ratio for CoV2 preS dTM-AS03 (B.1.351) vs Pfizer/BioNTech vaccines with individual neutralising titre against Omicron BA.1 at D28 – PPAS

	CoV2 preS dTM-AS03 (B.1.351) booster (N=65)			Pfizer/BioNTech booster (N=70)			CoV2 preS dTM-AS03 (B.1.351) / Pfizer/BioNTech booster		
Strain Readout	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)***	**GMT ratio**	**(95% CI)***	**Superiority†**
B.1.1.529 (Omicron BA.1)	65	211.1	(164.4; 271.1)	70	109.8	(89.4; 135.0)	1.9	(1.4; 2.6)	Yes

M: number of participants available for the endpoint; N: number of participants in PPAS.
* 2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers.
† Superiority is concluded if the lower limit of the 2-sided 95% CI of the GMT ratio > 1.2.
Microneutralization assay performed at IHU Méditerranée, Marseille, France
Source: Modified from 5.3.5.1 VAT00013 - Post-hoc Analyses, Table 1

The secondary objective of the post-hoc analyses related to the comparison of the neutralising seroresponse rate against Omicron BA.1, and the post-boosting neutralisation and seroresponse rate against wild-type D614G strain 28 days after booster vaccination between the groups receiving the CoV2 preS dTM-AS03 (B.1.351) and Pfizer/BioNTech vaccines.

The difference of neutralising seroresponse rate against Omicron BA.1 variant strain between CoV2 preS dTM-AS03 (B.1.351) vaccine and Pfizer/BioNTech vaccine was 13.6 (95% CI: 1.0; 25.8) which meets the non-inferiority criterion of lower limit of the 2 sided 95% CI of the difference > -10%.

The neutralising Ab GMTR against D614G strain of CoV2 preS dTM-AS03 (B.1.351) vaccine relative to Pfizer/BioNTech vaccine was 1.8 (95% CI: 1.3; 2.6) which meets the superiority criterion of lower limit of the 2 sided 95% CI of GMTR > 1.2. The difference of neutralising seroresponse rate against D614G strain between CoV2 preS dTM-AS03 (B.1.351) vaccine and Pfizer/BioNTech vaccine was 6.7 (95% CI: -3.8; 17.2) which meets the non-inferiority criterion of lower limit of the 2 sided 95% CI of the difference > -10%.

The exploratory objectives of the post-hoc analyses (#4 and #5) were to assess post-booster neutralising Ab GMT ratios and post-booster differences of neutralising seroresponse rates between the 3 pairs of booster vaccine by variant (Omicron BA.1, D614G, Beta, and Delta) at D15 and D28. Regardless of the variants tested, the neutralising Ab GMTs induced by a single booster injection of CoV2 preS dTM-AS03 (B.1.351) vaccine at D28 were:

- Approximately twice to 3 times as high as those observed with Pfizer/BioNTech vaccine
- 1.5 to approximately 3 times as high as those observed with CoV2 preS dTM-AS03 (D614) vaccine

The neutralising Ab GMTs for all variants observed with CoV2 preS dTM-AS03 (D614) vaccine were similar to those of Pfizer/BioNTech vaccine with GMT ratios against the variants tested and between this pair of booster vaccines (CoV2 preS dTM-AS03 [D614] vaccine over Pfizer/BioNTech vaccine) ranging from 1.1 to 1.3 at D28.

The neutralising seroresponse rate observed with CoV2 preS dTM-AS03 (B.1.351) vaccine at D28 was higher than those observed with CoV2 preS dTM-AS03 (D614) and Pfizer/BioNTech vaccines, irrespective of the variant tested. The Pfizer/BioNTech vaccine presented higher neutralising seroresponse rates than CoV2 preS dTM-AS03 (D614) vaccine for all variants except the Beta variant.

Primary and secondary immunogenicity analysis

The below outcomes and estimations are presented based on the non-validated MNA in the PPAS.

Neutralising antibody response

The primary objective of VAT00013 study was to assess the immunogenicity of each booster vaccine in adults previously primed with Pfizer/BioNTech vaccine by evaluating the number of participants with at least a 10-fold increase in neutralising Ab titres against D614 and B.1.351 strains from D0 to D15 after the booster dose.

At D15, a higher proportion of participants with a 10-fold increase of neutralising Ab against D614G strain was observed in CoV2 preS dTM-AS03 (B.1.351) booster group (76.1%) compared to CoV2 preS dTM-AS03 (D614) booster (55.3%) and Pfizer/BioNtech booster groups (63.2%). A statistically significant difference between the 3 groups is observed ($p < 0.05$).

Against B.1.351 strain, the proportion of participants with a 10-fold increase of neutralising Ab was higher in CoV2 preS dTM-AS03 (B.1.351) booster group compared to the other booster groups with > 84% of participants having a 10-fold increase of neutralising Ab and a statistically significant difference between the 3 groups was observed ($p < 0.0001$).

Table 11: VAT00013: Proportion of participants with an increase of at least 10 fold in neutralising antibodies titres between D0 and D15

	CoV2 preS dTM-AS03 (D614) booster group	CoV2 preS dTM-AS03 (B.1.351) booster group	Pfizer/BioNTech booster group	
Analysis set / Strain Readout	**n % (CI 95%)**	**n % (CI 95%)**	**n % (CI 95%)**	**p-value**
PP population	**n=76**	**n=71**	**n=76**	
D614G	42 55.3 (43.4 ; 66.7)	54 76.1 (64.5 ; 85.4)	48 63.2 (51.5 ; 73.9)	0.030
B.1.351	34 44.7 (33.3 ; 56.6)	60 84.5 (74.0 ; 92.0)	39 51.3 (39.6 ; 63.0)	<0.0001
ITT population	**n=84**	**n=78**	**n=80**	
D614G	48 57.1 (45.9 ; 67.9)	61 78.2 (67.4 ; 86.8)	51 63.8 (52.2 ; 75.2)	0.016
B.1.351	41 48.8 (37.7 ; 60.0)	66 84.6 (74.7 ; 91.8)	41 51.3 (39.8 ; 62.6)	<0.0001

Abbreviation: ITT population, Intention To Treat population; PP population, Per Protocol population
D614=Wild strain; B.1.351=Beta strain
p-value: Pearson's chi-squared test used to compare primary endpoint (10-fold increase rate) between the 3 groups
Microneutralization assay performed at IHU Méditerrannée, Marseille, France
Source: Modified from 5.3.5.1 VAT00013 Interim CSR, Table 4

The secondary objective #1 of VAT00013 study was to compare the increase in neutralising Ab titres with regard to age groups (18-64 years and > 65 years of age). However, as only 6 participants aged > 65 years were enrolled due to operational constraints (booster vaccination national campaign in France had already been launched at the time of the study conduct), the cut-off age for analysis was set at < 40 years old and ≥ 40 years old. Overall and regardless of the strain tested, the age did not have any impact on the 10-fold increased rates of neutralising Ab titres pre-booster dose to post-booster at D15.

The secondary objective #5 was to evaluate the immunogenicity of the 3 booster vaccines on VOCs (table below). Regardless of the variant strain tested, including B.1.1.529 variant (Omicron), the highest neutralising Ab titres at D15 and D28 were observed for CoV2 preS dTM-AS03 (B.1.351) booster group. For both the 2 VOCs, Delta and Omicron (BA.1 subvariant), neutralising Ab titres induced in the CoV2 preS dTM-AS03 (B.1.351) booster group were about twice as high as those observed for the 2 other booster groups. Increase in neutralising Ab titres against D614G, Beta, and Delta variants from D0 to D15 were comparable for CoV2 preS dTM-AS03 (D614) and Pfizer/BioNTech booster groups. For the CoV2 preS dTM-AS03 (B.1.351) booster group, the increase of neutralising Ab titres against Beta variant from D0 to D15 was higher than those observed for D614G and Delta variants (31.7-fold increase versus 21.4-fold and 21.7-fold increases, respectively).

A markedly lower increase of neutralising Ab titres against Omicron (BA.1) variant from D0 to D15 was observed for all booster groups; however, this increase of neutralising Ab titres was substantially higher for CoV2 preS dTM-AS03 (B.1.351) booster group versus CoV2 preS dTMAS03 (D614) booster and Pfizer/BioNTech booster groups (14.5-fold increase versus 5.5-fold and 7.3-fold increases, respectively). Similar patterns of neutralising Ab titres increase from D0 to D28 were observed. Against Omicron variant strain, about a 12-fold increase from D0 to D28 was observed for CoV2 preS dTM-AS03 (B.1.351) booster group versus about 5.5-fold and 6-fold increase for CoV2 preS dTM-AS03 (D614) booster and Pfizer/BioNTech booster groups, respectively.

Table 12: VAT00013: Neutralising antibody titres for variants of concern - PP population

	CoV2 preS dTM-AS03 (D614) booster group n=76		CoV2 preS dTM-AS03 (B.1.351) booster group n=71		Pfizer/BioNTech booster group n=76		CoV2 preS dTM-AS03 (B.1.351) booster / CoV2 preS dTM-AS03 (D614) booster	CoV2 preS dTM-AS03 (B.1.351) booster / Pfizer/BioNTech booster	CoV2 preS dTM-AS03 (D614) booster / Pfizer/BioNTech booster
Analysis set / Strain Readout	**n***	**GMT (95% CI)**	**n***	**GMT (95% CI)**	**n***	**GMT (95% CI)**	**GMT ratio (95% CI)**	**GMT ratio (95% CI)**	**GMT ratio (95% CI)**
D614G (Wild)									
D0	76	86.8 (66.0 ; 114.3)	71	84.0 (67.5 ; 104.6)	76	96.0 (71.7 ; 128.6)	1.0 (0.7 ; 1.4)	0.9 (0.6 ; 1.3)	0.9 (0.6 ; 1.3)
D15	76	1168.4 (928.0 ; 1471.2)	71	1801.4 (1414.8 ; 2293.6)	76	1364.4 (1091.9 ; 1704.8)	1.5 (1.1 ; 2.1)	1.3 (1.0 ; 1.8)	0.9 (0.6 ; 1.2)
D28	73	990.5 (788.6 ; 1244.1)	65	1454.7 (1092.6 ; 1936.9)	70	787.9 (645.3 ; 962.1)	1.5 (1.0 ; 2.1)	1.8 (1.3 ; 2.6)	1.3 (0.9 ; 1.7)
D15/D0	76	13.5 (10.0 ; 18.1)	71	21.4 (16.0 ; 28.7)	76	14.2 (10.8 ; 18.7)	1.6 (1.1 ; 2.4)	1.5 (1.0 ; 2.3)	0.9 (0.6 ; 1.4)
D28/D0	73	11.5 (8.5 ; 15.5)	65	18.2 (13.3 ; 24.9)	70	8.3 (6.4 ; 10.9)	1.6 (1.0 ; 2.4)	2.2 (1.5 ; 3.3)	1.4 (0.9 ; 2.1)
B.1.351 (Beta)									
D0	76	38.6 (29.4 ; 50.5)	71	33.2 (27.5 ; 40.2)	76	38.6 (31.2 ; 47.7)	0.9 (0.6 ; 1.2)	0.9 (0.6 ; 1.1)	1.0 (0.7 ; 1.4)
D15	76	416.9 (334.2 ; 520.0)	71	1053.0 (840.3 ; 1319.5)	76	428.4 (346.6 ; 529.7)	2.5 (1.8 ; 3.5)	2.5 (1.8 ; 3.3)	1.0 (0.7 ; 1.3)
D28	73	311.0 (241.4 ; 400.7)	65	853.5 (652.9 ; 1115.8)	70	284.1 (226.9 ; 355.9)	2.7 (1.9 ; 4.0)	3.0 (2.1 ; 4.2)	1.1 (0.8 ; 1.5)
D15/D0	76	10.8 (8.1 ; 14.4)	71	31.7 (24.3 ; 41.3)	76	11.1 (8.7 ; 14.1)	2.9 (2.0 ; 4.3)	2.9 (2.0 ; 4.1)	1.0 (0.7 ; 1.4)
D28/D0	73	8.2 (5.9 ; 11.2)	65	27.0 (20.0 ; 36.3)	70	7.4 (5.8 ; 9.5)	3.3 (2.1 ; 5.1)	3.7 (2.5 ; 5.3)	1.1 (0.7 ; 1.7)

	CoV2 preS dTM-AS03 (D614) booster group n=76		CoV2 preS dTM-AS03 (B.1.351) booster group n=71		Pfizer/BioNTech booster group n=76		CoV2 preS dTM-AS03 (B.1.351) booster / CoV2 preS dTM-AS03 (D614) booster	CoV2 preS dTM-AS03 (B.1.351) booster / Pfizer/BioNTech booster	CoV2 preS dTM-AS03 (D614) booster / Pfizer/BioNTech booster
B.1.617.2 (Delta)									
D0	76	45.9 (34.7 ; 60.6)	71	39.2 (32.0 ; 48.1)	76	41.5 (33.1 ; 52.0)	0.9 (0.6 ; 1.2)	0.9 (0.7 ; 1.3)	1.1 (0.8 ; 1.6)
D15	76	491.3 (393.3 ; 613.7)	71	849.4 (678.6 ; 1063.3)	76	551.1 (443.2 ; 690.2)	1.7 (1.3 ; 2.4)	1.5 (1.1 ; 2.1)	0.9 (0.7 ; 1.2)
D28	73	429.5 (335.1 ; 550.6)	65	743.0 (586.8 ; 941.0)	70	360.4 (292.5 ; 444.0)	1.7 (1.2 ; 2.4)	2.1 (1.5 ; 2.8)	1.2 (0.9 ; 1.6)
D15/D0	76	10.7 (8.0 ; 14.4)	71	21.7 (16.4 ; 28.6)	76	13.3 (10.5 ; 16.9)	2.0 (1.3 ; 3.0)	1.6 (1.1 ; 2.3)	0.8 (0.6 ; 1.2)
D28/D0	73	9.5 (7.1 ; 12.7)	65	20.0 (15.2 ; 26.4)	70	8.7 (6.9 ; 10.8)	2.1 (1.4 ; 3.1)	2.3 (1.6 ; 3.3)	1.1 (0.8 ; 1.6)
B.1.1.529 (Omicron BA.1 subvariant)									
D0	76	22.5 (18.8 ; 27.0)	71	17.4 (15.3 ; 19.8)	76	19.1 (16.3 ; 22.4)	0.8 (0.6 ; 1.0)	0.9 (0.7 ; 1.1)	1.2 (0.9 ; 1.5)
D15	76	123.9 (101.5 ; 151.4)	71	252.2 (201.8 ; 315.0)	76	139.5 (115.0 ; 169.3)	2.0 (1.5 ; 2.8)	1.8 (1.4 ; 2.4)	0.9 (0.7 ; 1.2)
D28	73	121.5 (94.4 ; 156.4)	65	211.1 (164.4 ; 271.1)	70	109.8 (89.4 ; 135.0)	1.7 (1.2 ; 2.5)	1.9 (1.4 ; 2.6)	1.1 (0.8 ; 1.5)
D15/D0	76	5.5 (4.3 ; 7.0)	71	14.5 (11.3 ; 18.6)	76	7.3 (5.9 ; 9.0)	2.6 (1.9 ; 3.7)	2.0 (1.4 ; 2.7)	0.8 (0.5 ; 1.0)
D28/D0	73	5.5 (4.1 ; 7.4)	65	12.3 (9.1 ; 16.5)	70	5.8 (4.5 ; 7.4)	2.2 (1.5 ; 3.4)	2.1 (1.4 ; 3.1)	0.9 (0.6 ; 1.4)

Abbreviation: D, Day; GMT, geometric mean titer
* Number of data items available
Microneutralization assay performed at IHU Méditerranée, Marseille, France
Source: Modified from 5.3.5.1 VAT00013 Interim CSR, Table 7 and VAT00013 - Post-hoc analyses, Table 5, Table 6, and Table 7

An additional analysis with the proportion of participants with ≥2-fold, ≥4-fold, and ≥10-fold rise of neutralisation Ab titres against VOCs (D614, B.1.351, B1.617.2, Omicron B.A1) was conducted. For Omicron, the proportion of participants with ≥10-fold rise of neutralisation Ab titres was about 2 times higher in CoV2 preS dTM-AS03 (B.1.351) booster group than in Pfizer/BioNTech booster and CoV2 preS dTM-AS03 (D614) booster groups.

Table 13: VAT00013: Number of participants with from >= 2-fold rise to >= 10 fold rise of neutralisation antibody titres for variant of concerns - PP population

		CoV2 preS dTM-AS03 (D614) booster group n=76		CoV2 preS dTM-AS03 (B.1.351) booster group n=71		Pfizer/BioNTech booster group n=76	
Strain Readout	**Fold rise**	**n***	**% (95% CI)**	**n***	**% (95% CI)**	**n***	**% (95% CI)**
D614 (Wild)	**>=2**	74	97.4 (90.8 ; 99.7)	69	97.2 (90.2 to 99.7)	73	96.1 (88.9 ; 99.2)
	>=4	67	88.2 (78.7 ; 94.4)	63	88.7 (79.0 to 95.0)	70	92.1 (83.6 ; 97.1)
B.1.351 (Beta)	**>=2**	73	96.1 (88.9 ; 99.6)	71	100.0 (94.9 to 100.0)	74	97.4 (90.8 ; 99.7)
	>=4	64	84.2 (74.0 ; 91.6)	69	97.2 (90.2 to 99.7)	67	88.2 (78.7 ; 94.4)
B.1.617.2 (Delta)	**>=2**	72	94.7 (97.1 ; 98.6)	70	98.6 (92.4 to 100.0)	74	97.4 (90.8 ; 99.7)
	>=4	63	82.9 (72.5 ; 90.6)	68	95.8 (88.1 ; 99.1)	72	94.7 (87.1 ; 98.6)
	>=10	38	50.0 (38.3 ; 61.7)	53	74.7 (62.9 ; 84.2)	42	55.3 (43.4 ; 66.7)
B.1.1.529 (Omicron BA.1 subvariant)	**>=2**	68	89.5 (80.3 ; 95.3)	71	100.0 (94.9 ; 100.0)	72	94.7 (87.1 ; 98.6)
	>=4	56	73.7 (62.3 ; 83.1)	67	94.4 (86.2 ; 98.4)	67	88.2 (78.7 ; 94.4)
	>=10	23	30.3 (20.3 ; 41.9)	39	54.9 (42.7 ; 66.8)	23	30.3 (20.3 ; 41.9)

*Number of participants experiencing the endpoint
Microneutralization assay performed at IHU Méditerranée, Marseille, France
Source: Modified from 5.3.5.1 VAT00013 Interim CSR, Table 17

Binding antibody response

The secondary objective #3 was to assess the humoral immune response in each of the booster groups at D15 and D28 by measuring anti-S1 (D614) and anti-RBD (D614 and B.1.351) IgG levels expressed in BAU/mL. It should be noted that only anti-S1 results were available. In addition, an ancillary analysis was performed in a subset of participants to assess the early humoral response in the 3 booster groups at D3 (secondary objective #8). Table below summarizes the results of anti-S1 Ab levels at D0, D3, D15 and D28. At D3, regardless of the booster group, there was no increased humoral response as anti-S1 levels remained in the same range from D0 pre-booster dose to D3 post-booster dose. From D0 to D15, the increase in anti-S1 levels ranged from approximatively 7-fold for CoV2 preS dTM-AS03 (D614) booster group to about 11-fold for CoV2 preS dTM-AS03 (B.1.351) booster group. At D28, anti-S1 levels remained high in all the 3 booster groups with a slight decrease for the anti-S1 Ab levels fold-rise in Pfizer/BioNTech group from approximately 9-fold (D0 to D15) to 7-fold (D0 to D28).

Table 14: VAT00013: Anti-S1 antibody levels against D614 strain at D0, D3, D15, and D28#

	CoV2 preS dTM-AS03 (D614) booster group		CoV2 preS dTM-AS03 (B.1.351) booster group		Pfizer/BioNTech booster group	
Analysis set / Timepoint	**n***	**GMT (95% CI)**	**n***	**GMT (95% CI)**	**n***	**GMT (95% CI)**
PP population		**n=76**		**n=71**		**n=76**
D0	76	277.1 (229.7 ; 334.3)	71	206.8 (134.5 ; 318.0)	76	253.6 (214.4 ; 300.0)
D3	23	189.7 (140.6 ; 255.9)	20	235.5 (180.7 ; 306.9)	18	185.6 (142.9 ; 241.0)
D15	76	1875.1 (1628.0 ; 2159.6)	71	2240.8 (1931.3 ; 2600.0)	76	2405.4 (2130.8 ; 2715.4)
		n=73		**n=65**		**n=70**
D28	73	1782.4 (1527.7 ; 2079.7)	65	2108.2 (1798.5 ; 2471.1)	70	1878.9 (1641.5 ; 2150.6)
ITT population		**n=84**		**n=78**		**n=80**
D0	84	277.7 (232.5 ; 331.6)	78	210.8 (142.2 ; 312.4)	80	251.8 (214.5 ; 295.7)
D3	23†	189.7 (140.6 ; 255.9)	23	220.0 (171.5 ; 282.2)	18	185.6 (142.9 ; 241.0)
D15	82‡	1944.3 (1695.5 ; 2229.5)	77§	2387.3 (2056.0 ; 2772.0)	79††	2449.7 (2173.5 ; 2761.0)
D28	84	1910.2 (1645.6 ; 2217.3)	77**	2327.1 (1985.4 ; 2727.7)	79‡‡	2024.5 (1765.2 ; 2321.9)

Abbreviation: GMT, geometric mean titer; ITT population, Intention To Treat population; PP population, Per Protocol population
* Number of data items available
† One participant infected with SARS-CoV-2 (D3 sampling not performed)
‡ One participant with insufficient serum volume, 1 participant infected with SARS-CoV-2 (D15 visit not performed)
§ One participant infected with SARS-CoV-2 (D15 visit performed by telephone, D15 sampling not performed)
** One participant not coming to the scheduled D28 visit at the site, visit performed by telephone
†† One participant with insufficient serum volume
‡‡ One participant infected with SARS-CoV-2, D28 visit not performed
Source: Modified from 5.3.5.1 VAT00013 Interim CSR, Table 6

- **Ancillary analyses**

The secondary objective #9 was to explore the CD4 and CD8 cellular response for the 3 booster vaccines in an ancillary study using ELISpot assay. Overall, 61 participants (27.4%) from the PP population participated in the ancillary study: 23 participants in CoV2 preS dTM-AS03 (D614) booster group, 20 participants in CoV2 preS dTM-AS03 (B.1.351) booster group, and 18 participants in Pfizer/BioNTech booster group.

In all booster groups, participants from this ancillary study mainly mounted cellular response for CD4+ T-cells (1.5-fold and 2-fold increase from D0 to D15) that secreted both interferon gamma (IFNγ) and interleukin (IL)-2 for D614G strain and IFNγ for Omicron BA.1. The fold increase of the cellular response for both D614G and Omicron strains from baseline to D15 post-booster was higher in CoV2 preS dTM-AS03 (D614) and CoV2 preS dTM-AS03 (B.1.351) booster groups than in Pfizer/BioNTech booster group. The proportion of participants with these CD4+ T-cells responses and the increase of these responses from D0 to D15 were remarkably higher in CoV2 preS dTM-AS03 (D614) and CoV2 preS dTM-AS03 (B.1.351) booster groups for both D614 and Omicron strains than Pfizer/BioNTech booster group. For Omicron strain, > 80% of participants showed cellular responses (CD4 IFNγ) for CoV2 preS dTM-AS03 (D614) and CoV2 preS dTM-AS03 (B.1.351) booster groups versus approximately 55% of participants for Pfizer/BioNTech booster group.

VAT00002 - Supplemental Phase III Cohort 2

The Phase III of study phase II/III VAT00002 includes 2 Supplemental Cohorts. Supplemental cohorts have a parallel, randomized and non-randomized, double-blind (Booster Cohort 2) or open-label (Booster Cohort 1), active comparator design. This Phase III part of the VAT00002 study is to assess the safety and immunogenicity of the CoV2 preS dTM-AS03 vaccine, for use as a booster.

The following assessment is limited to the aspects relevant for the analysis of Supplemental Cohorts 2, i.e. for participants randomised to receive a booster dose of the vaccine formulation adapted to the B.1.351 variant (or the comparator group).

Methods

- **Study Participants**

Inclusion criteria

- Aged 18 years or older on the day of inclusion
- A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:
    - Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile, or;
    - Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to the first vaccination until at least 12 weeks after the last vaccination (i.e., second dose of primary series or booster injection).
    - A participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 4 hours before any dose of study intervention.
- Informed consent form has been signed and dated
- Able to attend all scheduled visits and to comply with all study procedures
- Covered by health insurance, only if required by local, regional, or national regulations
- SARS-CoV-2 rapid serodiagnostic test performed at the time of enrollment to detect presence of SARS-CoV-2 antibodies (Original Phase II Cohort)
- For persons living with human immunodeficiency virus (HIV), stable HIV infection determined by participant currently on ARVs with CD4 count > 200/mm3
- Does not intend to receive an authorized/approved COVID-19 vaccine from first vaccination to 3 weeks after the second vaccination (D43) despite encouragement by the Investigator to receive the authorized vaccine available to them at the time of enrollment
- **Supplemental cohorts:** for participants originally enrolled in the Phase II Cohort of the study, informed consent has to be signed and dated for transitioning to Supplemental Cohort 2
- **Supplemental Cohorts, Booster Arms:** received a complete primary vaccination series with an authorized/conditionally approved mRNA COVID-19 vaccine (mRNA-1273 [Moderna] or BNT162b2 [Pfizer/BioNTech]) or adenovirus-vectored COVID-19 vaccine (ChAdOx1 nCoV-19 [Oxford University/AstraZeneca] or Ad26.CoV2.S [J&J/Janssen]), with the last dose

administered a minimum of 4 months prior to inclusion but not longer than 10 months prior to inclusion.

Exclusion Criteria

- Participation at the time of study enrollment (or in the 30 days preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure
- 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.
- **Applicable to Original Phase II Cohort, Supplemental Cohort 1, Cohort 2 Comparator Group:** Prior administration of a coronavirus vaccine (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], SARS-CoV, Middle East Respiratory Syndrome [MERS-CoV])
- 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
- Dementia or any other cognitive condition at a stage that could interfere with following the study procedures based on Investigator's judgment
- Self-reported thrombocytopenia, contraindicating (IM) vaccination based on Investigator's judgment
- Bleeding disorder, or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating IM vaccination based on Investigator's judgment
- Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
- Unstable acute or chronic illness that in the opinion of the Investigator or designee poses additional risk as a result of participation or that could interfere with the study procedures
- Receipt of solid-organ or bone marrow transplants in the past 180 days
- Receipt of anti-cancer chemotherapy in the last 90 days
- Receipt of immunoglobulins, blood, or blood-derived products in the past 3 months
- Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥38.0°C).
- Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member of the Investigator or employee with direct involvement in the proposed study
- Exclusion criterion for the Supplemental Cohort 1 and Cohort 2 Comparator Group: positive rapid diagnostic test for SARS-CoV-2 antibodies at time of enrollment
- Exclusion criterion for Supplemental Cohort 2 CoV2 preS dTM-AS03 (D614) primed individuals (i.e. primed as participant in the Original Phase II Cohort of the present study): Receipt of authorized/conditionally approved COVID-19 vaccine after enrollment in Original Phase II Cohort
- **Exclusion criterion for all Booster Groups:** Documented virologically-confirmed SARS-CoV-2 infection (by NAAT) after first dose of primary immunization

Criteria for Evidence of Prior SARS-CoV-2 Infection at Baseline and at Second Injection (for Comparator Group Only)

The numbers and proportions of participants with unrecognized prior SARS-CoV-2 infection prior to booster dose in the intervention cohorts (booster cohorts) is currently not known. To further evaluate the potential impact of prior infection, the applicant has retrospectively evaluated the baseline samples of booster arms for the presence of antibodies to SARS-CoV-2 nucleoprotein.

- **Treatments**

The study design is aiming to assess the nAB immune response of a booster dose of the MV (B1.351) protein vaccine after priming with 2 different COVID-19 vaccine platforms, i.e. after priming with either 2 mRNA or 2 Ad-vector COVID-19 vaccines. Moreover, a homologous protein booster is assessed.

mRNA and Ad-vector primed groups

In the Supplemental Phase III Cohort 2 part of study VAT00002 participants in the mRNA and Ad-vector primed groups received either MV CoV2 preS dTM-AS03 (5 µg B.1.351) or BV CoV2 preS dTM-AS03 (2.5 µg D614 + 2.5 µg B.1.351) vaccines as a single booster injection. Participants were previously primed (4 to ≤10 months prior the booster injection) with one of the following vaccine candidates:

- 2 COVID-19 mRNA vaccine candidates: BNT162b2: International Non-Proprietary Name (INN)-Tozinameran, COVID-19 mRNA vaccine (nucleoside-modified) from Pfizer/BioNTech, or mRNA-1273: INN-COVID-19 mRNA vaccine (nucleoside-modified) from Moderna
- 2 adenovirus-vectored vaccine candidates (Ad-vector primed groups): ChAdOx1-nCOV-19: INN- COVID-19 vaccine (ChAdOx1-S [recombinant]) vaccine from Oxford University/AstraZeneca, or Ad26.COV2-S: INN- COVID-19 vaccine (Ad26.COV2-S [recombinant]) from Johnson & Johnson/Janssen

Protein Primed Group

Participants in the Protein primed vaccine group were previously primed (4 to ≤10 months prior the booster injection) with either 5 µg, 10 µg, or 15 µg antigen dose of CoV2 preS dTM-AS03 (D614) vaccine in the VAT00002 Original Phase II Cohort. They received 1 dose of 5 µg antigen of either MV (D614) vaccine or MV (B.1.351) vaccine in Supplemental Cohort 2.

Comparator group

In the Comparator Group SARS-CoV-2 naïve, unvaccinated participants were to receive 2 injections of 10 µg antigen dose of the CoV2 preS dTM MV (D614).

- **Objectives and endpoints**

Only immunogenicity variables are listed here. The study included (primary) safety endpoints. It corresponds to Protocol Amendment 6 (version 10.0).

The immunogenicity objectives and endpoints relevant to this application are presented in the below table.

Table 15: Immunogenicity objectives and endpoints of Study VAT00002 - Supplemental Phase III Cohorts relevant to this application

Objectives	Endpoints
Primary Immunogenicity-Supplemental Cohort 2	
Co-primary objectives: 1) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 2) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is superior to that observed immediately before booster.	• Individual serum neutralising titre at D01 and D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups. • Individual serum neutralising titre at D01 and D15 against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group. • Individual serum neutralising titre against the D614G strain at D36 (Comparator Group)
Secondary Immunogenicity†-Supplemental Cohort 2 †***Note:*** *The numbering, description, and associated endpoints of secondary immunogenicity objectives are as introduced in the study protocol.*	
Conditional co-secondary objectives: conditional on meeting the primary immunogenicity objectives for Supplemental Cohort 2: 1) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with CoV2 preS dTMAS03 (D614) vaccine in naïve, previously unvaccinated individuals. 2) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is superior to that observed immediately before booster. Conditional secondary objective: conditional on meeting the primary immunogenicity objectives (1) and (2) and the co-secondary objectives for Supplemental Cohort 2: 3) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 +	Endpoints for conditional secondary objectives #1 and #2: • Individual serum neutralising titre at D01 and D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups. • Individual serum neutralising titre at D01 and D15 against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group. • Individual serum neutralising titre against the D614 strain at D36 (Comparator Group). Endpoints for conditional secondary objectives #3: • Individual serum neutralising titre at D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups • Individual serum neutralising titre at D36 against the B.1.351 variant for the Comparator Group. Endpoints for conditional secondary objectives #4 and #5: • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralising titre (post/pre) at D15 relative to D01, against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-

B.1.351) vaccine induces an immune response against the B.1.351 variant at D15 that is superior to that against the B.1.351 variant at D36 in the Comparator Group. <u>Conditional secondary objectives: conditional on meeting the conditional secondary objective (3) for Supplemental Cohort 2, the following objectives will be sequentially tested:</u> 4) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two-dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 5) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals.	AS03 (D614 + B.1.351) vaccine Intervention Groups. • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralising titre [post/pre] at D15 relative to D01, against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group. • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralising titre [post/pre] against the D614G strain at D36 relative to D01 (Comparator Group).
<u>Secondary objectives:</u> 6) To describe, in adults 18-55 years of age and previously vaccinated with an adenovirus-vectored COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine compared to the response induced by a two dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 7) To describe, in adults 18-55 years of age and previously vaccinated with an adenovirus-vectored COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine compared to that observed immediately before booster. 8) To describe, in adults 18-55 years of age previously vaccinated with the Moderna vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 9) To describe, in adults 18-55 years of age previously vaccinated with the Oxford/AstraZeneca vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine.	<u>Endpoints for secondary objectives #6 - #11:</u> • Individual serum neutralising titre at D01 and D15 against the D614G strain and to the B.1.351 variant in each Intervention Group • Individual serum neutralising titre fold-rise post-vaccination relative to D01 at D15 against the D614G strain and to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralising titre [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain and to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralising titre [post/pre] at D15 relative to D01, against the D614G strain and to the B.1.351 variant in each study Intervention Group <u>Endpoints for secondary objective #12:</u> • Individual serum neutralising titre at D01 and D15 to the B.1.351 variant in each Intervention Group • Individual serum neutralising titre at D01 and D36 to the B.1.351 variant in the Comparator Group <u>Endpoints for secondary objective #13:</u> • Individual serum neutralising titre at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralising titre at D01 and D36 against the D614G strain in the Comparator Group

10) To describe, in adults 18-55 years of age previously vaccinated with the J&J/Janssen vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 11) To describe, in adults 18-55 years previously vaccinated with any COVID-19 vaccine, the immune response a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 12) To compare the neutralising antibody profile to the B.1.351 variant at D15 in each study Intervention Group and D36 in the Comparator Group, overall, by priming platform, and by priming vaccine. 13) To compare the neutralising antibody profile against the D614G strain at D15 following a booster dose of CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine and at D36 in the Comparator Group. 14) To describe, among adults previously primed with CoV2 preS dTM-AS03 (D614) vaccine, the immune response induced by a booster dose of CoV2 preS dTM-AS03 (D614) vaccine[‡] or CoV2 preS dTM-AS03 (B.1.351) vaccine, overall, by priming dose, and by age. 17) To describe, in adults over 55 years of age, the neutralising antibody profile to the B.1.351 variant and to the D614G strain at D01 and D15 by Intervention Group, overall, by priming platform, and by priming vaccine.	<u>Endpoints for secondary objective #14:</u> • Individual serum neutralising titre at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralising titre fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralising titre [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralising titre [post/pre] at D15 relative to D01, against the D614G strain in each study Intervention Group • Individual serum neutralising titre at D01 and D15 profile to the B.1.351 variant in each Intervention Group • Individual serum neutralising titre fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralising titre [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralising titre [pre/post] at D15 relative to D01, profile to the B.1.351 variant in each study Intervention Group <u>Endpoints for secondary objective #17:</u> • Individual serum neutralising titre at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralising titre fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralising titre [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold-or greater rise in serum neutralising titre [pre/post] at D15 relative to D01, against the D614G strain in each study Intervention Group • Individual serum neutralising titre at D01 and D15 profile to the B.1.351 variant in each Intervention Group • Individual serum neutralising titre fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralising titre [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the

	B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold-or greater rise in serum neutralising titre [pre/post] at D15 relative to D01, profile to the B.1.351 variant in each study Intervention Group
‡ ***Note:*** *Summary results for Protein primed participants boosted with MV CoV2 preS dTM-AS03 (D614) vaccine were presented in Booster Cohort 1 brief CSR. This brief CSR only includes summary results for Protein primed participants boosted with MV CoV2 preS dTM-AS03 (B.1.351) vaccine.*	
Exploratory Immunogenicity-Supplemental Cohort 2	
Supplemental Cohort 2: 5) To describe the neutralising antibody response to emergent SARS-CoV-2 variant strains	Endpoints for exploratory immunogenicity objective #5: Neutralising antibody responses to emergent variant strains will be measured: • Individual serum neutralising titre at each pre-defined time point • Individual serum neutralising titre fold-rise post-vaccination relative to D01 at each pre-defined time point • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralising titre [post/pre] at each pre-defined post-vaccination timepoint
Supplemental Cohort 2: 7) To describe the neutralising antibody response, by presence or absence of baseline high-risk medical condition	Endpoints for exploratory immunogenicity objective #7: Neutralising antibody responses to D614G and B.1.351 strains will be measured: • Individual serum neutralising titre at each pre-defined time point • Individual serum neutralising titre fold-rise post-vaccination relative to D01 at each pre-defined time point • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralising titre [post/pre] at each pre-defined post-vaccination timepoint

- **Sample size**

The study was powered to show that (1) the immune response induced by the booster vaccination (B.1.351 or D614 + B.1.351) is not inferior to the one generated by the priming series (D614); (2) the booster vaccine induces an immune response that is superior to that observed immediately before booster.

The study design included co-primary endpoints (to be tested both for superiority and non-inferiority), sequential secondary endpoints and various treatment arms, so that several considerations and assumptions drove the sample size calculation, including: the control of the type 1 error, attrition rates, previous estimates on several immunogenicity parameters, stratification factors (age and primer vaccine). Overall, 2180 participants were included in cohort 2 main arms plus 515 participants in the comparator arm (i.e. primary series) as reflected in the table below.

Table 16: planned sample sizes for supplemental cohorts 1 and 2

		Cohort 1	Cohort 2 Main Arms			Comparator
		Booster	Booster	Booster	Booster	Primary Series
		CoV2 preS dTM-AS03 (D614)	CoV2 preS dTM-AS03 (B.1.351)	CoV2 preS dTM-AS03 (D614 + B.1.351)	CoV2 preS dTM-AS03 (D614)	CoV2 preS dTM-AS03 (D614)
Total Overall		565	970	865	345	515
SARS-CoV-2-naïve, Unvaccinated, Adults (18-55 years)		--	--	--	--	515
Pfizer/BioNTech	Adults (18-55 years)	215	515	515	--	--
	Older adults (≥ 56 years)	50	50	50	--	--
CoV2 preS dTM-AS03 (Original Phase II Cohort participants)	Adults (18-55 years)	--	30	--	270	--
	Older adults (≥ 56 years)	--	75	--	75	--
Moderna	Adults (18-55 years)	75	75	75	--	--
	Older adults (≥ 56 years)	25	25	25	--	--
Oxford University/ AstraZeneca	Adults (18-55 years)	75	75	75	--	--
	Older adults (≥ 56 years)	25	25	25	--	--
J&J/Janssen	Adults (18-55 years)	75	75	75	--	--
	Older adults (≥ 56 years)	25	25	25	--	--

400 participants were planned to be enrolled in the cohort 2 exploratory arms; this sample size was not based on hypothesis to be tested but rather to provide information on potential future adjustments of the booster vaccines. this sample size was not based on hypothesis to be tested but rather to provide information on potential future adjustments of the booster vaccines, as included in the below table.

Table 17: planned sample sizes for Supplemental cohort 2 exploratory B.1.351 arms

		CoV2 preS dTM (B.1.351) Treatment Groups			
		2.5 µg with full-dose AS03	5 µg with half-dose AS03	5 µg with no adjuvant	2.5 µg with half-dose AS03
Total Overall		100	100	100	100
Age Groups	Adults (18-55 years)	75	75	75	75
	Older adults (≥ 56 years)	25	25	25	25

Interim analysis

For Supplemental Cohort 2, an interim analysis may have been carried out once the following conditions apply:

- Primary immunogenicity data is available up to D15 and primary safety data is available up to D22 for the booster groups in Supplemental Cohort 2
- Primary immunogenicity data is available up to D36 and primary safety data is available up to D43 in the Comparator group for Supplemental Cohorts 1 and 2
- Partial database lock is performed

For Supplemental Cohort 2, a prespecified independent statistical group who will be unblinded at participant level was to generate interim outputs including tables, listings, and figures. The treatment code was to be masked from the interim outputs. A group of study members will review the interim outputs unblinded at group level, to perform decision-making. Furthermore, the study team will remain blinded on data collected after date cut-off of the interim analysis.

- **Randomisation and Blinding (masking)**

All participants in the study were randomised to receive one of the three formulations of the CoV2 preS dTM-AS03 experimental vaccine, with no other vaccine or placebo to be used as external comparator.

Randomisation of the participants into the supplemental cohorts study arms was planned to be stratified based on age, priming vaccine, exploratory vs. non-exploratory ("main") arms, and high-risk medical condition. The Supplemental Cohort 2 Main Arm contained several subarms; in most cases, participants were assigned on a 1:1 ratio to the treatments available for their characteristics (possible subarms: CoV2 preS dTM-AS03 (B.1.351) vs CoV2 preS dTM-AS03 (D614 + B.1.351); CoV2 preS dTM-AS03 (D614) vs CoV2 preS dTM-AS03 (B.1.351)). Younger adults (18-55 years) previously vaccinated with the protein-based vaccine in the Original Phase II Cohort were randomised on a 9:1 ratio to the D614 : B.1.351 vaccine formulations. Participants were only assigned to the Supplemental Cohort 2 Exploratory Arm when a sufficient number of corresponding participants had been allocated to the main arms in a 1:1:1:1 ratio. The Supplemental Cohort Comparator Group was open-label, thus not randomised, and consisted of previously unvaccinated participants.

- **Statistical methods**

The assessment below refers to the portions of study VAT00002 - cohort 2 which assess the CoV2 preS dTM-AS03 (B.1.351) vaccine.

Analysis Populations/Sets

Safety Analysis Set (SafAS): Participants randomized and who have received at least one dose of the study vaccines. All participants will have their safety data analyzed after each dose according to the vaccine they truly received, and after any dose according to the vaccine received at the first dose.

Full analysis set (FAS): All randomized participants who receive at least one study injection. Participants will be analyzed according to the intervention to which they were randomized.

Per-protocol analysis set (PPAS): Subset of the FAS excluding participants who underwent prespecified protocol deviations regarding inclusion/exclusion criteria, vaccine administration, or schedule of study procedures.

Cellular Immunity and Mucosal analysis set (CMIAS), Variant Testing analysis set (VTAS): further subsets of FAS for which additional analyses concerning immunity and variant-specific analyses were planned.

SARS-CoV-2 Naïve at baseline (Naïve-D01): Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND Negative NAAT for SARS-CoV-2 on respiratory sample collected on D01.

SARS-CoV-2 Naïve at second injection (Naïve-D01+D22): Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND Negative NAAT for SARS-CoV-2 on respiratory sample collected on D01 and D22.

Analysis set used in analysis is included in the below table.

Table 18: Analysis set used in analyses

Cohort	Type of Analyses		Intervention group(s)	Comparator group
Supplemental Cohort 1, Supplemental Cohort 2	Primary immunogenicity	Main	PPAS	PPAS Naïve at D01+D22
		Sensitivity	FAS	FAS Naïve at D01 FAS Naïve at D01+D22
	Secondary immunogenicity	Main	PPAS	PPAS Naïve at D01+D22
		Sensitivity	FAS	FAS Naïve at D01 FAS Naïve at D01+D22
	Exploratory immunogenicity regarding objective #11		PPAS	PPAS Naïve at D01+D22
	Exploratory immunogenicity in CMI subset for Cohort 2		CMIAS	CMIAS
	Exploratory immunogenicity in Variant Testing subset		VTAS Variant Testing Subset	VTAS Naïve at D01+D22 Variant Testing Subset Naïve at D01+D22
Supplemental Cohorts	Primary, Secondary safety		SafAS	SafAS

Primary Endpoint(s) / Primary Estimand(s)

Co-primary objectives regarding CoV2 preS dTM-AS03 (B.1.351):

1) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech mRNA COVID-19 vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) induces an immune response that is non-inferior to the response induced by a two-dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals.
2) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech mRNA COVID-19 vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) induces an immune response that is superior to that observed immediately before booster.

Endpoints: Individual serum neutralising titre at D01 and D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351); individual serum neutralising titre against the D614G strain at D36 (Comparator Group).

Hypotheses:

Primary objective 1: Non-inferiority to the comparator for participants primed with the Pfizer/BioNTech vaccine. The non-inferiority in terms of GMT will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of the GMT is greater than (1/1.5):

Null hypothesis (H0) : GMT(booster) / GMT(comparator) ≤(1/1.5)

Alternative hypothesis (H1) : GMT(booster) / GMT(comparator) > (1/1.5)

Primary objective 2: superiority to pre-booster for participants primed with the Pfizer/BioNTech vaccine. The superiority will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio

of serum neutralisation titre is greater than 2:

Null hypothesis (H0) : Ratio (post-booster/pre-booster) ≤ 2

Alternative hypothesis (H1) : Ratio (post-booster/pre-booster) > 2

Due to the nature of immunogenicity titre, logarithm transformation of the individual data (titres or concentrations) (log10(data)) were to be calculated and assumed to be normally distributed. The statistical inference was to be based on the use of the two-sided 98.3% CI (Supplemental Cohorts 1 and 2) for non-inferiority of difference in means of post-vaccination log10 transformed concentrations between the 2 groups with normal approximation. Confidence interval for the GMT ratio between booster arms and comparator group were to be calculated via Welch's t-interval. Confidence interval for paired GMTR were to be used for the pre- vs. post-booster comparison (assumed normal approximation).

The primary analysis was to be conducted in the PPAS.

A sensitivity analysis was planned to be repeated in the FAS.

Analyses of pooled primary series were planned only to be conducted if the number of evaluable Supplemental Phase III Cohorts Comparator Group participants is < 260 (i.e. power < 70% for the primary objectives).

Subgroup analyses, were planned to be performed by age-group (18-55 years and ≥ 56 years) for intervention groups, by priming vaccine (Supplemental Cohorts 1 and 2), and by priming platform (Supplemental Cohorts 1 and 2), in addition to the Overall group.

Secondary Endpoints / Secondary Estimand(s) and Subgroup Analyses

Conditional secondary objectives:

1.1) non-inferiority to the comparator in participants primed with an mRNA vaccine; analysis method as above

1.2) superiority to pre-booster in participants primed with an mRNA vaccine; analysis method as above

2) superiority to the comparator in terms of GMT against B.1.351 (Pfizer/BioNTech vaccine only); analysis method as above

3) non-inferiority in terms of seroresponse rate for participants primed with the Pfizer/BioNTech or mRNA vaccines (hierarchically). The non-inferiority will be demonstrated if the lower limit of the two-sided 98.3% CI of the difference between the 2 proportions is great than -10%:

Null hypothesis (H0) : p(booster) - p(comparator) ≤ -10%

Alternative hypothesis (H1) : p(booster) - p(comparator) > -10%

Multiplicity

Each supplemental cohort (testing the monovalent vaccines against D614, the monovalent vaccine against B.1.351 and the bivalent vaccine against both D614 and B.1.351, respectively) was tested one-sided at α/3 with α = 0.025. For the monovalent vaccine against B.1.351 (2nd row in figure 9.1 from the study protocol), the two co-primary endpoints (non-inferiority of antibody titres in boosted vs. control group; superiority of antibody titres pre-booster vs. post-booster) were planned to be first tested in the Pfizer/BioNTech primed group, then, hierarchically in participants primed with an mRNA vaccine. Further secondary endpoints were tested hierarchically. The primary and secondary endpoints

are described above.

Results

- **Participant flow**

1326 participants received a booster dose of either MV CoV2 (B.1.351) vaccine or BV (D614 + B.1.351) vaccine. Overall, 705 participants previously primed with either an mRNA, Ad-vector, or with the MV CoV2 (D614) protein vaccine received a single booster dose of MV (B.1.351) vaccine and 621 participants previously primed with either an mRNA or Ad-vector priming vaccine received a single booster dose of BV (D614 + B.1.351) vaccine. Participants were stratified by primary vaccine platform, booster vaccine received, and age (see table below).

Table 19: VAT00002 - Supplemental Phase III Cohort 2: Disposition of Booster Group participants by prime/boost vaccine

Prior Prime Vaccination	Pfizer Primed		Moderna Primed		AZ Primed		J&J Primed		Protein Primed	All Booster	
Booster Vaccine Allocated	MV (B.1.351) (N=378) n/M (%)	BV (D614+B.1.351) (N=378) n/M (%)	MV (B.1.351) (N=112) n/M (%)	BV (D614+B.1.351) (N=108) n/M (%)	MV (B.1.351) (N=101) n/M (%)	BV (D614+B.1.351) (N=101) n/M (%)	MV (B.1.351) (N=38) n/M (%)	BV (D614+B.1.351) (N=38) n/M (%)	MV (B.1.351) (N=78) n/M (%)	MV (B.1.351) (N=707) n/M (%)	BV (D614+B.1.351) (N=625) n/M (%)
Enrolled	378/378 (100)	378/378 (100)	112/112 (100)	108/108 (100)	101/101 (100)	101/101 (100)	38/38 (100)	38/38 (100)	78/78 (100)	707/707 (100)	625/625 (100)
Completed booster dose	378/378 (100)	375/378 (99.2)	111/112 (99.1)	108/108 (100)	100/101 (99.0)	100/101 (99.0)	38/38 (100)	38/38 (100)	78/78 (100)	705/707 (99.7)	621/625 (99.4)
Participant received an authorized / approved COVID-19 vaccine prior to D15	0/378	2/378 (0.5)	0/112	0/108	1/101 (1.0)	0/101	0/38	0/38	0/78	1/707 (0.1)	2/625 (0.3)
Discontinuation status at D22:											
• Adverse event	0/378	0/378	0/112	0/108	0/101	0/101	0/38	0/38	0/78	0/707	0/625
• Death	0/378	0/378	0/112	0/108	0/101	0/101	0/38	0/38	0/78	0/707	0/625
• Withdrawal by participant	5/378 (1.3)	2/378 (0.5)	1/112 (0.9)	0/108	1/101 (1.0)	0/101	0/38	0/38	1/78 (1.3)	8/707 (1.1)	2/625 (0.3)
• Lost to follow-up	3/378 (0.8)	1/378 (0.3)	2/112 (1.8)	0/108	1/101 (1.0)	0/101	0/38	0/38	0/78	6/707 (0.8)	1/625 (0.2)
• Protocol deviation	12/378 (3.2)	14/378 (3.7)	5/112 (4.5)	4/108 (3.7)	2/101 (2.0)	1/101 (1.0)	0/38	4/38 (10.5)	1/78 (1.3)	20/707 (2.8)	23/625 (3.7)

N: number of participants randomized in each group; n: number of participants fulfilling the item listed; M: number of participants randomized in each vaccine and subgroup
Prior prime vaccination: Pfizer = Pfizer/BioNTech, Moderna = Moderna, AZ = Oxford University/AstraZeneca, J&J = Johnson & Johnson/Janssen, Protein = CoV2 preS dTM-AS03 (D614) vaccine.
Booster vaccine received: MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351) vaccine, BV (D614 + B.1.351) = CoV2 preS dTM-AS03 (2.5 µg D614 + 2.5 µg B.1.351) vaccine
Source: Modified from 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Section 8, Table 8.5, Table 8.8 and Table 8.28

mRNA and Ad-vector primed group

A total of 1248 participants primed with either mRNA or adenovirus-vectored priming platform received a single booster dose of either MV (B.1.351) or BV (D614 + B.1.351) vaccines in a 1:1 ratio. 627 participants primed with either an mRNA or an Ad-vector vaccine received a single booster dose of (B.1.351) vaccine, 488 of them were 18-55 years and 139 ≥56 years. 378 participants were previously primed with the Pfizer/BioNTech vaccine, 111 with the Moderna vaccine, 100 participants with Oxford/AstraZeneca vaccine, and 38 participants with J&J/Janssen. The majority of participants was 18-55 years of age.

Protein primed group

In the Protein primed group, participants primed with CoV2 (D614) vaccine in the VAT00002 - Original Phase II Cohort were enrolled to receive a single booster dose of either MV (D614) or MV (B.1.351) vaccines. The Protein primed group participants were not randomized to receive the BV (D614 + B.1.351) booster vaccine.

Overall, 78 participants from the FAS (4 aged 18-55 years and 74 aged ≥56 years) received the MV (B.1.351) vaccine. Among them, 23 (29.5%) participants were primed with 5 µg of MV (D614) vaccine, 33 (42.3%) were primed with 10 µg of MV (D614) vaccine, and 22 (28.2%) were primed with 15 µg of MV (D614) vaccine. 4 participants were 18-55 years and 74 participants ≥56 years.

Comparator group

In the Comparator Group, a total of 479 participants (463 aged 18-55 years, 16 aged ≥56 years) were enrolled to receive CoV2 preS dTM-AS03 (D614) vaccine as a primary series vaccination of 2 injections given 21 days apart. Of those, 473 participants (459 aged 18-55 years, and 14 aged ≥56 years) received at least a study injection.

For the data collection period of this report, the study duration for all Cohort 2 participants was 180 days and the mean duration (standard deviation in the study) of participation was 144 (± 30.9) days.

Disposition of participants ≥ 56 years

Of the 615 participants in the PPAS who were boosted with the MV (B.1.351) vaccine, 180 participants were ≥ 56 years and of the 561 participants boosted with BV (D614 + B.1.351) vaccine 132 participants were ≥56 years.

Overall, 140 (10.5%) participants (all priming platforms including the protein vaccine platform together) were ≥65 years, including 88 (12.4%) participants in the MV (B.1.351) vaccine group and 52 (8.3%) participants in BV (D614 + B.1.351) vaccine group. A more detailed overview for the age distribution of participants 65 years of age and older is provided in the below table.

Table 20: Number and percentage of elderly participants by priming vaccine and randomized group for VAT00002 Booster Cohort 2 and Comparator Group

	Pfizer Primed		Moderna Primed		mRNA Primed		AZ Primed		J&J Primed		Ad-vector Primed		Protein Primed	All Booster		All Booster (N=1332)	Comparator Group
	MV (B.1.351) (N=378)	BV (D614 + B.1.351) (N=378)	MV (B.1.351) (N=112)	BV (D614 + B.1.351) (N=108)	MV (B.1.351) (N=490)	BV (D614 + B.1.351) (N=486)	MV (B.1.351) (N=101)	BV (D614 + B.1.351) (N=101)	MV (B.1.351) (N=38)	BV (D614 + B.1.351) (N=38)	MV (B.1.351) (N=139)	BV (D614 + B.1.351) (N=139)	MV (B.1.351) (N=78)	MV (B.1.351) (N=707)	BV (D614 + B.1.351) (N=625)		
Age group	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 65 years	17 (4.5)	23 (6.1)	15 (13.4)	13 (12.0)	32 (6.5)	36 (7.4)	15 (14.9)	14 (13.9)	3 (7.9)	2 (5.3)	18 (12.9)	16 (11.5)	38 (48.7)	88 (12.4)	52 (8.3)	140 (10.5)	3 (0.6)
≥ 75 years	2 (0.5)	2 (0.5)	1 (0.9)	1 (0.9)	3 (0.6)	3 (0.6)	1 (1.0)	2 (2.0)	0	0	1 (0.7)	2 (1.4)	15 (19.2)	19 (2.7)	5 (0.8)	24 (1.8)	0
≥ 85 years	0	0	0	0	0	0	0	0	0	0	0	0	3 (3.8)	3 (0.4)	0	3 (0.2)	0

N: number of participants in each group; n: number of participants fulfilling the item listed
Prior prime vaccination: Pfizer = Pfizer/BioNTech, Moderna = Moderna, AZ = Oxford University/AstraZeneca, J&J = Johnson & Johnson/Janssen, Protein = CoV2 preS dTM-AS03 (D614)
Prior prime vaccination platform: mRNA = mRNA, Ad-vector = adenovirus-vectored
MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351), BV (D614 + B.1.351) = CoV2 preS dTM-AS03 (2.5 µg D614 + 2.5 µg B.1.351)
Comparator: Monovalent (D614) (10 µg antigen) + AS03 (full-dose adjuvant) as a primary series vaccination of 2 injections given 21 days apart.

Median interval between last priming dose and booster dose

The median interval between the primary vaccination and the booster dose was comparable across participants who received MV (B.1.351) vaccine and those who received BV (D614 + B.1.351) vaccine. The median interval from the last injection of the primary series to receipt of booster injection was as 5.98 months for the Oxford/AstraZeneca primed group, 6.64 months for the Pfizer/BioNTech, 7.36 month for the Moderna, and 7.84 months for the J&J/Janssen primed groups. A slightly longer median interval of 8.21 months was reported for the Protein primed group.

- **Recruitment**

Supplemental Phase III Cohorts: 29 July 2021 first participant first visit.

Booster Groups: 09 March 2022 last participant last D15 Visit.

Comparator Group: 27 December 2021 last participant last D36 Visit.

- **Conduct of the study**

According to the Applicant, VAT00002 was conducted according to GCP Guidelines and current version

of the Declaration of Helsinki.

The protocol was amended several times. Protocol version 10.0 was valid on 20th January 2022. The current Interim CSR (up to date 43, version 1.0, dated 8 June 2022) is based on protocol version 10.0. All protocol versions have been provided together with an overview of the major protocol changes.

- **Baseline data**

Most of the mRNA and Ad-vector primed participants were aged 18-55 years. The mean age (standard deviation [SD]) of participants was 46.0 (15.8) years for those boosted with MV CoV2 preS dTM-AS03 (B.1.351) vaccine and 43.7 (14.3) years for those boosted with BV CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine.

The distribution of participants in countries was similar between participants who received MV CoV2 preS dTM-AS03 (B.1.351) vaccine and those who received BV CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. The vast majority of participants primed with mRNA platform were from the US with about 60% of participants, then from France (approximately 21% of participants), then from Spain, the United Kingdom (UK), and Australia. Those primed with Ad-vector priming platform were mainly from the UK (55% of all participants), then from the US (about 26% of participants), then France, Australia, and Spain. All Ad-vector-primed participants in the UK had been primed with Oxford/AstraZeneca vaccine while all Ad-vector-primed participants in the US were primed with the J&J/Janssen vaccine.

In the per-protocol analysis population primed with mRNA vaccines and receiving VidPrevtyn Beta booster, the mean age of participants was 41.2 years (range 18-83 years); 347 (83.0%) were 18 to 55 years of age, 71 (17.0%) were 56 years of age and older, 25 (6.0%) were 65 years of age and older. Among them, 44.0% were male, 56.0% were female, 67.7% were White, 13.2% were Black or African American, 2.6% were Asian, and 1.0% were American Indian or Alaska Native.

In the per-protocol analysis population primed with adenoviral vector vaccines and receiving VidPrevtyn Beta booster, the mean age of participants was 50.4 years (range 24-77 years); 84 (67.2%) were 18 to 55 years of age, 41 (32.8%) were 56 years of age and older, 17 (13.6%) were 65 years of age and older. Among them, 52.8% were male, 47.2% were female, 78.4% were White, 13.6% were Black or African American, 4.0 % were Asian, and 2.4% were American Indian or Alaska Native.

The Protein primed group encompassed participants who were primed in the VAT00002 - Original Phase II Cohort that included 2 countries, the US and Honduras, and about half of participants who received MV CoV2 preS dTM-AS03 (B.1.351) vaccine were from the US and the other half from Honduras (52.6% of participants and 47.4% of participants, respectively).

Overall, in this Booster Cohort 2, the distribution of participants with different racial origins was similar between participants who received MV CoV2 preS dTM-AS03 (B.1.351) vaccine and those who received BV CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. Most participants were White (66.0% of participants), not Hispanic or Latino, and about 15% of participants were Black or African American. The other racial groups included Asian (3.5% of participants) and American Indian or Alaska Native (2.9% of participants). There was only one Native Hawaiian or Other Pacific Islander participant.

The most common high-risk medical conditions (≥ 5% of participants) were obesity, smoking, hypertension/high blood pressure, and type 2 diabetes mellitus.

In the Comparator Group, among the 479 enrolled participants, a total of 473 participants (459 participants aged 18-55 years and 14 participants aged ≥56 years) received at least a study injection. There were more males than females, with a male to female sex ratio of 1.25. The Comparator Group mostly included participants aged 18-55 years (16 participants aged ≥56 years were also randomized and among them, 14 were vaccinated) and the mean age (SD) of participants was 37.5 (± 11.2) years

overall. More than half of the participants were from Australia (60.9% of participants) and the others were from the US (39.1% of participants). The most common high-risk medical conditions (> 5% of participants) were obesity, smoking, and hypertension/high blood pressure.

- **Numbers analysed**

Population analysed in the PPAS for immunogenicity

The PPAS included 615 participants boosted with MV CoV2 preS dTM-AS03 (B.1.351) vaccine (435 participants aged 18-55 years and 180 participants aged ≥56 years). The sample size for each intervention booster group was not balanced. The majority of participants were included in the Pfizer/BioNTech primed group. In more detail, the MV (B.1.351) booster cohort PPAS included:

- 325 Pfizer/BioNTech primed adults: 279 aged 18-55 years and 46 aged ≥56 years
- 93 Moderna primed adults: 68 aged 18-55 years and 25 aged ≥56 years
- 94 Oxford/AstraZeneca primed adults: 62 aged 18-55 years and 32 aged ≥56 years
- 31 J&J/Janssen primed adults: 22 aged 18-55 years and 9 aged ≥56 years
- 72 Protein primed adults: 4 aged 18-55 years and 68 aged ≥56 years
- 418 mRNA primed adults: 347 aged 18-55 years and 71 aged ≥56 years
- 125 Ad-vector primed adults: 84 aged 18-55 years and 41 aged ≥56 years

The BV (D614 + B.1.351) booster cohort PPAS included 561 participants, including 433 participants primed with mRNA platform (335 with Pfizer/BioNTec and 98 with Moderna) and 128 primed with Adeno-vectored platform (94 with Oxford/Astra Zeneca and 34 with J&J). 429 participants were 18-55 years of age and 132 participants ≥56 years.

Approximately 58% of participants in the PPAS of Booster Cohort 2 presented at least one high-risk medical condition: approximately 58% of participants boosted with MV CoV2 preS dTM-AS03 (B.1.351) vaccine and 59% of participants boosted with BV CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. Of the 220 (57.1%) participants in the PPAS who presented with at least one high-risk medical condition, 213 participants were 18-55 years and 7 participants ≥56 years. An overview of all key booster group analysis sets by age and high-risk medical conditions is given the table below.

Table 21: Supplemental Phase III Cohort 2: Key analysis sets by age group, prior SARS-CoV-2 infection at baseline and second injection, and high-risk medical condition group

Prior Prime Vaccination		Pfizer Primed		Moderna Primed		AZ Primed		J&J Primed		Protein Primed	All Booster	
Booster Vaccine Allocated		MV (B.1.351) (N=378)	BV (D614+B.1.351) (N=378)	MV (B.1.351) (N=112)	BV (D614+B.1.351) (N=108)	MV (B.1.351) (N=101)	BV (D614+B.1.351) (N=101)	MV (B.1.351) (N=38)	BV (D614+B.1.351) (N=38)	MV (B.1.351) (N=78)	MV (B.1.351) (N=707)	BV (D614+B.1.351) (N=625)
Age group/ Status	Analysis set	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)
18-55 years	FAS	318/318 (100)	315/318 (99.1)	78/79 (98.7)	76/76 (100)	64/65 (98.5)	64/65 (98.5)	28/28 (100)	28/28 (100)	4/4 (100)	492/494 (99.6)	483/487 (99.2)
	PPAS	279/318 (87.7)	277/318 (87.1)	68/79 (86.1)	69/76 (90.8)	62/65 (95.4)	58/65 (89.2)	22/28 (78.6)	25/28 (89.3)	4/4 (100)	435/494 (88.1)	429/487 (88.1)
	VTAS*	13/16 (81.3)	9/12 (75.0)	--	--	--	--	--	--	0/0	13/16 (81.3)	9/12 (75.0)
	SafAS	318/318 (100)	315/318 (99.1)	78/79 (98.7)	76/76 (100)	64/65 (98.5)	64/65 (98.5)	28/28 (100)	28/28 (100)	4/4 (100)	492/494 (99.6)	483/487 (99.2)
>= 56 years	FAS	60/60 (100)	60/60 (100)	33/33 (100)	32/32 (100)	36/36 (100)	36/36 (100)	10/10 (100)	10/10 (100)	74/74 (100)	213/213 (100)	138/138 (100)
	PPAS	46/60 (76.7)	58/60 (96.7)	25/33 (75.8)	29/32 (90.6)	32/36 (88.9)	36/36 (100)	9/10 (90.0)	9/10 (90.0)	68/74 (91.9)	180/213 (84.5)	132/138 (95.7)
	VTAS*	--	--	--	--	--	--	--	--	--	--	--
	SafAS	60/60 (100)	60/60 (100)	33/33 (100)	32/32 (100)	36/36 (100)	36/36 (100)	10/10 (100)	10/10 (100)	74/74 (100)	213/213 (100)	138/138 (100)
All	FAS	378/378 (100)	375/378 (99.2)	111/112 (99.1)	108/108 (100)	100/101 (99.0)	100/101 (99.0)	38/38 (100)	38/38 (100)	78/78 (100)	705/707 (99.7)	621/625 (99.4)
	PPAS	325/378 (86.0)	335/378 (88.6)	93/112 (83.0)	98/108 (90.7)	94/101 (93.1)	94/101 (93.1)	31/38 (81.6)	34/38 (89.5)	72/78 (92.3)	615/707 (87.0)	561/625 (89.8)
	VTAS*	13/16 (81.3)	9/12 (75.0)	--	--	--	--	--	--	0/0	13/16 (81.3)	9/12 (75.0)
	SafAS	378/378 (100)	375/378 (99.2)	111/112 (99.1)	108/108 (100)	100/101 (99.0)	100/101 (99.0)	38/38 (100)	38/38 (100)	78/78 (100)	705/707 (99.7)	621/625 (99.4)
High risk medical condition group (all age groups)												
YES	FAS	201/201 (100)	217/219 (99.1)	69/70 (98.6)	63/63 (100)	50/51 (98.0)	54/55 (98.2)	32/32 (100)	30/30 (100)	63/63 (100)	415/417 (99.5)	364/367 (99.2)
	PPAS	167/201 (83.1)	196/219 (89.5)	58/70 (82.9)	57/63 (90.5)	45/51 (88.2)	50/55 (90.9)	26/32 (81.3)	26/30 (86.7)	58/63 (92.1)	354/417 (84.9)	329/367 (89.6)
	VTAS*	4/5 (80.0)	5/7 (71.4)	--	--	--	--	--	--	0/0	4/5 (80.0)	5/7 (71.4)
	SafAS	201/201 (100)	217/219 (99.1)	69/70 (98.6)	63/63 (100)	50/51 (98.0)	54/55 (98.2)	32/32 (100)	30/30 (100)	63/63 (100)	415/417 (99.5)	364/367 (99.2)
NO	FAS	177/177 (100)	158/159 (99.4)	42/42 (100)	45/45 (100)	50/50 (100)	46/46 (100)	6/6 (100)	8/8 (100)	15/15 (100)	290/290 (100)	257/258 (99.6)
	PPAS	158/177 (89.3)	139/159 (87.4)	35/42 (83.3)	41/45 (91.1)	49/50 (98.0)	44/46 (95.7)	5/6 (83.3)	8/8 (100)	14/15 (93.3)	261/290 (90.0)	232/258 (89.9)
	VTAS*	9/11 (81.8)	4/5 (80.0)	--	--	--	--	--	--	0/0	9/11 (81.8)	4/5 (80.0)
	SafAS	177/177 (100)	158/159 (99.4)	42/42 (100)	45/45 (100)	50/50 (100)	46/46 (100)	6/6 (100)	8/8 (100)	15/15 (100)	290/290 (100)	257/258 (99.6)

N: number of participants in each group; n: number of participants fulfilling the item listed; M: number of participants randomized in each subgroup
*Applicable to Pfizer primed group and Protein primed group aged 18-55 years only
Prior prime vaccination: Pfizer = Pfizer/BioNTech, Moderna = Moderna, AZ = Oxford University/AstraZeneca, J&J = Johnson & Johnson/Janssen, Protein = CoV2 preS dTM-AS03 (D614) vaccine
Booster vaccine received: MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351), BV (D614 + B.1.351) = CoV2 preS dTM-AS03 (2.5 µg D614 + 2.5 µg B.1.351)
Note: a participant may be associated with more than one criterion
Source: Modified from 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Section 8, Table 8.10, Table 8.11, Table 8.13, and Table 8.14

There is a high rate of follow-up. Overall, 60 (4.5%) Booster Group participants discontinued the study: 37 (4.9%) Pfizer/BioNTech primed, 12 (5.5%) Moderna primed, 5 (2.5%) Oxford/AstraZeneca primed, 4 (5.3%) J&J/Janssen primed, and 2 (2.6%) Protein primed. Protocol deviation was the most frequently reported reason in all Booster Groups (43 [3.2%] of participants). No Booster Group participants discontinued the study due to an adverse event. It should be noted, that 8 participants in the MV (B.1.351) booster group and 2 in the BV (D614+B.1.351) withdraw consent and the reason is unknown (i.e. withdrawal due to AEs cannot be excluded). Almost all enrolled participants received their booster dose, i.e. 99.7% of participants in the MV (B.1.351) and 99.4% in the BV (D614+B.1.351) vaccine booster cohort completed their booster dose. Overall, only 6 enrolled participants did not receive their booster dose.

- **Outcomes and estimation**

Co-primary endpoints

The two co-primary immunogenicity objectives were to demonstrate that a 5µg booster dose of MV CoV2 preS dTM-AS03 (B.1.351) vaccine given to adults (18-55 years of age) previously vaccinated with the Pfizer/BioNTech vaccine induces an immune response against B.1.351 strain at D15 that is

- non-inferior to the immune response against D614G strain induced by a 2-dose 10 µg primary series of CoV2 preS dTM-AS03 (D614) vaccine in naïve individuals at day 36 (Comparator Group)
- Superior to that observed immediately before booster.

Both co-primary objectives were met. For the age cohort 18-55 years of age and in an additional analysis for the cohort 18 years of age and older.

For the first co-primary objective, the neutralising Ab geometric mean titre ratio (GMTR) of MV CoV2 preS dTM-AS03 (B.1.351) vaccine booster dose in Pfizer/BioNTech primed participants aged 18-55 years at D15 to the 2-dose primary series in the Comparator Group at D36 was 1.96 (98.3% confidence interval [CI]: 1.54; 2.50). This meets the non-inferiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 0.667. Results are presented in the table below.

Table 22: VAT00002 - Supplemental Phase III Cohort 2: Non-inferiority of MV (B.1.351) as booster in Pfizer/BioNTech Primed against B.1.351 at D15 versus Comparator Group against D614G at D36 in adults 18-55 years old - PPAS/PPAS Naïve at D01+D22,

	Pfizer Primed MV (B.1.351) (N=279)			Comparator (N=331)				Pfizer Primed MV (B.1.351) / Comparator			
Strain Readout	**M**	**GMT**	**(95% CI)**	**Strain Readout**	**M**	**GMT**	**(95% CI)**	**Strain comparison**	**GMT ratio**	**(98.3% CI)**	**Non-inferiority***
B.1.351	279	7172	(6363; 8083)	**D614G**	302	3658	(3123; 4286)	**B.1.351 vs D614G**	1.96	(1.54; 2.50)	Yes

M: number of participants with available data; N: number of participants in PPAS for Booster Group or PPAS Naive at D01+D22 for Comparator Group
2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers
2-sided 98.3% CI is based on the Welch's t-distribution of logarithmic transformation of the individual titers for GMT ratio between two groups
Antilog transformations were applied to the results
* Non-inferiority on GMTs is concluded if the lower limit of the 2-sided 98.3% CI of the ratio of GMTs between groups is > 0.667
Prior prime vaccination: Pfizer = Pfizer/BioNTech
MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant strains
Source: modified from Section 8, Table 8.1.69

For the second co-primary objective, the geometric mean of individual ratio of post-booster neutralising Ab GMTs at D15 relative to pre-booster neutralising Ab GMTs in Pfizer/BioNTech primed participants aged 18-55 years at D01 was 35.41 (98.3% CI: 26.71; 46.95), which meets the superiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 2. Results are shown in the table below.

Table 23: VAT00002 - Supplemental Phase III Cohort 2: Superiority of post-booster of MV (B.1.351) versus pre-booster in adults 18-55 years old Pfizer/BioNTech Primed - individual neutralising titre against B.1.351 at D15 relative to D01 – PPAS

	Pfizer Primed MV (B.1.351) Post-booster / Pre-booster				
Strain Readout	**N**	**M**	**Geometric mean (of Individual Ratio)**	**(98.3% CI)**	**Superiority***
B.1.351	279	256	35.41	(26.71; 46.95)	Yes

M: number of participants with available data in both post-booster and pre-booster; N: number of participants in PPAS
2-sided 98.3% CI is based on the Student t-distribution of logarithmic transformation of the individual titers
Antilog transformations were applied to the results
* Superiority is concluded if the lower limit of the 2-sided 98.3% CI of the fold rise on post-booster versus pre-booster > 2
Prior prime vaccination: Pfizer = Pfizer/BioNTech
MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant strains
Source: modified from Section 8, Table 8.171

Co-primary objectives-hypothesis testing in adults 18 years of age and older

Both co-primary objectives including hypothesis testing were additionally analysed in the PPAS of adults 18 years of age and older. The same non-inferiority and superiority criterion as for the PPAS 18-55 years of age applied. The results do not notably differ from the adult PPAS population 18-55 years of age. Both, the non-inferiority and the superiority criterion was met. The neutralising Ab GMTR of MV CoV2 preS dTM-AS03 (B.1.351) vaccine booster dose in Pfizer/BioNTech primed participants aged 18 years and older at D15 to the 2-dose primary series in the Comparator Group at D36 was 1.94 (98.3% CI: 1.54; 2.46), compared to 1.96 (98.3% confidence interval [CI]: 1.54; 2.50) in the 18-55 PPAS population. The geometric mean of individual ratio of post-booster neutralising ABs relative to pre-booster was slightly higher in the PPAS 18 years of age and older compared to the PPAS 18-55 years of age. The geometric mean of individual ratio of post-booster neutralising Ab GMTs in the PPAS 18 years of age and older at D15 relative to pre-booster neutralising Ab GMTs at D01 was 39.15 (98.3% CI: 30.03; 51.04) compared to 35.41 (98.3% CI: 26.71; 46.95) in the PPAS 18-55 years of age.

Secondary immunogenicity with hypothesis testing

The co-secondary immunogenicity objectives #1 and #2 were to demonstrate that a 5 µg booster dose of MV CoV2 preS dTM-AS03 (B.1.351) vaccine given to adults (18-55 years of age) previously vaccinated with an mRNA vaccine induces an immune response against B.1.351 strain at D15 that is

1) non-inferior to the immune response against D614G strain induced by a 2-dose 10 µg primary series of CoV2 preS dTM-AS03 (D614) vaccine in naïve individuals (Comparator Group)

2) superior to that observed immediately before booster.

Non-inferiority and superiority criteria were met for individuals primed with any of the two mRNA vaccines (Pfizer/BioNTech and mRNA-1273/Moderna).

The neutralising Ab GMTR of MV CoV2 preS dTM-AS03 (B.1.351) vaccine booster dose in mRNA primed participants at D15 to the 2-dose primary series in the Comparator Group at D36 was 2.06 (98.3% CI: 1.62; 2.61), which meets the non-inferiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 0.667. The result is tabled below.

Table 24: Non-inferiority of MV (B.1.351) as booster in mRNA Primed against B.1.351 at D15 vs Comparator against D614G at D36 in adults 18 - 55 years old - PPAS/PPAS Naïve at D01+D22 (secondary objective#1)

	mRNA Primed MV (B.1.351) (N=347)			Comparator (N=331)				mRNA Primed MV (B.1.351) / Comparator			
Strain Readout	M	GMT	(95% CI)	Strain Readout	M	GMT	(95% CI)	Strain comparison	GMT ratio	(98.3% CI)	Non-inferiority *
B.1.351	347	7522	(6718; 8422)	D614G	302	3658	(3123; 4286)	B.1.351 vs D614G	2.06	(1.62; 2.61)	Yes

M: number of participants with available data; N: number of participants in PPAS for Booster Group or PPAS Naive at D01+D22 for Comparator Group
2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers
2-sided 98.3% CI is based on the Welch's t-distribution of logarithmic transformation of the individual titers for GMT ratio between two groups
Antilog transformations were applied to the results
* Non-inferiority on GMTs is concluded if the lower limit of the 2-sided 98.3% CI of the ratio of GMTs between groups is > 0.667
Prior prime vaccination platform: mRNA = mRNA; MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant strains

The geometric mean of individual ratio of post-booster neutralising Ab GMTs at D15 relative to pre-booster neutralising Ab GMTs at D01 was 34.19 (98.3% CI: 26.58; 43.98), which meets the superiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 2.

Table 25: Superiority of post-booster of MV (B.1.351) vs pre-booster in adults 18 - 55 years old mRNA Primed - individual neutralisation titre against B.1.351 at D15 relative to D01 – PPAS (secondary objective #2)

	mRNA Primed MV (B.1.351) (N=347) Post-booster / Pre-booster			
Strain Readout	M	Geometric mean (of Individual Ratio)	(98.3% CI)	Superiority*
B.1.351	321	34.19	(26.58; 43.98)	Yes

M: number of participants with available data in both post-booster and pre-booster; N: number of participants in PPAS
2-sided 98.3% CI is based on the Student t-distribution of logarithmic transformation of the individual titers
Antilog transformations were applied to the results
* Superiority is concluded if the lower limit of the 2-sided 98.3% CI of the fold rise on post-booster versus pre-booster > 2
Prior prime vaccination platform: mRNA = mRNA; MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant strains
Source: modified from Section 8, Table 8.179

The co-secondary immunogenicity objective #3 was to demonstrate that

- a 5µg booster dose of MV CoV2 preS dTM-AS03 (B.1.351) vaccine given to adults (18-55 years of age) previously vaccinated with the Pfizer/BioNTech vaccine induces an immune response against B.1.351 strain at D15 that is superior to the immune response against B.1.351 strain induced by a 2-dose 10 µg primary series of CoV2 preS dTM-AS03 (D614) vaccine in naïve individuals (Comparator Group)

As shown in below, the neutralising Ab GMTR against B.1.351 strain of 5 µg of MV CoV2 preS dTM-AS03 (B.1.351) vaccine booster dose in Pfizer/BioNTech primed participants at D15 compared to the 2-dose primary series in the Comparator Group at D36 was 17.36 (98.3% CI: 13.39; 22.50), which meets the superiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 1.5.

Table 26: Superiority of GMT against B.1.351 of MV (B.1.351) as booster in Pfizer Primed at D15 vs Comparator at D36 in adults 18 - 55 years old - PPAS/PPAS Naïve at D01+D22 (secondary objective #3)

Pfizer Primed MV (B.1.351) (N=279)			Comparator (N=331)			Pfizer Primed MV (B.1.351) / Comparator		
Strain Readout	M	GMT (95% CI)	Strain	M	GMT (95% CI)	Strain comparison	GMT ratio (98.3% CI)	Superiority*
B.1.351	279	7172 (6363; 8083)	B.1.351	291	413 (346; 493)	B.1.351 vs B.1.351	17.36 (13.39; 22.50)	Yes

M: number of participants with available data; N: number of participants in PPAS for Booster Group or PPAS Naive at D01+D22 for Comparator Group
2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers
2-sided 98.3% CI is based on the Welch's t-distribution of logarithmic transformation of the individual titers for ratios of GMT between two groups
Antilog transformations will be applied to the result
* Superiority is concluded if the lower limit of the 2-sided 98.3% CI of the ratio of GMTs between groups is > 1.5
Prior prime vaccination: Pfizer = Pfizer/BioNTech; MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant strains
Source: modified from Section 8, Table 8.185

The co-secondary immunogenicity objectives #4 and #5 were to demonstrate that the seroresponse rate against B.1.351 strain observed after a 5µg booster dose of MV (B.1.351) vaccine

- in Pfizer/BioNTech primed (#4)
- and mRNA primed adults (#5) 18-55 years of age

was non-inferior to the seroresponse rate against D614G strain observed after a 2-dose 10 µg primary series of CoV2 preS dTM-AS03 (D614) vaccine in naïve individuals (Comparator Group). The seroresponse rate is defined as participants responders with ≥4-fold-rise or greater in serum neutralisation titre [post/pre].

The differences of the seroresponse rate against B.1.351 strain in both Pfizer/BioNTech primed and mRNA primed participants following a booster dose of MV CoV2 preS dTM-AS03 (B.1.351) vaccine versus seroresponse rate against D614G strain in Comparator Group were -16.58% (98.3% CI: -22.99; -11.01) and -17.07% (98.3% CI: -22.79; -11.86), respectively. Therefore, these co-secondary objectives were not met, i.e., the lower limit of 2-sided 98.3% CI of the difference of seroresponse between groups was < -10%.

Table 27: Non-inferiority of seroresponse rate of MV (B.1.351) as booster against B.1.351 in Pfizer Primed at D15 vs Comparator against D614G at D36 in adults 18 - 55 years old - PPAS/PPAS Naïve at D01+D22 (#4)

	Pfizer Primed MV (B.1.351) (N=279)			Comparator (N=331)				Pfizer Primed MV (B.1.351) - Comparator		
Strain	n/M	Seroresponse rate (%)	(95% CI)	Strain	n/M	Seroresponse rate (%)	(95% CI)	Strain comparison	Difference (%)	(98.3% CI)	Non-inferiority*
B.1.351	211/256	82.4	(77.2 : 86.9)	D614G	298/301	99.0	(97.1 : 99.8)	B.1.351 vs D614G	-16.58	(-22.99 :	No

n: Number of participants who achieve seroresponse; M: number of participants with available data
N: number of participants in PPAS for Booster Group or PPAS Naive at D01+D22 for Comparator Group
Seroresponse: defined as a 4-fold or greater rise in serum neutralization titer [post/pre]
95% CI of the single proportion calculated from the exact binomial method.
98.3% CI of the difference calculated from the Wilson Score method without continuity correction.
* Non-inferiority is concluded if the lower limit of the 2-sided 98.3% CI of the difference in seroresponse rate between groups is > -10%.
Prior prime vaccination: Pfizer = Pfizer/BioNTech; MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
Note: available data within proper time window included in table summary.

Table 28: Non-inferiority of seroresponse rate of MV (B.1.351) as booster against B.1.351 in mRNA Primed at D15 vs Comparator against D614G at D36 in adults 18 - 55 years old - PPAS/PPAS Naïve at D01+D22 (#5)

		mRNA Primed MV (B.1.351) (N=347)				Comparator (N=331)				mRNA Primed MV (B.1.351) - Comparator		
Strain	n/M	Seroresponse rate (%)	(95% CI)	Strain	n/M	Seroresponse rate (%)	(95% CI)	Strain comparison	Difference (%)	(98.3% CI)	Non-inferiority*	
B.1.351	263/321	81.9	(77.3 ; 86.0)	D614G	298/301	99.0	(97.1 ; 99.8)	B.1.351 vs D614G	-17.07	(-22.79 ; -11.86)	No	

n: Number of participants who achieve seroresponse; M: number of participants with available data
N: number of participants in PPAS for Booster Group or PPAS Naive at D01+D22 for Comparator Group
Seroresponse: defined as a 4-fold or greater rise in serum neutralization titer [post/pre]
95% CI of the single proportion calculated from the exact binomial method.
98.3% CI of the difference calculated from the Wilson Score method without continuity correction.
* Non-inferiority is concluded if the lower limit of the 2-sided 98.3% CI of the difference in seroresponse rate between groups is > -10%.
Prior prime vaccination platform: mRNA = mRNA; MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
Note: available data within proper time window included in table summary.

The study failed to demonstrate in participants 18-55 years that the seroresponse rate against B.1.351 strain observed after a 5 µg booster dose of the MV (B.1.351) vaccine is non-inferior to that observed against D614G after 2 doses of MV (D614) vaccine. This is for both, Pfizer/BioNTech primed and mRNA primed adults. Among naïve individuals included in the Comparator group, the vaccination with MV (D614) induced a very high rate of seroresponse in participants 18-55 years of age, the proportion of participants in the Comparator exhibiting a 4-fold rise in neutralising titres to the D614G strain 14 days after the second dose was 99%. In previously primed individuals, although a booster dose may robustly restore the immune responses to levels notably higher than what is achieved following the primary series, the proportion achieving seroresponse of ≥4-fold increase might be limited by the (higher) baseline titres. The clinical relevance of seroresponse with regard to vaccine protection against SARS-CoV-2 is not clear. The assessment of nAB GMTs is deemed a (more) relevant parameter in the assessment of immune response after vaccination against COVID-19. The study is also limited in that the Comparator used was not an approved COVID-19 vaccine.

Secondary immunogenicity: descriptive analysis: Post-booster versus pre-booster neutralising antibody profile

Neutralising antibody GMTs post/pre-booster

The descriptive analysis describes the neutralising Ab response against D614G and B.1.351 strains, induced by a 5µg booster dose of MV (B.1.351) vaccine by priming vaccine, priming platform and age group (18-55 years, ≥56 years, and all age groups). This analysis was conducted in the PPAS.

A notable increase of neutralising antibodies against B.1.351 and D614 strains from pre-booster dose (Day 0) to post-booster dose (Day 15) is observed after a single 5µg dose of MV (B.1.351) vaccine for all tested priming vaccines/priming platforms. Neutralising antibody titre GMTs 14 days post booster dose are higher against D614 than against the B.1.351 strain irrespective of the priming vaccine/platform. Although post-booster neutralising Ab GMTs against D614G strain were higher than those observed against B.1.351 strain, post-/pre-booster GMTRs against B.1.351 strain were higher than those against D614G strain regardless of the priming vaccine/platform group. It should be noted, that in both age cohorts irrespective of the priming vaccine/priming platform baseline GMTs against the B.1.351 strain were lower compared to baseline GMTs against the D614 strain.

Baseline GMTs against B.1.351 irrespective of age (i.e. for all ages) ranged from 260 (95% CI: 121; 561) in the J&J primed vaccine group to 44.4 (95% CI: 32.6; 60.6) in the AZ primed vaccine group and against D614 from 1188 (95% CI: 874; 1615) in the Moderna primed vaccine group to 140 (95% CI: 99.1; 196) in the AZ primed vaccine group. The lower baseline GMTs against the B.1.351 strain

compared to the D614G strain as well as the different baseline GMTs in the different booster groups and age cohorts must be considered. This underlines the importance of considering the GMTRs. The increase of GMTRs against B.1.351 from pre-booster to 15 days post-booster dose irrespective of age ranged from approximatively 27-fold in the J&J primed group to 101-fold in the AZ primed group, and against the D614 strain from approximately 12-fold (95% CI: 8.72; 16.3) in the Moderna to 39-fold (95% CI: 28.2; 53.4) in the AZ primed vaccine group. GMTs on Day 15 against B.1.351 irrespective of age ranged from 9449 (95% CI: 7376; 12104) in the Moderna primed vaccine group to 4610 (95% CI: 3689; 5760) in the AZ primed vaccine group and against D614 from 14240 (95% CI: 11257; 18013) in the Moderna primed vaccine group to 6817 (95% CI: 5453; 8521) in the AZ primed vaccine group. The highest increase of GMTs from pre-to post booster was observed in the protein primed group. GMTs against B.1.531 irrespective of age increased from 72.1 (95% CI: 48.5; 107) to 13300 (95% CI: 9817; 18018) with a corresponding GMTR of 180 (95% CI: 109; 298). The GMTR against D614 is 148 (95% CI: 85.8; 257) with an increase of the GMT from 164 (95% CI: 99.3; 271) on Day 0 to 25002 (18441; 33897) on Day15. A comparable increase has previously been observed with a 5µg booster dose of MV CoV2 preS dTM-AS03 (D614) after a 2-dose protein priming with 10µg of CoV2 preS dTM-AS03 (D614). GMTs against D614 irrespective of age increased from 214 (95% CI: 127; 363) on Day 0 to 24277 (95% CI: 18922; 31147), corresponding GMTR is 113. This means that the results of the booster immune response are reproducible for the two protein vaccines after homologous priming. This could support the thesis that the different immune response is rather related to the priming vaccine with its specific mode of action and composition than to differences in the study populations of homologous or heterologous primed individuals. GMTs and GMTRs by priming vaccines and priming platforms in all age groups are shown below.

Table 29: VAT00002 - Supplemental Phase III Cohort 2: Summary of neutralising antibody profile of MV CoV2 preS dTM-AS03 (B.1.351) based on GMT and GMTR by priming vaccines and priming platforms in all age groups – PPAS

			Pfizer Primed (N=325)		Moderna Primed (N=93)		AZ Primed (N=94)		J&J Primed (N=31)		mRNA Primed (N=418)		Ad-vector Primed (N=125)		Protein Primed (N=72)	
Age group	Strain Readout	Time point /ratio	M	GMT/GMTR (95% CI)	M	GMT/GMTR (95% CI)	M	GMT/GMTR (95% CI)	M	GMT/GMTR (95% CI)	M	GMT/GMTR (95% CI)	M	GMT/GMTR (95% CI)	M	GMT/GMTR (95% CI)
18-55 years	D614G	D01	274	739 (599; 913)	68	1331 (917; 1931)	55	165 (105; 258)	22	741 (267; 2059)	342	831 (690; 1001)	77	253 (162; 396)	4	189 (NC; NC)
		D15	279	10165 (9082; 11377)	68	13189 (9836; 17684)	62	6817 (5453; 8521)	22	11424 (7948; 16419)	347	10697 (9611; 11907)	84	7804 (6435; 9462)	4	37633 (NC; NC)
		D15/D01	274	13.9 (11.3; 17.1)	68	9.91 (6.92; 14.2)	55	41.0 (27.0; 62.2)	22	15.4 (6.18; 38.5)	342	13.0 (10.8; 15.6)	77	31.0 (20.8; 46.1)	4	199 (NC; NC)
	B.1.351	D01	256	200 (157; 254)	65	296 (200; 440)	57	49.7 (32.7; 75.6)	22	306 (114; 822)	321	216 (176; 267)	79	82.5 (53.3; 128)	4	76.2 (NC; NC)
		D15	279	7172 (6363; 8083)	68	9146 (6734; 12421)	62	5643 (4468; 7128)	21	7900 (5309; 11754)	347	7522 (6718; 8422)	83	6145 (5032; 7503)	4	15509 (NC; NC)
		D15/D01	256	35.4 (28.1; 44.6)	65	29.8 (18.6; 47.7)	57	108 (71.2; 163)	21	27.9 (10.5; 74.3)	321	34.2 (27.8; 42.0)	78	74.8 (49.6; 113)	4	203 (NC; NC)
>= 56 years	D614G	D01	41	298 (164; 541)	24	861 (500; 1483)	32	105 (61.4; 179)	9	1456 (319; 6639)	65	441 (285; 681)	41	187 (102; 343)	60	162 (95.9; 275)
		D15	46	9022 6404; 12709)	25	17545 (12042; 25562)	32	3700 (2300; 5953)	9	10046 (3184; 31699)	71	11402 (8757; 14846)	41	4607 (2958; 7176)	68	24407 (17705; 33647)
		D15/D01	41	29.5 (15.7; 55.3)	24	20.2 (10.6; 38.4)	32	35.3 (21.0; 59.2)	9	6.90 (1.36; 20.2)	65	25.6 (16.3; 40.3)	41	24.7 (15.0; 40.4)	60	146 (81.7; 259)
	B.1.351	D01	43	83.4 (49.7; 140)	19	158 (71.7; 350)	30	35.8 (23.0; 55.7)	8	167 (47.0; 595)	62	102 (66.2; 156)	38	49.6 (31.4; 78.3)	60	71.9 (47.2; 109)
		D15	46	6175 (4271; 8927)	25	10324 (6738; 15818)	32	3115 (1962; 4945)	9	4964 (1412; 17450)	71	7400 (5583; 9809)	41	3450 (2247; 5298)	68	13180 (9571; 18151)
		D15/D01	43	71.2 (38.3; 132)	19	72.0 (33.2; 156)	30	89.5 (53.0; 151)	8	23.3 (4.32; 125)	62	71.4 (44.3; 115)	38	67.4 (39.6; 115)	60	179 (105; 305)
All	D614G	D01	315	657 (537; 803)	92	1188 (874; 1615)	87	140 (99.1; 196)	31	902 (402; 2023)	407	751 (633; 892)	118	228 (159; 325)	64	164 (99.3; 271)
		D15	325	9995 (8976; 11129)	93	14240 (11257; 18013)	94	5536 (4496; 6910)	31	11005 (7533; 16078)	418	10814 (9793; 11941)	125	6565 (5397; 7986)	72	25002 (18441; 33897)
		D15/D01	315	15.3 (12.6; 18.7)	92	11.9 (8.72; 16.3)	87	38.8 (28.2; 53.4)	31	12.2 (6.07; 24.6)	407	14.5 (12.2; 17.2)	118	28.6 (21.1; 38.9)	64	148 (85.8; 257)
	B.1.351	D01	299	176 (141; 220)	84	257 (184; 365)	87	44.4 (32.6; 60.6)	30	260 (121; 561)	383	191 (158; 231)	117	69.9 (50.3; 97.2)	64	72.1 (48.5; 107)
		D15	325	7021 (6262; 7873)	93	9419 (7376; 12104)	94	4610 (3689; 5760)	30	6872 (4482; 10537)	418	7501 (6754; 8330)	124	5077 (4168; 6185)	72	13300 (9817; 18018)
		D15/D01	299	39.2 (31.5; 48.7)	84	36.4 (24.3; 54.5)	87	101 (73.3; 139)	29	26.5 (12.0; 58.6)	383	38.5 (31.8; 46.6)	116	72.3 (52.4; 99.8)	64	180 (109; 298)

M: number of participants with available data for the relevant endpoint; N: number of participants in PPAS for Booster Group or PPAS Naive at D01+D22 for Comparator Group
GMTR (geometric mean titer ratio): geometric mean of individual titer ratios (post-vaccination/pre-vaccination)
NC: not computed as the number of participants in this age group was limited
2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers. Antilog transformations will be applied to the results.
Prior prime vaccination: Pfizer = Pfizer/BioNTech, Moderna = Moderna, AZ = Oxford University/AstraZeneca, J&J = Johnson & Johnson/Janssen, Protein = CoV2 preS dTM-AS03 (D614)
Prior prime vaccination platform: mRNA = mRNA, Ad-vector = adenovirus-vectored
MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant strains
Source: Modified from 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Section 8, Table 8.193

A booster response to VidPrevtyn Beta was demonstrated regardless of the vaccine used for primary vaccination with the Geometric Mean Titres Ratio (GMTR, fold increase) 14 days post-booster relative to pre-booster against B.1.351 strain ranging from 38.5 to 72.3, and from 14.5 to 28.6 for D614G strain (Table 31).

Seroresponse rates (≥4-fold-rise in neutralising Ab titres)

In general, no clinically meaningful difference in seroresponse rates could be observed after a single booster dose of 5µg of MV (B.1.351) vaccine for the different priming vaccines/priming platforms. Seroresponse rates irrespective of age (i.e. considering all ages) in the three priming platforms ranged from 73.5% (68.9; 77.7) against D614G in the mRNA primed vaccine group to 90.6% (80.7; 96.5) for both the B1.351 and the D614G vaccine strain in the protein primed group. Comparable to what was observed with regard to GMTRs, the proportion of participants with ≥4-fold-rise in neutralising Ab titres was higher against the B.1.351 strain than that against D614G regardless of priming vaccine group and age group. An overview of seroresponse rates by priming vaccine/priming platform and by age groups in given in the table below.

Table 30: VAT00002 - Supplemental Phase III Cohort 2: Number of participants with >= 2-fold rise and >= 4-fold rise of neutralisating antibody titres for MV CoV2 preS dTM-AS03 (B.1.351) at D15 relative to baseline (pre-booster) by age group – PPAS

			Pfizer Primed (N=325)		Moderna Primed (N=93)		AZ Primed (N=94)		J&J Primed (N=31)		mRNA Primed (N=418)		Ad-vector Primed (N=125)		Protein Primed (N=72)	
Age group	Strain Readout	Fold rise	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)
18-55 y	D614G	>=2	230/274	83.9 (79.0; 88.1)	57/68	83.8 (72.9; 91.6)	54/55	98.2 (90.3; 100)	18/22	81.8 (59.7; 94.8)	287/342	83.9 (79.6; 87.6)	72/77	93.5 (85.5; 97.9)	4/4	100 (39.8; 100)
		>=4	198/274	72.3 (66.6; 77.5)	47/68	69.1 (56.7; 79.8)	49/55	89.1 (77.8; 95.9)	14/22	63.6 (40.7; 82.8)	245/342	71.6 (66.5; 76.4)	63/77	81.8 (71.4; 89.7)	4/4	100 (39.8; 100)
	B.1.351	>=2	235/256	91.8 (87.7; 94.9)	59/65	90.8 (81.0; 96.5)	56/57	98.2 (90.6; 100)	20/21	95.2 (76.2; 99.9)	294/321	91.6 (88.0; 94.4)	76/78	97.4 (91.0; 99.7)	4/4	100 (39.8; 100)
		>=4	211/256	82.4 (77.2; 86.9)	52/65	80.0 (68.2; 88.9)	55/57	96.5 (87.9; 99.6)	15/21	71.4 (47.8; 88.7)	263/321	81.9 (77.3; 86.0)	70/78	89.7 (80.8; 95.5)	4/4	100 (39.8; 100)
>= 56 y	D614G	>=2	37/41	90.2 (76.9; 97.3)	22/24	91.7 (73.0; 99.0)	31/32	96.9 (83.8; 99.9)	8/9	88.9 (51.8; 99.7)	59/65	90.8 (81.0; 96.5)	39/41	95.1 (83.5; 99.4)	56/60	93.3 (83.8; 98.2)
		>=4	34/41	82.9 (67.9; 92.8)	20/24	83.3 (62.6; 95.3)	29/32	90.6 (75.0; 98.0)	4/9	44.4 (13.7; 78.8)	54/65	83.1 (71.7; 91.2)	33/41	80.5 (65.1; 91.2)	54/60	90.0 (79.5; 96.2)
	B.1.351	>=2	40/43	93.0 (80.9; 98.5)	18/19	94.7 (74.0; 99.9)	29/30	96.7 (82.8; 99.9)	8/8	100 (63.1; 100)	58/62	93.5 (84.3; 98.2)	37/38	97.4 (86.2; 99.9)	58/60	96.7 (88.5; 99.6)
		>=4	38/43	88.4 (74.9; 96.1)	18/19	94.7 (74.0; 99.9)	28/30	93.3 (77.9; 99.2)	7/8	87.5 (47.3; 99.7)	56/62	90.3 (80.1; 96.4)	35/38	92.1 (78.6; 98.3)	54/60	90.0 (79.5; 96.2)
All	D614G	>=2	267/315	84.8 (80.3; 88.5)	79/92	85.9 (77.0; 92.3)	85/87	97.7 (91.9; 99.7)	26/31	83.9 (66.3; 94.5)	346/407	85.0 (81.2; 88.3)	111/118	94.1 (88.2; 97.6)	60/64	93.8 (84.8; 98.3)
		>=4	232/315	73.7 (68.4; 78.4)	67/92	72.8 (62.6; 81.6)	78/87	89.7 (81.3; 95.2)	18/31	58.1 (39.1; 75.5)	299/407	73.5 (68.9; 77.7)	96/118	81.4 (73.1; 87.9)	58/64	90.6 (80.7; 96.5)
	B.1.351	>=2	275/299	92.0 (88.3; 94.8)	77/84	91.7 (83.6; 96.6)	85/87	97.7 (91.9; 99.7)	28/29	96.6 (82.2; 99.9)	352/383	91.9 (88.7; 94.4)	113/116	97.4 (92.6; 99.5)	62/64	96.9 (89.2; 99.6)
		>=4	249/299	83.3 (78.6; 87.3)	70/84	83.3 (73.6; 90.6)	83/87	95.4 (88.6; 98.7)	22/29	75.9 (56.5; 89.7)	319/383	83.3 (79.2; 86.9)	105/116	90.5 (83.7; 95.2)	58/64	90.6 (80.7; 96.5)

Abbreviation: y, years
n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint; N: number of participants in PPAS for Booster Group or PPAS Naive at D01+D22 for Comparator Group
2-sided exact 95% CI for the single proportion is based on the Clopper-Pearson method
Prior prime vaccination: Pfizer = Pfizer/BioNTech, Moderna = Moderna, AZ = Oxford University/AstraZeneca, J&J = Johnson & Johnson/Janssen, Protein = CoV2 preS dTM-AS03 (D614)
Prior prime vaccination platform: mRNA = mRNA, Ad-vector = adenovirus-vectored
MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant strains.
Source: Modified from 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Section 8, Table 8.205

Post-booster versus primary series neutralising antibody profile

The neutralising Ab profile of a single booster dose of MV (B.1.351) vaccine by priming vaccines/platforms at Day 15 versus Comparator Group at Day36 is summarized based on neutralising Ab GMTs and seroresponse rates in participants aged 18-55 years and 18 years of age and older.

Regardless of strain, age and priming vaccine/platform, the immune response induced by a single booster dose of MV (B.1.351) vaccine based on neutralising GMTs 14 days after booster dose was higher than the immune response at the same timepoint (i.e. 14 days post-dose 2) induced by a 2-dose primary series of 10µg MV (D614G) vaccine in the comparator group. Baseline titres against the different strains varied by age cohort and by priming platform group. Baseline titres were the lowest in the comparator group which reflects the naive SARS-CoV-2 serostatus of the participants. Baseline titres, GMTs and GMTRs for B.1.351 and D614G by priming platform group and by age group (18-55 years and 18 years of age and older) are tabled below. It should be noted that the majority of participants in the protein-primed group was older than 56 years of age. Only 4 participants were 18-55 years of age.

Table 31: VAT00002 - Supplemental Phase III Cohort 2: Summary of neutralis*ation antibody GMT and GMTR in Monogram PVN assay by priming platform group and by age group (18-55 years and 18 years and older) - PPAS/PPAS Naïve at D01+D22*

			mRNA Primed MV (B.1.351) (N=418)			Ad-vector Primed MV (B.1.351) (N=125)			Protein Primed MV (B.1.351) (N=72)			Comparator Group (N=437)		
Age group (years)	Strain Readout	Time point /ratio	M	GMT / GMTR	(95% CI)	M	GMT / GMTR	(95% CI)	M	GMT / GMTR	(95% CI)	M	GMT / GMTR	(95% CI)
18-55	D614G	D01	342	831	(690 ; 1001)	77	253	(162 ; 396)	4	189	(NC ; NC)	330	20.3	(19.7 ; 21.0)
		D15*	347	10697	(9611 ; 11907)	84	7804	(6435 ; 9462)	4	37633	(NC ; NC)	-	-	-
		D36†	-	-	-	-	-	-	-	-	-	302	3658	(3123 ; 4286)
		D15/D01*	342	13.0	(10.8 ; 15.6)	77	31.0	(20.8 ; 46.1)	4	199	(NC ; NC)	-	-	-
		D36/D01†	-	-	-	-	-	-	-	-	-	301	181	(152 ; 214)
	B.1.351	D01	321	216	(176 ; 267)	79	82.5	(53.3 ; 128)	4	76.2	(NC ; NC)	329	20.3	(19.7 ; 20.8)
		D15*	347	7522	(6718 ; 8422)	83	6145	(5032 ; 7503)	4	15509	(NC ; NC)	-	-	-
		D36†	-	-	-	-	-	-	-	-	-	291	413	(346 ; 493)
		D15/D01*	321	34.2	(27.8 ; 42.0)	78	74.8	(49.6 ; 113)	4	20	(NC ; NC)	-	-	-
		D36/D01†	-	-	-	-	-	-	-	-	-	290	20.3	(16.9 ; 24.3)
≥ 18	D614G	D01	407	751	(633 ; 892)	118	228	(159 ; 325)	64	164	(99.3 ; 271)	336	20.3	(19.7 ; 21.0)
		D15*	418	10814	(9793 ; 11941)	125	6565	(5397 ; 7986)	72	25002	(18441 ; 33897)	-	-	-
		D36†	-	-	-	-	-	-	-	-	-	307	3611	(3086 ; 4224)
		D15/D01*	407	14.5	(12.2 ; 17.2)	118	28.6	(21.1 ; 38.9)	64	148	(85.8 ; 257)	-	-	-
		D36/D01†	-	-	-	-	-	-	-	-	-	306	178	(151 ; 211)
	B.1.351	D01	383	191	(158 ; 231)	117	69.9	(50.3 ; 97.2)	64	72.1	(48.5 ; 107)	335	20.3	(19.7 ; 20.8)
		D15*	418	7501	(6754 ; 8330)	124	5077	(4168 ; 6185)	72	13300	(9817 ; 18018)	-	-	-
		D36†	-	-	-	-	-	-	-	-	-	296	413	(346 ; 493)
		D15/D01*	383	38.5	(31.8 ; 46.6)	116	72.3	(52.4 ; 99.8)	64	180	(109 ; 298)	-	-	-
		D36/D01†	-	-	-	-	-	-	-	-	-	295	20.3	(16.9 ; 24.3)

M: number of participants with available data for the relevant endpoint; N: number of participants in PPAS for Booster Group or PPAS Naive at D01+D22 for Comparator Group
NC: not computed as the number of participants in this age group was limited
*applicable to Booster Group; †applicable to Comparator Group
GMTR (geometric mean titer ratio): geometric mean of individual titer ratios (post-vaccination/pre-vaccination)
2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers. Antilog transformations will be applied to the results.
Prior prime vaccination: Protein = CoV2 preS dTM-AS03 (D614)
Prior prime vaccination platform: mRNA = mRNA, Ad-vector = adenovirus-vectored
MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant strains
Note: available data within proper time window included in table summary
Source: Modified from 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Section 8, Table 8.193

Neutralising Ab GMTs against the D614G strain in mRNA and Ad-vector priming vaccine/platform was about 2 to 3-fold higher than neutralising Ab GMTs against D614G strain in the Comparator Group. For the Protein primed group, neutralising Ab GMT against D614G strain were even about 10-fold higher that that observed in the Comparator Group. Respectively, GMTs against the B.1.351 strain were about 15 to 19-fold higher in the mRNA and the Ad-vector primed booster cohorts compared to the comparator group and about 37-fold higher in the protein primed group compared with the comparator group.

In contrast to GMTs, the seroresponse rates were lower in the booster groups compared with the comparator group. In the comparator group 99.0% of the participants aged 18-55 years showed a response ≥4-foldrise in neutralising Abs at D36. The difference between the post-booster neutralising Ab seroresponse rate in the booster groups against D614G strain versus the seroresponse rate in the Comparator Group ranged from -35.4% (95% CI: -56.1; -18.6) for the J&J/Janssen primed group to -9.9% (95% CI: -20.8; -3.8) for the Oxford/AstraZeneca primed group. Against the B.1.351 strain, the difference ranged from -15.1% (95% CI: -36.8; 0.3) for the J&J/Janssen primed group to 9.9% (95% CI: 0.8; 15.0) in the Oxford/AstraZeneca primed group, respectively. This can be explained by the high seroresponse in the comparator group due to the naïve serostatus of participants.

Immune response by age

Disposition

Of the 615 participants boosted with MV (B.1.351) 180 participants were ≥56 years and of the 561 participants boosted with BV (D614 + B.1.351) vaccine 132 participants were ≥56 years.

Overall, 140 (10.5%) participants (all priming platforms including the protein vaccine platform together) were ≥65 years, including 88 (12.4%) participants in the MV (B.1.351) vaccine group and 52 (8.3%) participants in BV (D614 + B.1.351) vaccine group. A more detailed overview for the age distribution of participants 65 years of age and older is provided in below.

Table 32: Number and percentage of elderly participants by priming vaccine and randomized group for VAT00002 Booster Cohort 2 and Comparator Group - Participants with Data in CRF

	Pfizer Primed		Moderna Primed		mRNA Primed		AZ Primed		J&J Primed		Ad-vector Primed		Protein Primed	All Booster		All Booster (N=1332)	Comparator Group
	MV (B.1.351) (N=378)	BV (D614 + B.1.351) (N=378)	MV (B.1.351) (N=112)	BV (D614 + B.1.351) (N=108)	MV (B.1.351) (N=490)	BV (D614 + B.1.351) (N=486)	MV (B.1.351) (N=101)	BV (D614 + B.1.351) (N=101)	MV (B.1.351) (N=38)	BV (D614 + B.1.351) (N=38)	MV (B.1.351) (N=139)	BV (D614 + B.1.351) (N=139)	MV (B.1.351) (N=78)	MV (B.1.351) (N=707)	BV (D614 + B.1.351) (N=625)		
Age group	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 65 years	17 (4.5)	23 (6.1)	15 (13.4)	13 (12.0)	32 (6.5)	36 (7.4)	15 (14.9)	14 (13.9)	3 (7.9)	2 (5.3)	18 (12.9)	16 (11.5)	38 (48.7)	88 (12.4)	52 (8.3)	140 (10.5)	3 (0.6)
≥ 75 years	2 (0.5)	2 (0.5)	1 (0.9)	1 (0.9)	3 (0.6)	3 (0.6)	1 (1.0)	2 (2.0)	0	0	1 (0.7)	2 (1.4)	15 (19.2)	19 (2.7)	5 (0.8)	24 (1.8)	0
≥ 85 years	0	0	0	0	0	0	0	0	0	0	0	0	3 (3.8)	3 (0.4)	0	3 (0.2)	0

N: number of participants in each group; n: number of participants fulfilling the item listed
Prior prime vaccination: Pfizer = Pfizer/BioNTech, Moderna = Moderna, AZ = Oxford University/AstraZeneca, J&J = Johnson & Johnson/Janssen, Protein = CoV2 preS dTM-AS03 (D614)
Prior prime vaccination platform: mRNA = mRNA, Ad-vector = adenovirus-vectored
MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351), BV (D614 + B.1.351) = CoV2 preS dTM-AS03 (2.5 µg D614 + 2.5 µg B.1.351)
Comparator: Monovalent (D614) (10 µg antigen) + AS03 (full-dose adjuvant) as a primary series vaccination of 2 injections given 21 days apart.

The primary analysis of the 2 co-primary immunogenicity objectives has been performed in individuals 18-55 years of age. However, a secondary analysis with the same statistical methods has been performed in the entire age population 18 years of age and older. Both the non-inferiority and the superiority criterion was met for the entire age population. Details are described in the co-primary objective section.

The applicant submitted subsequently an additional analysis of the 2 co-primary objectives in Pfizer/BioNTech primed participants aged ≥56 years for both the non-inferiority versus the Comparator Group (aged 18-55 years) and the superiority of post-booster versus pre-booster recognizing that this is an additional analysis with limited sample size of participants aged ≥56 years. Both, the non-inferiority and the superiority criteria were met. The neutralising Ab GMTR of a MV (B.1.351) vaccine booster dose in Pfizer/BioNTech primed participants aged 56 years and older in the PPAS at D15 to the 2-dose primary series in the Comparator Group aged 18-55 years in PPAS Naïve at D01+D22 at D36 was 1.69 (98.3% CI: 1.03; 2.76). This meets the non-inferiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 0.667. The GMTR of post-booster neutralising Ab GMTs at D15 relative to pre-booster neutralising Ab GMTs at D01 in the PPAS was 71.20 (98.3% CI: 33.20; 152.71), which meets the superiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 2.

The applicant provided subsequently a strain-to-strain comparison for adults ≥56 years of age. Similarly as in participants aged 18-55 years, regardless of the strain-to-strain comparison, the immune response induced by a booster dose of MV (B.1.351) vaccine in participants aged ≥56 years and older based on neutralising GMTs was with one exception higher than the immune response induced by a 2-dose primary series of CoV2 (D614G) vaccine in participants aged 18-55 years. This was irrespective of the priming vaccine/platform. The only exception was the strain comparison B.1.351 vs D614G with an GMTR of 0.85 (0.52; 1.38).

The proportion of participants ≥65 years of age is rather limited. The descriptive GMTs and GMTRs provided for participants ≥65 years of age for each priming vaccine including the protein primed group indicate notable GMTs and GMTRs for all priming vaccine groups.

Immune response in individuals with high-risk medical conditions

The immune response in individuals with high-risk medical conditions was pre-specified in the protocol and assessed within exploratory objective #7. Approximately 58% of participants in the PPAS of Booster Cohort 2 presented at least one high-risk medical condition, approximately 58% of participants boosted with MV (B.1.351) and 59% of participants boosted with BV (D614 + B.1.351) vaccine. The most common high-risk medical conditions (≥5% of participants) were obesity, hypertension/high blood pressure, and type 2 diabetes mellitus.

Notable GMTRs could be observed in individuals with high-risk medical conditions after boosting with either MV (B.1.351) or BV (D614+B.1.351) across both age cohorts and irrespective of priming platform/priming vaccine. In individuals 18-55 years of age in the Pfizer/BioNTech primed vaccine group the MV (B.1.351) vaccine tended to induce higher GMTs 14 days post booster against the D614G and the B.1.3512 strain compared with the BV (D614+B.1.351) vaccine. It should be noted that baseline titres in the MV (B.1.351) vaccine group were slightly higher than in the BV (D614+B.1.351) vaccine group. GMTs against D614G on Day 15 were 11686 (9797; 13940) versus 8270 (7210; 9485) in the MV (B.1.351) and the BV (D614+B.1.351) vaccine group, and 8183 (6799; 9848) versus 4983 (4310; 5761) against B.1.351, respectively. GMTRs against D614G in the MV vaccine group was 16.2 (11.8; 22.2) in the MV (B.1.351) vaccine group and 14.3 (10.8; 18.9) in the BV (D614+B.1.351) vaccine group. GMTRs against B.1.351 were 36.5 (25.7; 52.0) versus 34.5 (24.7; 48.1), respectively. This finding was also observed for the GMTRs against both strains in the older adult cohort ≥56 years with high-risk medical conditions, were GMTRs against D614 G were 37.5 (16.2; 86.8) versus 18.2 (9.62; 34.3) and against B.1.351 94.5 (41.9; 213) versus 29.5 (14.8; 58.8). This observation is not observed in individuals without high-risk medical conditions and it is not observed in the Ad-vector primed vaccine groups. In the Moderna primed vaccine groups it is observed against the B.1.351 strain in both age cohorts, but against D614 only in the older age cohort.

Neutralising antibody titres against variant of concern (VoC)

Neutralising Ab response against VoC (exploratory objective #5) were assessed in different populations for different VoC and with different assays.

Methodology and populations tested

Delta variant

The neutralising Ab response against the SARS-CoV-2 Delta (B.1.617.2) variant strain was assessed in the whole Protein primed vaccine group (not only in a subset) boosted with the MV CoV2 preS dTM-AS03 (B.1.351) vaccine and in the Comparator Group. The immune response in the 2 groups has been compared. Analyses were performed in the PPAS/PPAS Naïve-D01+D22 and in the FAS. In addition, neutralising Ab response against Delta variant testing on Pfizer primed adults aged 18-55 years boosted with either both MV CoV2 preS dTM-AS03 (B.1.351) and BV CoV2 preS dTM-AS03 (D614 + B.1.351) vaccines was analysed in the Variant Testing Subset (VTS) and the Variant Testing Subset Analysis Set, which is a subset of the VTS. The VTAS was designed in order to know the per-protocol participants immunogenicity response. The immune response in the Pfizer/BioNTech primed group was not compared to the Comparator group.

Omicron variants

In a small subset from Pfizer/BioNTech-primed participants boosted with either 5µg MV (D614), 5µg MV (B.1.351), or BV (2.5 µg D614 + 2.5 µg B.1.351) vaccines preliminary exploratory testing of

neutralising Ab titres against different Omicron subvariants (BA.1, BA.2, and BA.4) has been performed. The random selection included samples from 20 adults 18-55 years of age and from 10 adults 56 years of age and older. No results for the immune response induced against BA.4 after a booster dose of the MV (D614) vaccine are available. The immune response against BA.4 after a MV (B1.351) or BV (D614+B.1.351) booster dose has been assessed.

Table 33: Summary of variant testing performed

Participants' subset	Variant tested	Laboratory & assay	Clinical Overview subsection
Protocol-defined subsets: • **VTAS/VTS for Pfizer/BioNTech participants** **Addional testing based on regulatory feedback:** • **Supplement for Protein primed group and Comparator group (PPAS/PPAS Naïve-D01+D22)**	**D614G** **Delta**	Nexelis Pseudovirus Neutralization assay	4.5.2.4.1 Neutralizing antibody titers against Delta variant
Exploratory analysis: **Random subset of Pfizer/BioNTech primed participants from the FAS**	**D614G** **Omicron (BA.1)**	Monogram Pseudovirus Neutralization assay	4.5.2.4.2 Neutralizing antibody titers against Omicron variant
	Delta **Omicron (BA.1 and BA.2)**	Institut Pasteur (Olivier Schwartz Lab) Live Virus Neutralization assay	4.5.2.4.2 Neutralizing antibody titers against Omicron variant
	Omicron (BA.1 and BA.4/5)	National Institute of Communicable Diseases (NICD), South Africa (Penny Moore Lab) Pseudovirus Neutralization assay	4.5.2.4.2 Neutralizing antibody titers against Omicron variant

Results

Delta variant - Protein primed group and Comparator Group

At day 15, the GMT against the Delta variant was approximately 8-fold higher in the Protein primed group boosted with the 5µg MV (B.1.351) vaccine than on day 36 in the Comparator Group primed with 2 doses of 10µg of MV (D614) vaccine. Post-booster GMTs against Delta variant increased by approximately 115-fold compared to baseline in the Protein Primed group versus 82-fold increase in Comparator group from baseline to post-primary series. Neutralising Ab seroresponse rates against the Delta strain in the Protein primed group were comparable to those observed in the Comparator group, i.e. 91.5% (82.5; 96.8) versus 96.4% (93.6; 98.2). When comparing the antibody response it should be noted, that baseline titres against the Delta strain were different in the 2 groups, i.e. 28.9 (19.5; 43.0) in the Protein primed and 5.13 (4.97; 5.30) in the Comparator group. Moreover, the sample size was notably smaller in the Protein Primed versus the Comparator group, i.e. 72 participants with available values versus 307 for the GMT on day 15/ day 36. Results for GMTs, GMTRs and seroresponse rates against the delta and the D614 strain are shown below.

Table 34: Summary of neutralising antibody profile of Protein primed group and Comparator Group to B.1.617.2 variant strain in all age groups - PPAS/PPAS Naïve at D01+D22

Neutralizing antibody GMTs							
		Protein Primed MV (B.1.351) (N=72)			Comparator (N=337)		
Strain Readout	Time point/ratio	M	GMT/ GMTR	(95% CI)‡	M	GMT/ GMTR	(95% CI)‡
D614G	D01	69	66.4	(42.2; 105)	326	5.32	(5.11; 5.55)
	D15* or D36†	72	6252	(4607; 8484)	308	721	(629; 826)
	D15/D01* or D36/D01†	69	95.1	(57.1; 158)	297	137	(118; 159)
B.1.617.2	D01	71	28.9	(19.5; 43.0)	333	5.13	(4.97; 5.30)
	D15* or D36†	72	3361	(2449; 4611)	307	420	(362; 487)
	D15/D01* or D36/D01†	71	115	(72.3; 183)	304	82.0	(69.9; 96.1)

Percentage of participants achieving neutralizing antibody seroresponse								
			Protein Primed MV (B.1.351) (N=72)			Comparator (N=337)		
Strain Readout	Time point /ratio	Fold rise	n/M	%	(95% CI)§	n/M	%	(95% CI)§
D614G	D15* or D36†	>= 2	63/69	91.3	(82.0; 96.7)	296/297	99.7	(98.1; 100)
		>= 4	61/69	88.4	(78.4; 94.9)	295/297	99.3	(97.6; 99.9)
B.1.617.2	D15* or D36†	>= 2	68/71	95.8	(88.1; 99.1)	298/304	98.0	(95.8; 99.3)
		>= 4	65/71	91.5	(82.5; 96.8)	293/304	96.4	(93.6; 98.2)

n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint; N: number of participants in PPAS for Booster Group and PPAS Naïve at D01+D22 for Comparator Group
*applicable to Booster Group; †applicable to Comparator Group
GMTR (geometric mean titer ratio): geometric mean of individual titer ratios (post-vaccination/pre-vaccination)
‡2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers
§2-sided exact 95% CI for the single proportion is based on the Clopper-Pearson method
Prior prime vaccination: Protein = CoV2 preS dTM-AS03 (D614); MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Nexelis for variant strains
Source: modified from Section 8, Table 8.217 and Table 8.219

Delta variant - Pfizer primed group: neutralising antibody response after boosting with either MV (B1.351) or BV (D614+B.1.351)

The sample size of the analysis performed in VTAS for Pfizer primed participants 18-55 years of age was limited to only 13 participants boosted with MV CoV2 (B.1.351) vaccine and 9 participants boosted with BV CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. For both the MV CoV2 preS (B.1.351) and the BV (D614 + B.1.351) vaccine, baseline and D15 post-booster antibody titres against the delta strain were lower than those against D614G variant strain. Likewise, GMTRs in the MV (B1.351) and in the BV (D614+B1.351) vaccine group against the Delta strain, though within the same range tended to be numerically lower than those against D614. The MV (B1.351) vaccine tended to induce slightly higher neutralising antibodies on day 15 compared with the BV (D614+B1.351) against both strains, D614 and the delta strain. Results are shown in the table below. Similar results were observed in the VTS.

Table 35: Summary of neutralising antibody profile of Pfizer/BioNTech group to B.1.617.2 variant strain in adults aged 18-55 years – VTAS

Neutralizing antibody GMTs								
		Pfizer Primed						
		MV (B.1.351) (N=13)			BV (D614 + B.1.351) (N=9)			
Strain Readout	Time point/ratio	M	GMT/ GMTR	(95% CI)*	M	GMT/ GMTR	(95% CI)*	
D614G	D01	13	293	(158; 543)	8	288	(113; 735)	
	D15	13	7286	(4803; 11052)	9	6394	(4062; 10066)	
	D15/D01	13	24.9	(12.9; 48.0)	8	23.4	(7.88; 69.3)	
B.1.617.2	D01	12	70.9	(38.3; 132)	8	73.5	(18.7; 289)	
	D15	13	2125	(1368; 3302)	9	1976	(1144; 3411)	
	D15/D01	12	33.4	(14.2; 78.5)	8	27.1	(5.66; 130)	
Percentage of participants achieving neutralizing antibody seroresponse								
			Pfizer Primed					
			MV (B.1.351) (N=13)			BV (D614 + B.1.351) (N=9)		
Strain Readout	Time point /ratio	Fold rise	n/M	%	(95% CI)†	n/M	%	(95% CI)†
D614G	D15	>= 2	13/13	100	(75.3; 100)	8/8	100	(63.1; 100)
		>= 4	11/13	84.6	(54.6; 98.1)	7/8	87.5	(47.3; 99.7)
B.1.617.2	D15	>= 2	12/12	100	(73.5; 100)	7/8	87.5	(47.3; 99.7)
		>= 4	10/12	83.3	(51.6; 97.9)	6/8	75.0	(34.9; 96.8)

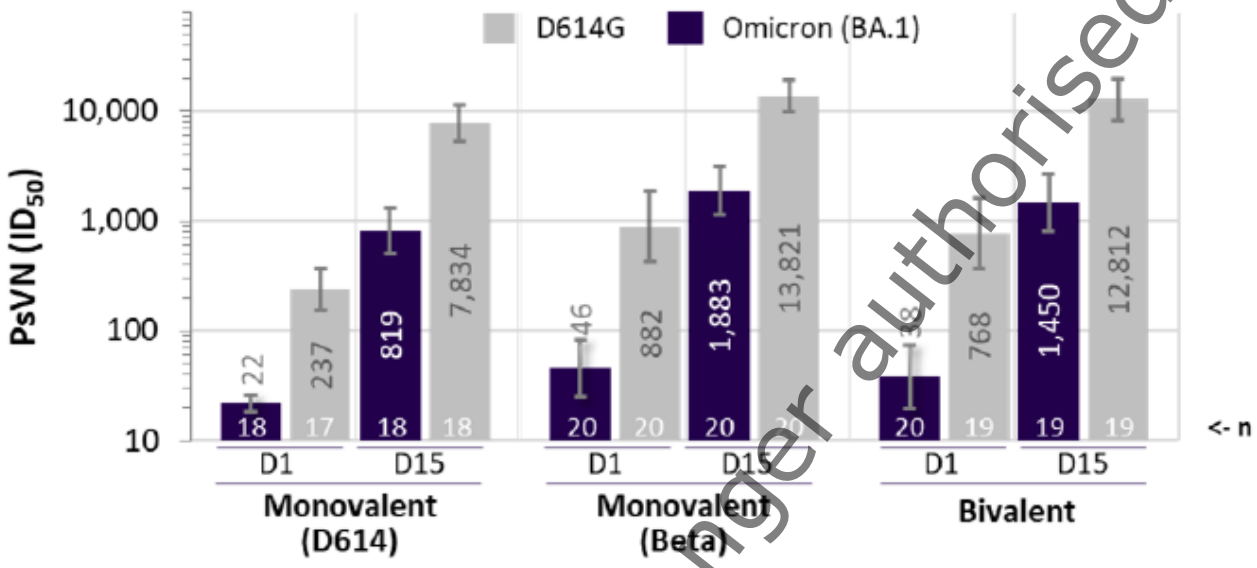
M: number of participants with available data for the relevant endpoint; N: number of participants in PPAS for Booster Group and PPAS Naïve at D01+D22 for Comparator Group; n: number of participants experiencing the endpoint
GMTR (geometric mean titer ratio): geometric mean of individual titer ratios (post-vaccination/pre-vaccination)
*2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers
†2-sided exact 95% CI for the single proportion is based on the Clopper-Pearson method
Prior prime vaccination: Protein = CoV2 preS dTM-AS03 (D614); MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Nexelis for variant strains
Source: modified from Section 8, Table 8.221 and Table 8.223

Omicron variants

Results with regard to the immune response after a booster dose of the MV (B.1.351) and the BV (D614+B.1.351) vaccine against the Omicron subvariants BA.1, BA.2, and BA.4 are limited. A random selection of samples from 20 adults 18-55 years of age and 10 older adults ≥56 years primed with the Pfizer/BioNTech vaccine were included for testing a booster dose of each formulation, i.e. for MV (D614), BMV (B.1.351), and BV (D614+B.1.351). For each substrain results from 3 different assays performed in 3 different laboratories are available, as summarised below. Information regarding the assays used is described in the clinical pharmacology section.

The results for all omicron subvariants for both age cohorts and all assays used for assessment are shown below.

Figure 3: VAT00002 - Supplemental Phase III Cohort 2: Neutralising antibody responses to D614G and BA.1 among Pfizer/BioNTech primed adult participants 18-55 years of age at baseline and after boosting with AS03-adjuvanted CoV2preSdTM recombinant protein from prototype and variant vaccines. Pseudovirus neutralisation assays performed by Monogram



GMTRs against Omicron BA.1 (Monogram assay) range from 94.15 in the MV (B.1.351) vaccine group to 72.5 in the BV (D614+B.1.351), and 45.5 in the MV (D614) group.

Figure 4 - VAT00002 - Supplemental Phase III Cohort 2: Neutralising antibody responses to D614G and BA.1 among Pfizer/BioNTech primed adult participants ≥ 56 years of age at baseline and after boosting with AS03-adjuvanted CoV2preSdTM recombinant protein from prototype and variant vaccines. Pseudovirus neutralisation assays performed by Monogram

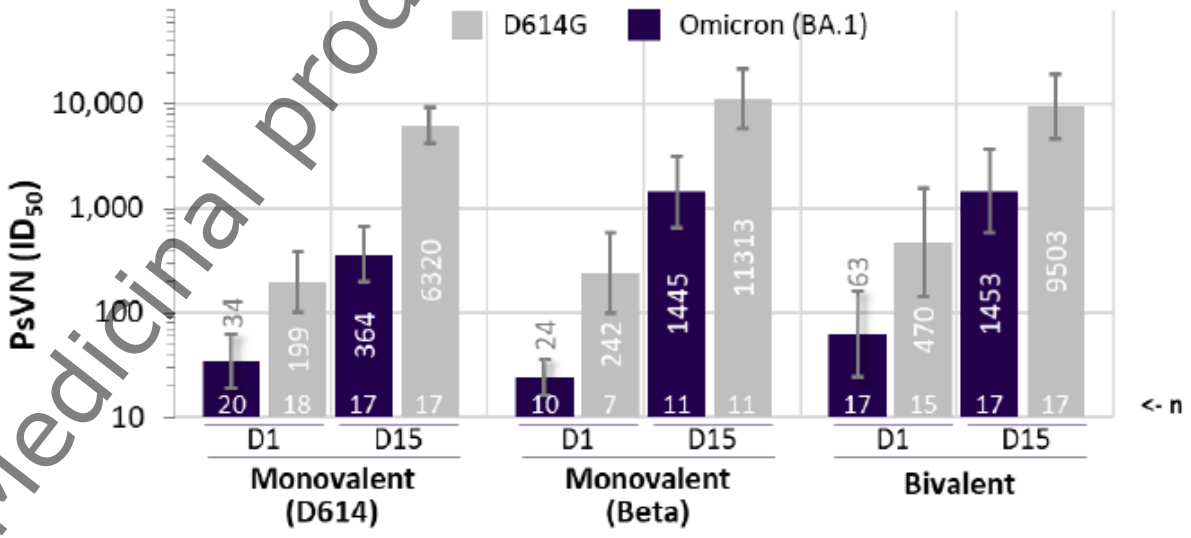


Figure 5 - VAT00002 - Supplemental Phase III Cohort 2: Neutralising antibody responses to Delta, BA.1 and BA.2 among Pfizer/BioNTech primed adult participants 18-55 years of age at baseline and after boosting with AS03-adjuvanted CoV2preSdTM recombinant protein from prototype and variant vaccines. Live virus neutralisation assays performed by Institut Pasteur

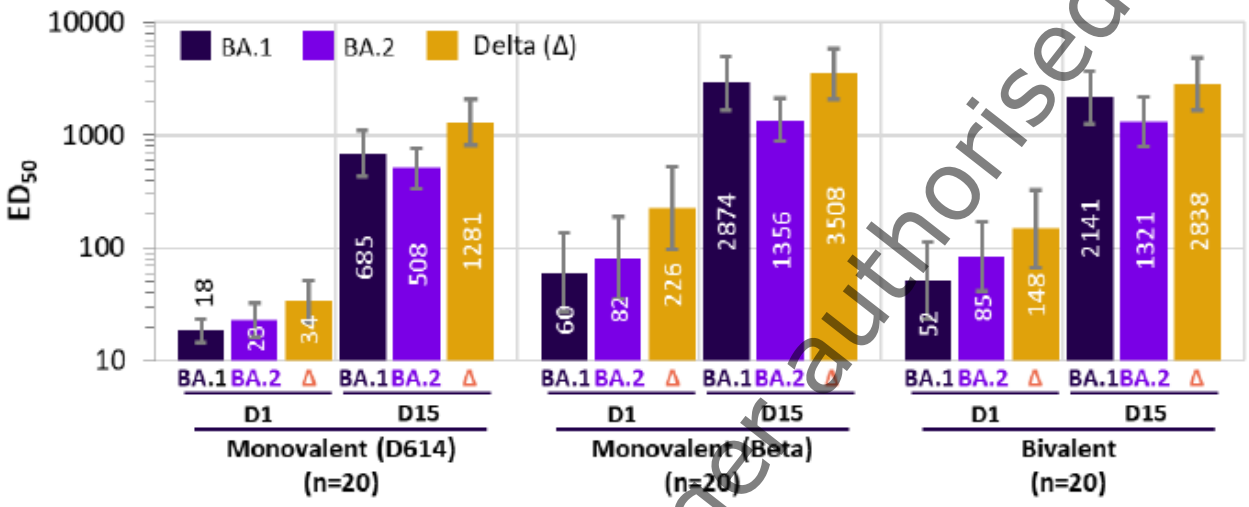
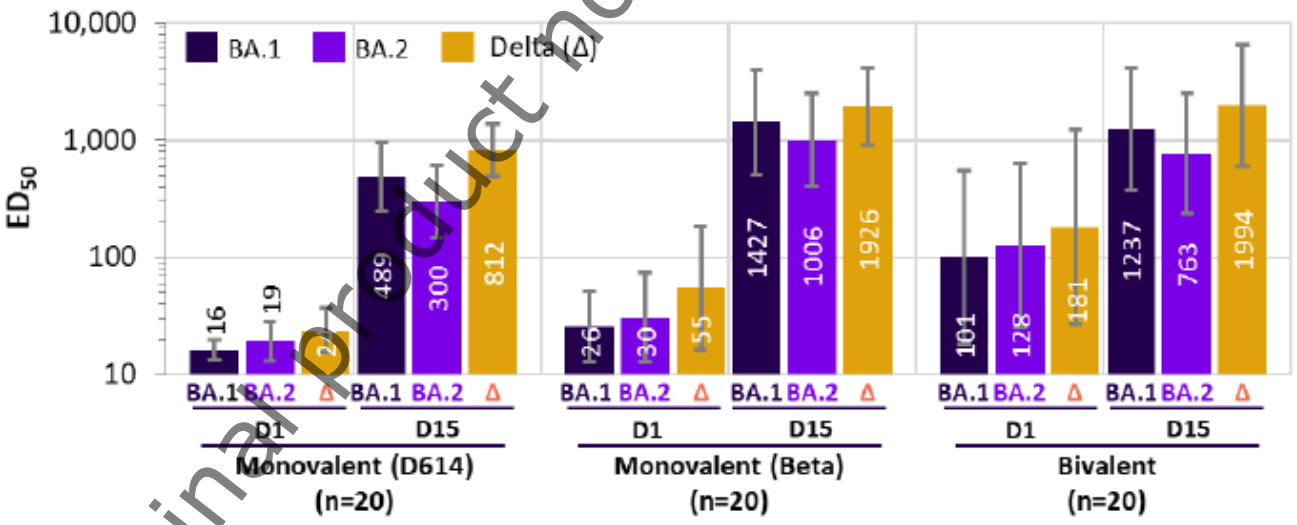


Figure 6 - - VAT00002 - Supplemental Phase III Cohort 2: Neutralising antibody responses to Delta, BA.1 and BA.2 among Pfizer/BioNTech primed adult participants ≥ 56 years of age at baseline and after boosting with AS03-adjuvanted CoV2preSdTM recombinant protein from prototype and variant vaccines. Live virus neutralisation assays performed by Institut Pasteur



GMTRs against BA.1 range from 47.9 in the MV (B.1.351) to 41.17 in the BV (D614+B.1.351) and 38.05 in the MV (D614) vaccine group. GMTRs against BA.2 ranged from 22.08 in the MV (D614) to 16.53 in the MV (B.1.351) and 15.54 in the BV (D614+B.1.351) vaccine group.

Table 36: VAT00002 - Supplemental Phase III Cohort 2: Neutralising antibody responses to BA.1 and BA.4 among Pfizer/BioNTech primed adult participants at baseline and after boosting with AS03-adjuvanted CoV2 preS dTM recombinant protein from variant vaccines, by

			Booster Cohort 2 Pfizer-primed MV[Beta] boost			Booster Cohort 2 Pfizer-primed Bivalent boost		
Age group (years)	**Variant**	**Time point/Ratio**	**M**	**GMT/ GMTR**	**(95% CI)***	**M**	**GMT/ GMTR**	**(95% CI)***
18-55	**BA.1**	**D01**	20	75.00	(33.61, 167.37)	20	78.95	(38.81, 160.62)
		D15	20	3188.01	(1836.11, 5535.29)	20	2418.68	(1308.36, 4471.24)
		D15/D01	20	42.51	(14.82, 121.95)	20	30.63	(15.97, 58.78)
	BA.4	**D01**	20	58.60	(29.63, 115.89)	20	45.52	(24.90, 83.23)
		D15	20	1142.65	(658.06, 1984.11)	20	1035.99	(607.72, 1766.04)
		D15/D01	20	19.50	(7.42, 51.27)	20	22.76	(10.91, 47.46)
≥ 56	**BA.1**	**D01**	10	31.58	(18.64, 53.48)	10	85.87	(18.93, 389.42)
		D15	10	829.54	(248.84, 2765.35)	10	792.19	(204.45, 3069.51)
		D15/D01	10	26.27	(6.01, 114.76)	10	9.23	(2.81, 30.24)
	BA.4	**D01**	10	27.48	(19.82, 38.10)	10	67.66	(22.86, 200.28)
		D15	10	737.84	(187.64, 2901.28)	10	666.17	(158.50, 2799.81)
		D15/D01	10	26.85	(6.56, 109.94)	10	9.85	(2.15, 45.12)

M: number of participants with available data for the relevant endpoint.
GMTR (geometric mean titer ratio): geometric mean of individual titer ratios (post-vaccination/pre-vaccination)
*2-sided 95% CI is based on the Student t-distribution of log_{10} transformation of the individual titers
MV (Beta) = CoV2 preS dTM-AS03 (5 µg Beta), BV (D614 + Beta) = CoV2 preS dTM-AS03 (2.5 µg D614 + 2.5 µg Beta)
SARS-CoV-2 Pseudovirus Neutralization Assay performed at the National Institute of Communicable Diseases for BA.1, BA.4.

All 3 booster vaccines, i.e. MV (B.1.351), BV (D614+B.1.531), MV (D614) induced in the small sub-populations tested notable increases in neutralising titres to all Omicron subvariants in younger and older adults primed with Pfizer/BioNTech on D15, when compared to pre-boost levels (D01). GMTs tended to be lower in the older age cohort. A direct and systematically comparison of the immune response against each Omicron subvariant (BA.1; BA.2; BA.4) for the 3 formulations MV (D614), MV (B.1.351) and BV (D614+B1.351) has not been performed. Comparison of the three formulations in light of the data presented is impeded by the fact that the assessment of immunogenicity was performed in different laboratories. Moreover, the subset of participants for the evaluation is small, and the baseline Ab levels are different against the different sub-strains and different in each booster vaccine group. The difference in baseline antibody titres is likely due to pre-existing immunity either induced by the primary vaccination or natural infection prior to booster administration (i.e. between day 1 and booster). No immunogenicity data assessing the nAB immune response against Omicron sub-variants are available for priming vaccines different from Pfizer/BioNTech.

2.5.5.3. Supportive study(ies)

VAT00008 - Stage 2

VAT00008 Stage 2, which has a randomized, modified double-blind, placebo-controlled design, is being conducted in adults 18 years of age and older to evaluate the efficacy, safety, and immunogenicity of a primary series of 2 injections of 10 µg antigen dose (5 µg antigen per strain) of the bivalent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine formulation with 2 recombinant prefusion delta TM proteins encoding the Spike (S) protein (preS dTM) AS03-adjuvanted sequence from the D614 strain and the Beta (B.1.351) variant (hereafter referred to as the CoV2 preS dTM-AS03 [D614 + B.1.351] vaccine) administered 21 days apart by intramuscular (IM) route.

Methods

- **Study participants**

Inclusion Criteria

- Aged 18 years or older on the day of inclusion
- For persons living with HIV, stable HIV infection determined by participant currently on antiretrovirals with CD4 count > 200/mm3
- SARS-CoV-2 rapid serodiagnostic test performed at the time of enrollment to detect presence of SARS-CoV-2 antibodies
- Does not intend to receive an authorized/approved COVID-19 vaccine despite encouragement by the Investigator to receive the authorized vaccine available to them at the time of enrolment
- A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:
    - Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile.

      OR

    - Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to the first study intervention administration until at least 12 weeks after the second study intervention administration.

      A participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 25 hours before any dose of study intervention.
- Informed consent form has been signed and dated
- Able to attend all visits and to comply with all study procedures
- Covered by health insurance, only if required by local, regional or national regulations

Exclusion Criteria

Medical conditions

- 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
- Dementia or any other cognitive condition at a stage that could interfere with following the study procedures based on Investigator's judgment
- Self-reported thrombocytopenia, contraindicating intramuscular (IM) vaccination based on Investigator's judgment
- Bleeding disorder, or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating IM vaccination based on Investigator's judgment
- Unstable acute or chronic illness that in the opinion of the Investigator or designee poses additional risk as a result of participation or that could interfere with the study procedures
- 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
- 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.
- Prior administration of a coronavirus vaccine (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], SARS-CoV, Middle East Respiratory Syndrome [MERS-CoV])
- Receipt of solid-organ or bone marrow transplants in the past 180 days
- Receipt of anti-cancer chemotherapy in the last 90 days
- Participation at the time of study enrolment (or in the 30 days preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure
- Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
- Identified as an Investigator or employee of the Investigator or study centre with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

  Depending on country regulations and feasibility, if the participant has a primary physician who is not the Investigator, the site may contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site may ask this primary physician to verify exclusion criteria including but not limited to previous therapies, such as previous vaccines.

- **Treatments**

Participants in Stage 2 will be randomized in a 1:1 ratio to receive 2 injections 21 days apart of either CoV2 preS dTMAS03 (5 µg D614 + 5 µg B.1.351) or Placebo 2.

- **Objectives and endpoints**

The primary objective was to assess the clinical efficacy of the BV CoV2 preS dTM-AS03 (5 µg D614 +

5 µg B.1.351) vaccine for the prevention of symptomatic COVID-19 occurring ≥14 days after the second injection in all participants regardless of prior SARS-CoV-2 infection. The objectives and endpoints relevant to this application are presented below.

Table 37: - Efficacy objectives and endpoints of Study VAT00008 - Stage 2 relevant to this application

Objectives	Endpoints
Primary Efficacy	
To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for prevention of symptomatic COVID-19 ≥ 14 days after the second injection.	• Occurrences of symptomatic COVID-19
Key Secondary Efficacy Objective ***Note:*** *The numbering, description, and associated endpoints of the key secondary efficacy objective applicable to Stage 2 are as introduced in the study protocol.*	
2) To assess: • Prevention of SARS-CoV-2 infection in participants who are SARS-CoV-2 naïve, occurring ≥ 14 days after the second injection • Prevention of severe COVID-19 in participants regardless of prior SARS-CoV-2 infection occurring ≥ 14 days after the second injection	Endpoints for secondary efficacy objective #2: • Occurrences of SARS-CoV-2 infection • Occurrence of severe COVID-19
Other Secondary Efficacy Objectives ***Note:*** *The numbering, description, and associated endpoints of the other secondary efficacy objectives applicable to Stage 2 are as introduced in the study protocol.*	
3) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 14 days after the first injection.	Endpoint for secondary efficacy objective #3: • Occurrences of symptomatic COVID-19
5) To assess, in participants who are SARS-CoV-2 non-naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Endpoints for secondary efficacy objective #5: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19
6) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of asymptomatic SARS-CoV-2 infection.	Endpoint for secondary efficacy objective #6: • Occurrences of asymptomatic SARS-CoV-2 infection
8) To assess, in all participants regardless of prior SARS-CoV-2 infection and in participants who are SARS-CoV-2 non-naïve and naïve, clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of CDC-defined COVID-19 • Prevention of hospitalized COVID-19 • Prevention of symptomatic COVID-19 with severity of moderate COVID-19 or	Endpoints for secondary efficacy objective #8: • Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19 • Occurrences of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of at least one of moderate or severe COVID-19)

Objectives	Endpoints
worse (composite endpoint of moderate or severe COVID-19)	
12) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic and severe COVID-19 occurring ≥ 14 days after the second injection.	Endpoint for secondary efficacy objective #12: • Occurrences of symptomatic COVID-19 • Occurrences of severe COVID-19
Exploratory Efficacy ***Note:*** *The numbering, description, and associated endpoints of the exploratory efficacy objectives applicable to Stage 2 are as introduced in the study protocol.*	
2) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in SARS-CoV-2 naïve participants by subgroups defined by age, high risk medical conditions, sex and race/ethnicity or a combination of those for: • Prevention of SARS-CoV-2 infection • Prevention of asymptomatic SARS-CoV-2 infection	Endpoints for exploratory efficacy objective #2: • Occurrences of SARS-CoV-2 infection • Occurrences of asymptomatic SARS-CoV-2 infection
3) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in participants regardless of prior SARS-CoV-2 infection and by baseline prior SARS-CoV-2 infection (naïve and non-naïve) by subgroups defined by age, high risk medical conditions and race/ethnicity or a combination of those for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19 • Prevention of hospitalized COVID-19 • Prevention of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of moderate or severe COVID-19) • Prevention of death associated with symptomatic COVID-19	Endpoints for exploratory efficacy objective #3: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19 • Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of at least one of moderate or severe COVID-19) • Deaths associated with symptomatic COVID-19
13) To assess if and how vaccine efficacy for the prevention of virologically-confirmed symptomatic COVID-19 depends on genotypic or neutralisation phenotypic characteristics of SARS-CoV-2 (sieve analysis for disease).	Endpoints for exploratory efficacy objective #13: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19

Source: Modified from 5.3.5.1 VAT00008 - Stage 2 Brief CSR, Appendix 1 Clinical study protocol

The study protocol includes secondary immunogenicity objectives that are not included in VAT00008 Stage 2 Brief CSR. The immunogenicity results for VAT0008 Stage 2 are not yet available.

The analysis sets are defined as follows:

Table 38: Criteria of evidence for prior SARS-CoV-2 infection at baseline and at second injection

Prior SARs-CoV-2 infection status	Description
SARS-CoV-2 Naïve at baseline (Naïve-D01)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by the anti-N immunoassay on D01 serum sample AND • Negative NAAT for SARS-CoV-2 on respiratory sample collected on D01
SARS-CoV-2 Non-Naïve at baseline (Non-Naïve-D01)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 serum sample OR • Positive NAAT for SARS-CoV-2 on respiratory sample collected on D01
SARS-CoV-2 Naïve at second injection (Naïve- D01+D22)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by anti-N immunoassay on D01 and D22 serum samples AND • Negative NAAT for SARS-CoV-2 on respiratory samples collected on D01 and D22
SARS-CoV-2 Non-Naïve at second injection (Non-Naïve - D01/D22)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 or D22 serum samples OR • Positive NAAT for SARS-CoV-2 on respiratory samples collected on D01 or D22

- **Sample size**

A total of 10 160 participants in Stage 1 and 10 886 participants in Stage 2 are planned to be enrolled and randomized with allocation ratio (1:1) into vaccine group and placebo group. Among those, up to 3048 participants in Stage 1 and 3266 participants in Stage 2 (approximately 30% proportion of each stage population) will be SARS-CoV-2 non-naïve. While the target of 30% of SARS-CoV-2 non-naïves may or may not be reached, the study will aim at capping the representation of SARS-CoV-2 non naïves to a maximum of 30%, to secure the sample size in the SARS-CoV-2 naïve population to demonstrate vaccine efficacy in each stage. To that end, the sample size of at least 7112 SARS-CoV-2 naïve participants in Stage 1 and 7620 SARS-CoV-2 naïve participants in Stage 2 is powered independently to demonstrate the primary objective of VE against symptomatic COVID-19 in SARS CoV-2 naïve adults in each stage.

Assumptions for sample size calculation are listed as follows:

- The LB of adjusted CI for the VE estimate is > 30% for both stages
- The expected true VE for symptomatic COVID-19 is 70%
- The 1-sided type I error for each stage is 0.025 with the sample size calculated based on adjusted alpha of 1-sided 0.02276 for final analysis including one interim at 70% data
- Power = 90% for each stage

Each stage is considered as independent of the other so that the type I error is controlled for each stage but not for the study. While the above assumptions remain the same for each stage of the study, the following assumptions are different for both stages because Stage 2 is expected to start after Stage 1.

- The incidence rate of symptomatic COVID-19 in Placebo is assumed as 2.25% illness rate in Stage 1 and 2.25% illness rate in Stage 2, per 2-months follow-up period
- Attrition rate = 25% in Stage 1 and 30% in Stage 2

For each stage, the type I error of hypothesis testing is controlled as 1-sided 0.025, and O'Brien Fleming (OBF) spending function is applied to adjust for multiplicity of interim analysis for efficacy with one potential interim analysis when accrual of approximately 50%-70% of the total number of events is reached (see Section 9.5). The sample size calculated based on the adjusted final alpha of 0.02276 will ensure at least 90% power to conclude on primary objective when the interim analysis is conducted between 50% - 70% range of data. Adjusted alpha by OBF alpha spending function is applied and the corresponding adjusted CI will be used for hypothesis testing at each interim and at final analysis against symptomatic COVID-19 in each stage independently.

In each stage, with assumptions described above, a total of approximately 78 symptomatic COVID-19 events are required. The expected follow-up time to accrue the required number of events for 90% power is approximately 2 months post-second dose, given the incidence rate assumption in each stage respectively. However, the number of events may be reached earlier or later than the assumed 2-month period.

It is considered success for the key secondary endpoints if the LB of the CI for the corresponding VE is > 0% against either the SARS-CoV-2 infection endpoint, or severe COVID-19. The Holm's procedure (19) will be applied to control the overall 1-sided alpha 0.025 against key secondary objectives. Assuming the VE against SARS-CoV-2 infection endpoint is at least 40%, a total of 162 infections will have at least 80% power to conclude at 0% LB. Assuming the VE against severe COVID-19 is 80%, a total of 22 events will provide at least 80% power to conclude at 0% LB.

The study is planned to have 5080 participants in the vaccine group in Stage 1 which will provide at least 92.1% probability to detect an event with 0.05% rate. In Stage 2, 5443 participants in vaccine group will provide at least 93.4% probability to detect an event with 0.05% rate.

Table 39: Planned sample size and approximate size of subsets in Stage 2

		Study Intervention Groups (Stage 2)	
		Vaccine 2	Placebo 2
		CoV2 preS dTM-AS03 (D614 + B.1.351)	Placebo
Total Overall		5443	5443
Prior exposure to SARS-CoV-2	**SARS-CoV-2 naïves**	3810	3810
	SARS-CoV-2 non-naïves	1633	1633
Reactogenicity Subset		2000	2000
Random Immunogenicity Subset*		1415	559

If the crossover is not implemented, recruitment will continue until the minimally required number of naïve participants to assess efficacy is enrolled (even if the overall enrollment target is reached).
* Details of the random subset and subcohort are described below and in Appendix 10.6.

- **Randomisation and blinding**

On the day of enrolment participants will be tested for presence of SARS-COV-2 antibodies using a rapid serodiagnostic test. Participants who meet the inclusion/exclusion criteria and sign the informed consent form (ICF) were randomly assigned to one of the study groups (vaccine versus placebo) with randomization ratio 1:1 in either Stage 1 only or Stage 2 only. In the event that the enrolment in Stage 1 overlaps with enrolment of Stage 2, an independent randomization of 1:1 will be applied to assign participants enrolled at that period to one of vaccine candidate groups and their matched placebo group. There will be no sharing of the placebo participants between the 2 stages. Stratified permuted block randomization will be applied for study group randomization where strata are age group (18-59 years and ≥60 years), baseline SARS-CoV-2 rapid serodiagnostic test positivity

(Positive/Negative), and sites. Participants who are positive by the rapid serodiagnostic test will be included in the study until a trigger is reached indicating an anticipated proportion of SARS-COV-2 non-naïve individuals of approximately 30% at the end of enrolment

The study will be performed in a modified double-blind (observer-blind) fashion:

- Investigators and study staff who conduct the safety assessment and monitoring for efficacy and the participant will not know which vaccine is administered in order to decrease the risk of potential bias. Study site staff who administer the vaccine may also be blinded if they are not involved in preparation of the vaccine.
- Only the study site staff who prepare and administer the vaccine and are not involved with the safety and efficacy evaluation will know which vaccine is administered
- Testing laboratories will be blinded

- **Statistical methods**

The full planned analyses and determination of sample size are described in the final version of the SAP and contained in Section 9 of the protocol.The analysis sets are included in the below table.

Table 40: VAT00008 - Stage 2: Analysis sets

Population	**Description**
Full analysis set (FAS)	All randomized participants who received at least one study injection. Participants were analysed according to the intervention to which they were randomized.
Modified full analysis set post-dose 1 (mFAS-PD1)	Subset of the FAS excluding: • Participants with onset of symptomatic COVID-19 episode between the date of the first injection and 14 days after the first injection. • Participants discontinued from study before 14 days after the first injection
Modified full analysis set post-dose 2 (mFAS-PD2)	Subset of the FAS excluding: • Participants who did not complete the vaccination schedule (2 injections) • Participants with onset of symptomatic COVID-19 episode between the date of the first injection and 14 days after the second injection • Participant received the second injection despite meeting any of the definitive contraindication criteria • Participant discontinued from study before 14 days after the second injection
Per-protocol analysis set (PPAS)	Subset of the mFAS-PD2. Participants presenting with at least one of the following relevant protocol deviations were excluded from the PPAS: • Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participant received a vaccine / placebo other than the one that he / she was randomized to receive • Preparation and / or administration of vaccine was not done as per-protocol • Participant did not receive vaccine / placebo in the proper time window
Safety Analysis Set (SafAS)	All randomized participants who had received at least one dose of the study vaccine or placebo. Participants had their safety analysed after each dose according to the study intervention they actually received, and after any dose according to the study intervention received at the first dose. Safety data recorded for participants not administered

Population	Description
	a study intervention was excluded from the analysis (and listed separately).
Reactogenicity safety analysis subset (RSafAS)	Subset of the SafAS and comprising all participants who received at least one study injection and were randomized into the reactogenicity subset.

Efficacy - Hypotheses and vaccine efficacy (VE) estimation

Hypothesis testing was conducted for the primary efficacy objective. The success criteria for demonstration of efficacy included: 1) the lower bound of confidence interval (CI) is > 30%, and 2) the point estimate of VE is > 50%.

Hypothesis testing for key secondary objectives were to be conducted when both of the following conditions were met:

- The primary objective was demonstrated
- 22 severe COVID-19 cases and 162 infections were collected

Yet, fewer than 22 severe COVID-19 cases were reported and thus, hypothesis testing was not conducted for assessing efficacy against severe COVID-19 in participants regardless of prior SARS CoV-2 infection. Hypothesis testing for key secondary efficacy objective was only conducted for assessing the prevention of SARS-CoV-2 infection in SARS-CoV-2 naïve participants. The efficacy was considered as demonstrated if the lower bound of 95% CI (exact method) was greater than 0%.

Analyses for the other efficacy objectives are descriptive. Analyses of the primary safety objectives, other secondary objectives, and exploratory objectives are descriptive.

Primary objective

The hypothesis testing of VE against the primary endpoint of symptomatic COVID-19 was as follows:

H0: VE ≤ 30%

HA: VE > 30%

The point estimate of VE was calculated by the incidence rate ratio (IRR):

$$\widehat{VE} = 1 - \frac{C_V/PY_V}{C_P/PY_P} \qquad \text{(Formula 1)}$$

where CV and CP represent the cases in vaccine group and placebo group respectively; PYV and PYP represent total # of 1000 person-years in vaccine group and placebo group, respectively. The CI for VE was calculated by an exact method assuming a binomial distribution of the number of cases in vaccine group conditional on the total number of cases in the study. As a sensitivity analysis for primary objective, the point estimate of VE was based on relative risk (RR) of COVID-19 case occurrence shown below:

$$\widehat{VE} = 1 - \frac{C_V/N_V}{C_P/N_P} \qquad \text{(Formula 2)}$$

where CV and CP represent the cases in vaccine group and placebo group respectively; NV and NP represent total # of participants in vaccine group and placebo group, respectively. The CI of VE by RR was calculated with the same method as described above for the CI of VE by IRR by replacing the 1000 person-years to number of participants at risk in the denominators, respectively.

Sensitivity Analysis 1

Sensitivity analysis against symptomatic COVID-19 was conducted with VE calculated by RR (Formula 2) in addition to person-year approach in the mFAS-PD2.

Sensitivity Analysis 2

Sensitivity analysis against symptomatic COVID-19 was conducted in the PPAS.

Both the mFAS-PD2 and PPAS capture endpoints occurring during the most relevant follow-up period (i.e., after 2 weeks from last immunization, allowing sufficient time for adequate adaptive immune responses to be elicited by the vaccine). The mFAS-PD2 is considered to better preserve the benefits of randomization compared to the PPAS, and it is also considered to approximate better to what may occur in real conditions external to the study (closer to an intent-to-treat population). The PPAS is expected to provide an estimate of the vaccine performance reflective of ideal conditions.

Survival Analysis

In addition to the hypothesis testing based on IRR, survival analyses based on Stratified Cox proportional hazard (PH) model were used to estimate the VE by one minus the hazard ratio (HR) (vaccine versus placebo), with score-based CI, as a supportive analysis. Specifically, Stratified Cox model used separate baseline strata of different age group, sex, high-risk medical condition group, and serostatus at D22. In addition to Cox model, Kaplan-Meier curves were also applied with 95% CI calculated by Greenwood formula.

Survival analysis was conducted in the mFAS-PD2 and PPAS analysis sets.

Key secondary objective (prevention of SARS-CoV-2 infection in SARS-CoV-2 naïve participants)

The following hypotheses were tested for the key secondary efficacy objective of SARS-CoV-2 infection:

H0: VE ≤ 0%

HA: VE > 0%

The VE of SARS-CoV-2 infection is computed by RR (Formula 2) and CI by exact binomial method (see above for primary efficacy objective). The RR is used for evaluating SARS-CoV-2 infection as the ascertainment of serological infection using blood samples collected at serial intervals does not enable robust assessments of person-time at risk for each individual.

Dates of data analyses

The number of primary endpoint events was reached on March 15, 2022. This triggered the primary analysis on the primary endpoint based on a data extraction performed on 9 June 2022 with data cut-off date of March 15, 2022 (i.e., all primary endpoint events with events' start date earlier than March 15, 2022 were included in the primary analysis at this time).

All analyses (including hypothesis testing of primary and secondary efficacy; secondary and exploratory efficacy analyses, sensitivity analysis on the primary endpoint and safety analysis) presented in this report correspond to data extracted on June 9, 2022. All adjudicated cases in the database at the time of data extraction were considered for the efficacy analyses. These primary analyses were conducted to support the registration of vaccine candidates in response to the ongoing pandemic and were based on data that were cleaned and quality checked to the fullest extent possible. However, data were not locked, thus the database continues to be updated following ongoing data collection.

To include more updated data on sequencing data, a subsequent data extraction was performed on June 29, with the same data cut-off date (i.e., March 15, 2022). Only the efficacy tables related to variant-specific efficacy were re-analysed after this data extraction. There were no re-analyses of the primary and secondary efficacy objectives.

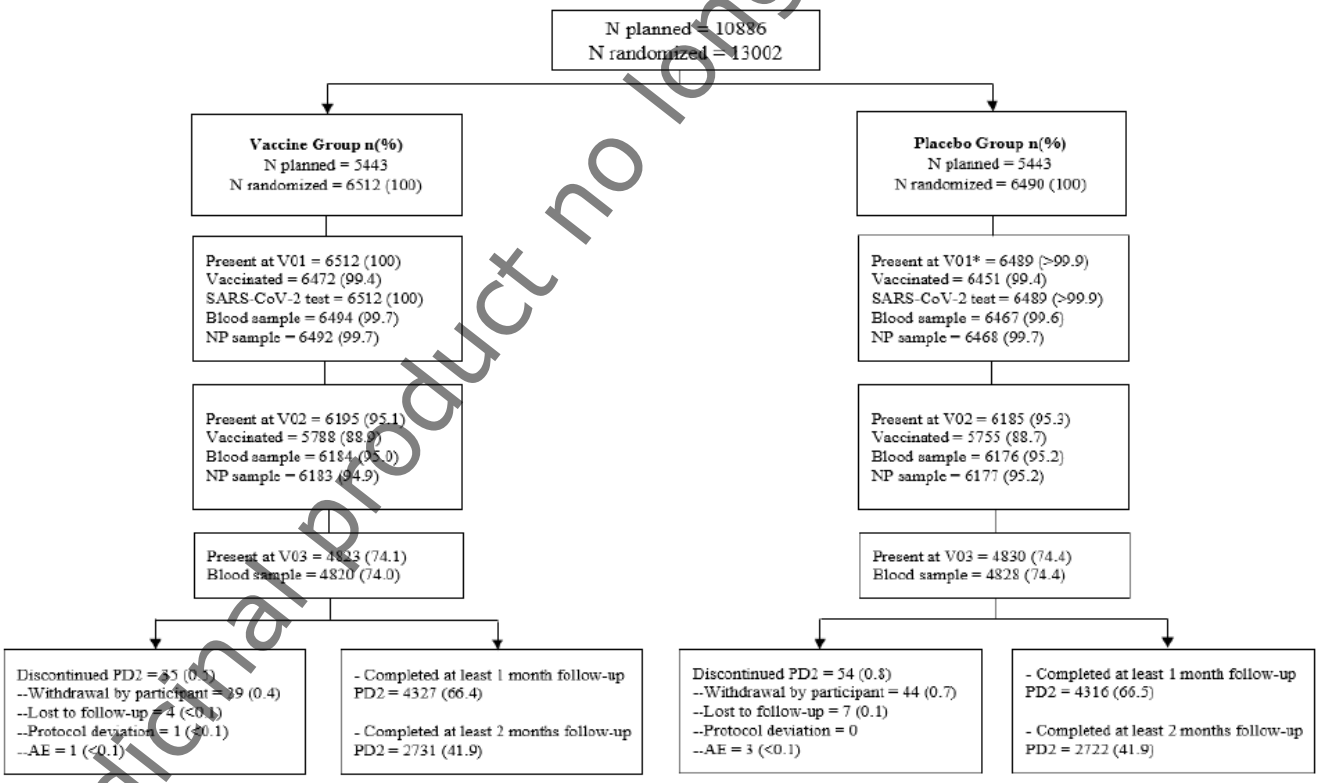
Changes in Planned Analyses Prior to Unblinding or Database Clean

Because Omicron is the prevalent variant during case accrual for Stage 2 and the expected vaccine efficacy against Omicron is expected to be lower than the original assumption of 70%, the expected true VE for symptomatic COVID-19 for Stage 2 was estimated at 60%. Therefore, a total of approximately 125 symptomatic COVID-19 events will be required to achieve 80% power with 1-side type I error rate of 0.025, assuming no interim analysis. If any interim analysis is planned for Stage 2, type I error rate will be adjusted appropriately.

Results

- **Participant flow**

Figure 7: Participant disposition flow chart



- **Recruitment**

19 October 2021 first participant first visit in Stage 2

Stage 2: Colombia, Mexico, Ghana, Kenya, Uganda, Ukraine, Nepal, India.

Ukrainian study sites participated in Stage 2. Due to the current situation in Ukraine, it was not feasible to confirm the completeness of the data collected. Therefore, none of the 498 participants from the FAS from the 4 study sites were included in the main analyses reported.

- **Conduct of the study**

According to the Applicant, VAT00008 was conducted according to GCP Guidelines and current version of the Declaration of Helsinki.

The protocol was amended several times. The brief CSR (version 1.0, dated 21 July 2022) was submitted. All protocol versions have been provided together with an overview of the major protocol changes.

- **Baseline data**

Out of the 13002 randomized participants, 12924 (99.4%) were included in the Full Analysis Set (FAS); 78 participants did not receive any injection and were, therefore, excluded from this analysis set.

In the FAS, 1176 participants were naïve at D01 and 683 participants were naïve at D01 and D22, 9693 participants were non-naïve at D01, and 10966 participants were non-naïve at D01 or D22. A total of 2055 participants had an undetermined status at D01 and 1275 participants had an undetermined status at D22. Among the 12924 participants in the FAS, the Modified Full Analysis Set post-dose 1 (mFASPD1) included a total of 12809 participants (6418 [99.2%] in the Vaccine Group and 6391 [99.1%] in the Placebo Group). Among the 1176 participants naïve at D01 in the FAS, 1153 (98.0%) participants were in the mFAS-PD1 population. Among the 9693 participants non-naïve at D01 and in the FAS, 9619 (99.2%) were in the mFAS-PD1 population.

Among the 12924 participants in the FAS, the Modified Full Analysis Set post-dose 2 (mFAS-PD2) included a total of 11416 participants (5736 [88.6%] in the Vaccine Group and 5680 [88.0%] in the Placebo Group).

Of the 683 participants in the FAS who were naïve at D01 and D22, 670 (98.1%) participants were in the mFAS-PD2. Among the 10966 participants non-naïve at D01 or D22 in the FAS, 9659 (88.1%) participants were in the mFAS-PD2 analysis set.

The longest duration of the follow-up post-dose 2 for participants in mFAS-PD2 aged 18 to 59 years was 118 days for each the Vaccine Group and the Placebo Group, and the median participant duration of the follow-up post-dose 2 was 58 days for each the Vaccine Group and the Placebo Group. For participants aged ≥ 60 years, the longest duration of the follow-up post-dose 2 was 104 days, 100 days for the Vaccine Group and 104 days for the Placebo Group, and the median participant duration of the follow-up post-dose 2 was 54 days for the Vaccine Group and 54 days for the Placebo Group. For participants aged ≥65 years, the longest duration of the follow-up post-dose 2 was 100 days for each the Vaccine Group and the Placebo Group, and the median participant duration of the follow-up post-dose 2 was 56 days for each the Vaccine Group and 51 days for the Placebo Group.

The Per-Protocol Analysis Set (PPAS), which is a subset of the mFAS-PD2, included a total of 10489 (91.9%) participants (5257 [91.6%] in the Vaccine Group and 5232 [92.1%] in the Placebo Group) out of the 11416 participants in the mFAS-PD2. Most exclusions (926 [8.1%] participants) from the PPAS were due to not receiving the vaccine in the proper time window.

Table 41: Disposition of participants, efficacy populations, treatment as randomized

Disposition	Vaccine Group N=6512	Placebo Group N=6490	Total N=13002
Completed 1 dose (n/N [%])	6472*/6512 (99.4)	6451*/6490 (99.4)	12923†/13002 (99.4)
Completed 2 doses (n/N [%])	5788/6512 (88.9)	5755/6490 (88.7)	11543/13002 (88.8)
Completed at least 1 month follow-up post-dose 2 (n/N [%])	4327/6512 (66.4)	4316/6490 (66.5)	8643/13002 (66.5)
Completed at least 2 months follow-up post-dose 2 (n/N [%])	2731/6512 (41.9)	2722/6490 (41.9)	5453/13002 (41.9)
Full Analysis Set (FAS) (n/N [%])	6472/6512 (99.4)	6452†/6490 (99.4)	12924/13002 (99.4)
Modified FAS Post-Dose 1 (mFAS-PD1) (n/N [%])	6418/6472 (99.2)	6391/6452 (99.1)	12809/12924 (99.1)
Modified FAS Post-Dose 2 (mFAS-PD2) (n/N [%])	5736/6472 (88.6)	5680/6452 (88.0)	11416/12924 (88.3)
mFAS-PD1 Naïve-D01 (n/N [%])	577/588 (98.1)	576/588 (98.0)	1153/1176 (98.0)
mFAS-PD2 Naïve D01+D22 (n/N [%])	327/333 (98.2)	343/350 (98.0)	670/683 (98.1)
mFAS-PD1 Non-Naïve-D01 (n/N [%])	4826/4860 (99.3)	4793/4833 (99.2)	9619/9693 (99.2)
mFAS-PD2 Non-Naïve D01/D22 (n/N [%])	4841/5478 (88.4)	4818/5488 (87.8)	9659/10966 (88.1)
Per-Protocol Analysis Set (PPAS) (n/N [%])	5257/5736 (91.6)	5232/5680 (92.1)	10489/11416 (91.9)
PPAS Naïve-D01+D22 (n/N [%])	298/327 (91.1)	324/343 (94.5)	622/670 (92.8)

*Among randomized participants, 40 participants in the Vaccine Group and 38 participants in the Placebo Group, 78 in total, did not receive any injection.
†V01 for one participant did not appear in the database during the data extraction dated 09 June 2022 because the site was entering additional data for V01 at the time the data extraction was performed. However, this participant was included in mFAS-PD1, mFAS-PD2, mFAS-PD2 non-naïve D01/D22 analysis sets because both V01 and V02 were performed.
N=number of participants randomized to each group; these values are the denominators for the percentage calculations.
n=number of participants with the specified disposition.
For a description of the analysis sets see Section 8.3.2
Follow-up time was calculated from the second injection to the data cut-off date, termination date, or death date, whichever date was earlier.
Follow-up time after the second injection for participants who did not receive the second injection was counted as 0.
Data analysis cut-off date: 15 March 2022
Source: modified from Section 8, Tables 8.3B, 8.4B, 8.5B

In the mFAS-PD2, the mean age (standard deviation [SD]) of participants in the mFAS-PD2 was 36.1 (12.8) years. The mean age was similar across both treatment groups. Most participants (94.2%) were aged between 18 and 59 years and a total of 662 (5.8%) participants were aged ≥60 years. Using a different age cut-off, the majority of participants (97.3%) were aged between 18 and 64 years and a total of 311 (2.7%) participants were aged ≥65 years.

Participants' predominant race was Black or African American (44.4%), followed by Asian (41.9%), American Indian or Alaska Native (4.8%), and White (0.6%). Most of participants (84.6% of 11416 participants from mFAS-PD2) were non-naïve at the first or second injection.

- **Numbers analysed**

The number of participants included in each analysis population is provided in the table below.

Table 42: Key analysis sets by age group, prior SARS-CoV-2 infection at baseline, and high-risk medical condition group - randomized participants

		Vaccine Group N=6512	Placebo Group N=6490	Total N=13002
		n/M (%)	n/M (%)	n/M (%)
Age group				
18-59 years	FAS	6078/6116 (99.4)	6069/6105 (99.4)	12147/12221 (99.4)
	mFAS-PD2	5404/6078 (88.9)	5350/6069 (88.2)	10754/12147 (88.5)
	SafAS	6078/6078 (100)	6067/6067 (100)	12147*/12221 (99.4)
	RSafAS	2040/2040 (100)	2037/2037 (100)	4077/4098 (99.5)
>= 60 years	FAS	394/396 (99.5)	383/385 (99.5)	777/781 (99.5)
	mFAS-PD2	332/394 (84.3)	330/383 (86.2)	662/777 (85.2)
	SafAS	394/394 (100)	383/383 (100)	777/781 (99.5)
	RSafAS	393/393 (100)	381/381 (100)	774/778 (99.5)
Prior SARS-CoV-2 infection at baseline				
Naïve-D01	FAS	588/589 (99.8)	588/588 (100)	1176/1177 (>99.9)
	mFAS-PD1	577/588 (98.1)	576/588 (98.0)	1153/1176 (98.0)
	SafAS	588/588 (100)	588/588 (100)	1176/1177 (>99.9)
	RSafAS	332/332 (100)	347/347 (100)	679/679 (100)
Non-Naïve-D01	FAS	4860/4864 (>99.9)	4833/4838 (99.9)	9693/9702 (>99.9)
	mFAS-PD1	4826/4860 (99.3)	4793/4833 (99.2)	9619/9693 (99.2)
	SafAS	4860/4860 (100)	4831/4831 (100)	9693/9702 (>99.9)
	RSafAS	1835/1835 (100)	1802/1802 (100)	3637/3640 (>99.9)
Prior SARS-CoV-2 infection at second injection				
Naïve-D01+D22	FAS	333/333 (100)	350/350 (100)	683/683 (100)
	mFAS-PD2	327/333 (98.2)	343/350 (98.0)	670/683 (98.1)
Non-Naïve-D01/D22	FAS	5478/5482 (>99.9)	5488/5493 (>99.9)	10966/10975 (>99.9)
	mFAS-PD2	4841/5478 (88.4)	4818/5488 (87.8)	9659/10966 (88.1)
High-risk medical condition group				
YES	FAS	2095/2111 (99.2)	2070/2081 (99.5)	4165/4192 (99.4)
	mFAS-PD2	1793/2095 (85.6)	1786/2070 (86.3)	3579/4165 (85.9)
	SafAS	2095/2095 (100)	2070/2070 (100)	4165/4192 (99.4)
	RSafAS	869/869 (100)	862/862 (100)	1731/1737 (99.7)
NO	FAS	4377/4401 (99.5)	4382/4409 (99.4)	8759/8810 (99.4)
	mFAS-PD2	3943/4377 (90.1)	3894/4382 (88.9)	7837/8759 (89.5)
	SafAS	4377/4377 (100)	4380/4380 (100)	8759*/8810 (99.4)
	RSafAS	1564/1564 (100)	1556/1556 (100)	3120/3139 (99.4)

Abbreviations: FAS, Full Analysis Set; IAS, mFAS-PD1, Modified Full Analysis Set post-dose 1; mFAS-PD2, Modified Full Analysis Set post-dose 2; RSafAS, Reactogenicity Safety Analysis Set; SafAS, Safety Analysis Set.

n: number of participants fulfilling the item listed.

N: number of participants randomized in each treatment group.

M: for FAS, mFAS-PD1 and mFAS-PD2: number of participants randomized in each group with available data for the relevant endpoint

- **Outcomes and estimation**

In the FAS, there were 322 participants (106 in the Vaccine Group and 216 in the Placebo Group) who reported a total of 324 OVID-19-like illness (CLI) episodes (2 participants experienced 2 CLIs) confirmed by the adjudication committee to meet the primary endpoint definition of symptomatic COVID-19.

In this population, 18 participants (10 in the Vaccine Group and 8 in the Placebo Group) met the case definition of severe COVID-19.

In the primary efficacy population (i.e., mFAS-PD2), there were 121 participants (32 in the Vaccine Group and 89 in the Placebo Group) who reported 121 CLI episodes confirmed by the adjudication committee to meet the primary endpoint definition of symptomatic COVID-19 at the time of the data extraction. The distribution of these cases by country were as follows 49 cases in Mexico, 35 in India, 16 in Nepal, 10 in Colombia 10 in Kenya, 1 in Ghana. There were no adjudicated cases in Uganda. In this population, 5 participants (3 in the Vaccine Group and 2 in the Placebo Group) met the case definition of severe COVID-19.

Primary Efficacy

Prevention of Symptomatic COVID-19 Occurring ≥14 Days After VAC2, regardless of prior SARS-CoV-2 infection

Primary efficacy was evaluated in the mFAS-PD2 as occurrences of symptomatic COVID-19 in each treatment group (see Section 3.2.5 for the definition of symptomatic COVID-19). As shown in below, the vaccine efficacy (VE) against symptomatic COVID-19 case occurrence was 64.7% (95% CI: 46.6; 77.2) meeting the primary efficacy objective (i.e., to obtain a point estimate of VE > 50%, as calculated by the incidence rate ratio [IRR], with the lower bound of the 95% CI > 30%).

Table 43: Vaccine efficacy (1-IRR) against symptomatic COVID-19 - mFAS-PD2

All participants ≥ 18 years	Vaccine Group (N=5736)			Placebo Group (N=5680)			Vaccine Efficacy		Efficacy Met
	Cases	1000 PYR	IR (95% CI)	Cases	1000 PYR	IR (95% CI)	%	95% CI	
Symptomatic COVID-19 †	32	0.604	52.953 (36.22 ; 74.75)	89	0.593	150.120 (120.56 ; 184.74)	64.7	(46.6 ; 77.2)	Yes

Abbreviations: CI, confidence interval; IR, incidence rate; PYR, person-years at risk
Cases: number of participants with at least one symptomatic COVID-19 episode from 14 days post-injection 2 in the analysis population. IR refers to cases per 1000 PYR.
† Vaccine efficacy analysis based on data extracted on 09 June 2022 with data cut-off date 15 March 2022 (EUA).
For a description of VE and CI calculation see Section 3.3.2.

Source: modified from Section 8, Table 8.16B

Additional sensitivity analyses of the primary efficacy endpoint were conducted to evaluate VE. Generally, VE point estimates by sensitivity analysis were consistent with the primary endpoint. It also includes the sensitivity analysis with participants from Ukraine sites with a VE of 64.0% (95% CI: 45.9; 76.6) in the mFAS-PD2.

Sensitivity Analysis 1:

The VE based on the relative risk (RR) of symptomatic COVID-19 case occurrence was 64.2% (95% CI: 45.8; 76.9).

Table 44: Sensitivity analysis 1: Vaccine efficacy (1-RR) against symptomatic COVID-19 - mFAS-PD2 - Stage 2

All participants ≥18 years	Vaccine Group (N=5736)			Placebo Group (N=5680)			Vaccine Efficacy	
	Cases	# of subjects at risk	CUMI (95% CI)	Cases	# of subjects at risk	CUMI (95% CI)	%	(95% CI)
Symptomatic COVID-19	32	5311	0.6 (0.4 ; 0.8)	89	5287	1.7 (1.4 ; 2.1)	64.2	(45.8 ; 76.9)

Abbreviations: CI, confidence interval; CUMI, cumulative incidence.
Cases: number of participants with at least one symptomatic COVID-19 episode from 14 days post-injection 2 in the analysis population. Cumulative incidence: cases divided by number of participants in each group*100%.
For a description of VE and CI calculation see Section 3.3.2.
Source: modified from Section 8, Table 8.17B

Sensitivity Analysis 2:

In the PPAS, VE was 63.4% (95% CI: 44.5; 76.4) as calculated by the IRR of symptomatic COVID-19 case occurrence.

Table 45: Sensitivity analysis 2: Vaccine efficacy (1-IRR) against symptomatic COVID-19 - PPAS - Stage 2

All participants ≥ 18 years	Vaccine Group (N=5257)			Placebo Group (N=5232)			Vaccine Efficacy	
	Cases	1000 PYR	IR (95% CI)	Cases	1000 PYR	IR (95% CI)	%	(95% CI)
Symptomatic COVID-19	32	0.563	56.809 (38.86 ; 80.20)	86	0.554	155.309 (124.23 ; 191.81)	63.4	(44.5 ; 76.4)

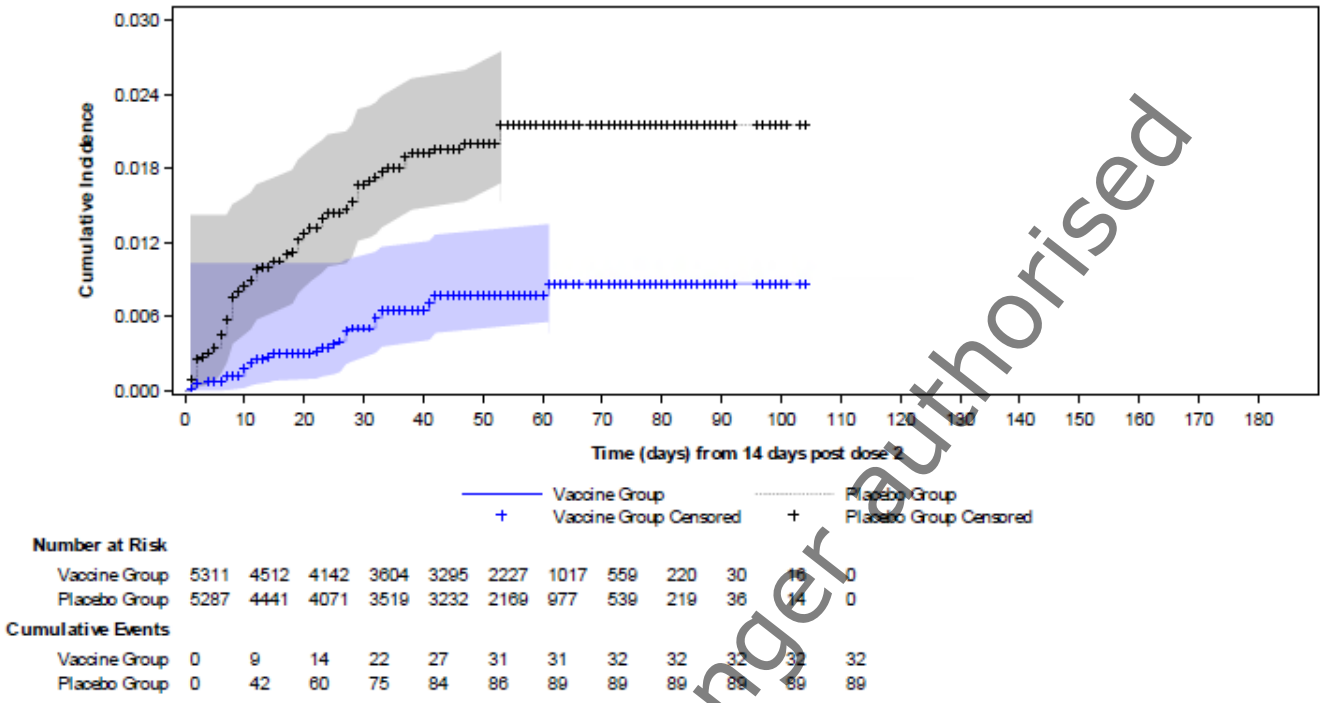
Abbreviations: CI, confidence interval; IR, incidence rate; PYR, person-years at risk
Cases: number of participants with at least one symptomatic COVID-19 episode from 14 days post-injection 2 in the analysis population
IR: cases per 1000 PYR.
For a description of VE and CI calculation see Section 3.3.2.
Source: modified from Section 8, Table 8.18B

Survival Analysis

In addition, survival analyses based on Stratified Cox proportional hazard model were used to estimate the VE against symptomatic COVID-19 case occurrence, as a supportive analysis. The model includes separate hazard functions for age group, sex, and high-risk medical condition group.

Based on the Stratified Cox proportional hazard model, the VE for symptomatic COVID-19 was 64.3% (95% CI: 46.5; 76.2) for the mFAS-PD2 and 62.7% (95% CI: 44.0; 75.2) for the PPAS. Kaplan-Meier curves were also generated with 95% CI. As shown below, the curves diverge 14 days after the second dose with a higher cumulative incidence in the Placebo group than the Vaccine group.

Figure 8: Kaplan-Meier curve for symptomatic COVID-19 - mFAS-PD2



Key Secondary Efficacy

Prevention of SARS-CoV-2 Infection Occurring ≥14 Days After VAC2 in Naïve Participants

The VE against SARS-CoV-2 infection (1-RR) occurring ≥14 days after the second injection in naïve participants is presented below. The number of cases of SARS-CoV-2 infection includes serologically-confirmed cases in addition to virologically-confirmed cases. The VE against SARS-CoV-2 infection was 9.6% (95% CI: -16.4; 29.9) not meeting the key secondary efficacy objective (i.e., the lower bound of 95% CI was < 0%).

Table 46: Vaccine efficacy (1-IRR or RR) against SARS-CoV-2 infection- mFAS-PD2 Naïve-D01+D22

	Vaccine Group (N= 327)	Placebo Group (N= 343)	Vaccine Efficacy		Efficacy Met
			%	(95% CI)	
Cases	118	138			
# of subjects at risk	315	333			
Cumulative incidence: % (95% CI)	37.5 (32.1 ; 43.1)	41.4 (36.1 ; 46.9)	9.6	(-16.4 ; 29.9)	No

SARS-CoV-2 infection was defined as a serologically-confirmed SARS-CoV-2 infection OR virologically-confirmed SARS-CoV-2 infection.

Cases (infection) = number of participants who met the pre-specified definition of SARS-CoV-2 infection from 14 days post-dose 2 in the analysis population.

# of subjects at risk: subjects with censor date after 14 days post-injection 2 in the analysis population

The vaccine efficacy is considered as demonstrated if the lower bound of 95% CI (exact method) is greater than 0%.

Source: modified from Section 8, Table 8.20B

Similar results to the ones observed for the mFAS-PD2 Naïve-D01+D22 set were observed in the PPAS Naïve-D01+D22 set with a VE of 8.7% (95% CI: -17.9; 29.4) against infection.

Prevention of Severe COVID-19 Occurring ≥14 Days After VAC2, regardless of prior SARS-CoV-2 infection

The VE against severe COVID-19 (1-IRR) occurring ≥14 days after the second injection in all participants regardless of prior SARS-CoV-2 infection has been presented. All cases of severe COVID-19 were symptomatic COVID-19 cases (i.e., virologically-confirmed) meeting severity criteria as determined by the adjudication committee. Hypothesis testing for this key secondary objective was conditional to the success of the primary objective and the collection of 22 severe cases. Yet, only 5 cases of severe COVID-19 cases were collected, and hypothesis testing was not performed. The very limited cases count (3 cases in the Vaccine Group and 2 cases in the Placebo Group) precludes any definite conclusion about efficacy against severe COVID-19. Same results were reported in the sensitivity analysis performed with the inclusion of participants from Ukraine. Based on the Stratified Cox proportional hazard model, the VE against severe COVID-19 was similar for the mFAS-PD2 and for the PPAS.

Table 47: Vaccine efficacy (1-IRR or RR) against severe COVID-19 - mFAS-PD2

	Vaccine Group (N= 5736)	Placebo Group (N=5680)	Vaccine Efficacy	
			%	(95% CI)
Cases	3	2		
Episodes	3	2		
1000 Person-years at risk	0.604	0.593		
Incidence rate (95% CI)	4.964 (1.02 ; 14.51)	3.373 (0.41 ; 12.19)	-47.2	(-1661.9 ; 83.1)
# of subjects at risk	5311	5287		
Cumulative incidence % (95% CI)	0.1 (0 ; 0.2)	0 (0 ; 0.1)	-49.3	(-1687.8 ; 82.9)

Cases (severe COVID-19) = number of participants assessed by the Adjudication Committee as having at least one occurrence of either PCR or local test confirmed symptomatic COVID-19 that met the definition of severe COVID-19, from 14 days post-dose 2 in the analysis population. Episodes: number of episodes of symptomatic COVID-19 with severity of severe from 14 days post-injection 2 in the analysis population. Incidence rate is calculated as cases per 1000 person-years at risk. Cumulative incidence: cases divided by number of subjects at risk in each group*100%

# of subjects at risk: subjects with censor date after 14 days post-injection 2 in the analysis population

The 95% CI for VE is based on an exact method assuming a binomial distribution of the number of cases in vaccine group conditional on the total number of cases in the study.

Source: modified from Section 8, Table 8.19B

Descriptive Efficacy – Multiple Disease Endpoints and by Variants in Various Populations

Efficacy for Multiple Disease Endpoints

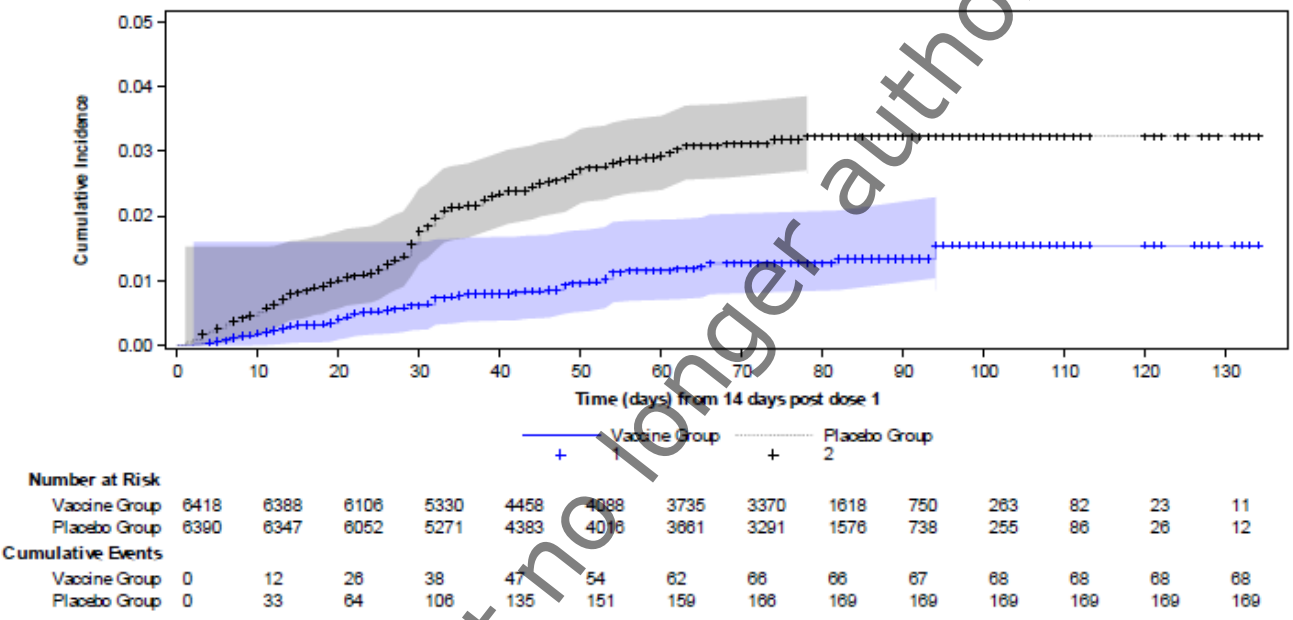
Overall, there was no death associated with COVID-19 and a limited number of severe COVID-19 and hospitalized symptomatic COVID-19 in both the Vaccine Group and the Placebo Group. Also, there were few cases of symptomatic COVID-19 with severity of moderate or worse. With a limited case count (no case in the Vaccine Group and a maximum of 2 cases in the Placebo Group), the point of estimate for VE against hospitalized symptomatic COVID-19 was 100%.

Sensitivity analyses with the inclusion of participants from Ukrainian sites were performed. Overall, results with and without participants from Ukraine sites were similar.

Efficacy in the Overall Population (regardless of prior infection status)

At PD1 (mFAS-PD1), the VE against symptomatic COVID-19 was 60.3% (95% CI: 47.1; 70.5) in all participants with 68 cases in the Vaccine Group and 169 in the Placebo Group. Kaplan-Meier curves were also generated with 95% CI. The curves diverge 14 days after the first dose with a higher cumulative incidence in the Placebo group than the Vaccine group.

Figure 9: Kaplan-Meier curve for symptomatic COVID-19 - mFAS-PD1



Number at Risk														
Vaccine Group	6418	6388	6106	5330	4458	4088	3735	3370	1618	750	263	82	23	11
Placebo Group	6390	6347	6052	5271	4383	4016	3661	3291	1576	738	255	86	26	12
Cumulative Events														
Vaccine Group	0	12	26	38	47	54	62	66	66	67	68	68	68	68
Placebo Group	0	33	64	106	135	151	159	166	169	169	169	169	169	169

Cases: number of subjects with at least one symptomatic COVID-19 episode from 14 days post-dose 1.

Source: modified from Appendix 4, ADH_Figure 3.4B

For VE against symptomatic COVID-19 at PD2, refer to primary efficacy section. The VE (1-IRR) PD2 against CDC-defined COVID-19 was 65.4% (95% CI: 47.4; 77.8) in all participants with 31 cases in the Vaccine Group and 88 in the Placebo Group.

With a limited case count for symptomatic COVID-19 with severity of moderate or worse (i.e., 5 cases in the Vaccine Group and 7 cases in the Placebo Group), the VE (1-IRR) PD2 was 29.9% (95% CI: -156.5; 82.5). For VE against severe COVID-19 at PD2, refer to key secondary efficacy objective.

Efficacy in Non-Naïve Participants

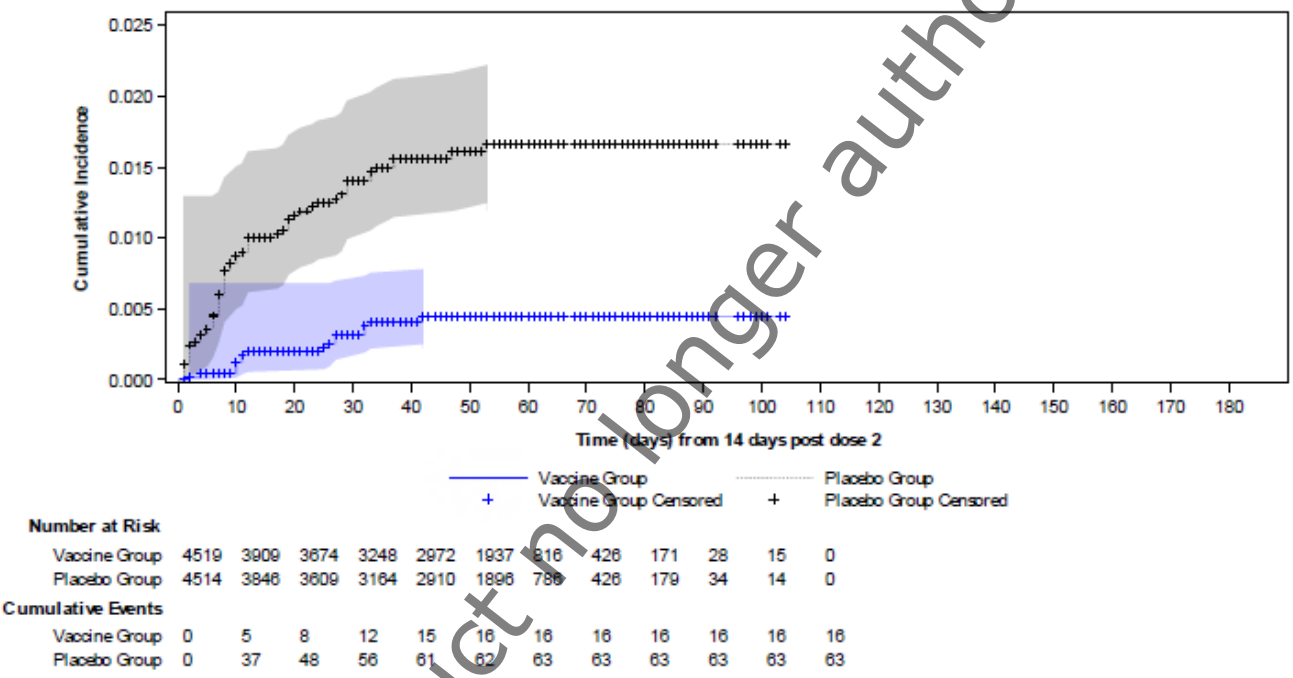
The VE was not assessed for SARS-CoV-2 infection and asymptomatic SARS-CoV-2 infection since those endpoints are only assessed in naïve participants.

The VE (1-IRR) PD1 against symptomatic COVID-19 in Non-Naïve participants was 75.9% (95% CI: 62.7; 84.9) with 26 cases in the Vaccine Group and 106 in the Placebo Group. At PD2, the VE was 75.1% (95% CI: 56.3; 86.6) with 16 cases in the Vaccine Group and 63 in the Placebo Group. Kaplan-Meier curves were also generated with 95% CI. The curves diverge 14 days after the second dose with a higher cumulative incidence in the Placebo group than the Vaccine group.

For the CDC-defined COVID-19, the VE (1-IRR) PD1 in Non-Naïve participants was 76.8% (95% CI: 63.9; 85.6) with 25 cases in the Vaccine Group and 106 in the Placebo Group. At PD2, the VE was 76.2% (95% CI: 57.7; 87.4) with 15 cases in the Vaccine Group and 62 in the Placebo Group.

There were only 2 cases of severe COVID-19 at PD1 and 1 case at PD2 in the Placebo Group. With a limited case count for symptomatic COVID-19 with severity of moderate or worse, the VE (1-IRR) PD1 was 60.6% (95% CI: -140.4; 96.3) with 2 cases in the Vaccine Group and 5 in the Placebo Group. At PD2, the VE (1-IRR) was 67.3% (95% CI: -307.7; 99.4) with 1 case in the Vaccine Group and 3 in the Placebo Group.

Figure 10: Kaplan-Meier curve for symptomatic COVID-19 - mFAS-PD2 Non-Naïve-D01/D22



Cases: number of subjects with at least one symptomatic COVID-19 episode from 14 days post-dose 2.

Source: Section 8, Figure 8.16B

Efficacy in Naïve Participants (mFAS-PD2 naïve D01 + D22)

The VE (1-IRR) PD1 against symptomatic COVID-19 in Naïve participants was 38.2% (95% CI: 0.5; 62.2) with 30 cases in the Vaccine Group and 48 in the Placebo Group. At PD2, the VE was 30.9% (95% CI: -39.8; 66.7) with 15 cases in the Vaccine Group and 22 in the Placebo Group.

For the CDC-defined COVID-19, the VE (1-IRR) PD1 in Naïve participants was 38.8% (95% CI: 2.3; 62.2) with 31 cases in the Vaccine Group and 50 in the Placebo Group. At PD2, the VE was 31.2% (95% CI: -38.8; 66.8) with 15 cases in the Vaccine Group and 22 in the Placebo Group.

The limited case count for severe COVID-19 and symptomatic COVID-19 with severity of moderate or worse, i.e., low and similar number of cases in the Vaccine Group and the Placebo Group, precludes any definite conclusion.

Both the VE against SARS-CoV-2 infection and asymptomatic SARS-CoV-2 infection were determined in Naïve participants. The VE (1-RR) PD1 against SARS-CoV-2 infection was 5.9% (95% CI: -9.7; 19.4) with 326 cases in the Vaccine Group and 346 in the Placebo Group. For the VE PD 2 against SARS-CoV-2 infection, refer to key secondary efficacy. The VE (1 RR) against asymptomatic SARS-CoV-2 infection

was ≤1.2% (PD1 and PD2) with 275 cases in the Vaccine Group and 266 in the Placebo Group at PD1; and with 100 cases in the Vaccine Group and 107 cases in the Placebo Group at PD2.

Efficacy by Variants

Viral genomic sequencing was performed on CLI respiratory samples from the cases to identify the causal SARS-CoV-2 variant.

In the FAS, out of the 322 participants (106 in the Vaccine Group and 216 in the Placebo Group) who reported a total of 324 CLI episodes (2 participants experienced 2 CLIs) confirmed by the adjudication committee, viral genomic sequencing on the CLI samples showed that 19 (5.9%) participants were infected with Delta and 146 (45.3%) with Omicron. Among them, 6 participants experienced 1 case each with both Delta and Omicron variants sequenced. The variant for the remaining CLI samples was unknown (128 [39.8%] samples for which sequencing results were not available at the time of the database extraction) or produced no valid result (37 [11.5%] samples that were tested but sequencing failed to produce a valid sequence). Viral genomic sequencing of the severe cases showed that 8 (2.5%) participants were infected with Omicron, 1 (0.3%) participant was infected with Delta, no valid result was produced for 1 (0.3%) participant, and the variant was unknown for 8 (2.5%) participants.

In the primary efficacy population (i.e., mFAS-PD2), among the 121 adjudicated cases in the primary efficacy population (mFAS-PD2; 32 in Vaccine Group and 89 in the Placebo Group), viral genomic sequencing identified the strain which caused the infection in 68 cases, 63 corresponded to the Omicron variant, 4 to Delta, and 1 to Omicron and Delta. Sequencing for other adjudicated cases did not produce a valid result in 13 cases. The 40 remaining cases were classified as unknown variants as the results were not available at the time of the database extraction. Further investigations were conducted which showed that for these 40 remaining cases (unknown), 7 were diagnosed exclusively based on an external local test, therefore, samples were not available for sequencing; 1 sample was not tested; 12 did not meet the minimal viral load threshold required to be tested for sequencing (2.8 log copies/mL); and 19 were tested for sequencing but failed quality controls, therefore, no sequencing results were available. Additionally, one case that was diagnosed exclusively by local test was mistakenly included in the unknown variant category.

Efficacy against Symptomatic COVID-19 by Variants

Omicron (B.1.1.529) variant

The Omicron variant was the variant responsible for the highest number of symptomatic infections. Only BA.1 and BA.2 subvariants were circulating at the time of the study and were detected by sequencing. None of the current circulating BA.4 and BA.5 sub-variants were identified.

Among cases for whom sequencing results were available, the VE (1-IRR) PD1 in participants regardless of prior infectious status was 64.8% (95% CI: 45.9; 77.6) with 30 cases in the Vaccine Group and 84 in the Placebo Group and the VE PD2 was 72.5% (95% CI: 49.5; 86.0) with 14 cases in the Vaccine Group and 50 cases in the Placebo Group.

In Non-Naïve participants, the VE (1-IRR) PD1 was 88.3% (95% CI: 70.4; 96.4) with 5 cases in the Vaccine Group and 42 in the Placebo Group and 93.9% (95% CI: 75.9; 99.3) at PD2 (2 cases in the Vaccine Group and 32 in the Placebo Group).

In Naïve participants, the VE (1-IRR) PD1 was 49.1% (95% CI: 5.9; 73.4) with 17 cases in the Vaccine Group and 33 in the Placebo Group and 20.4% (95% CI: -88.7; 67.3) PD2 (11 cases in the Vaccine Group and 14 in the Placebo Group).

However, the number of cases with no valid results or unknown variants (i.e., samples for which results of sequencing testing was not available in the database at the time of the extraction) was

approximately 44%. Therefore, additional sensitivity analyses were performed to account for cases without confirmed sequencing results. This sensitivity analysis assumed that cases with no sequencing results were caused by the Omicron variant considering that this variant was responsible for the majority of the symptomatic infections and that the temporal distribution of the cases with unknown variant and those with no valid results matched the distribution of cases due to Omicron variant. As most of participants were non-naïve, similar distribution of unknown and non-valid results cases was observed.

Results of this sensitivity analysis for the mFAS-PD2 (all participants) showed that the VE (1-IRR) PD2 was 63.1% (95% CI: 43.9; 76.2) with 32 cases in the Vaccine Group and 85 in the Placebo Group.

In Non-Naïve participants, the efficacy against symptomatic COVID-19 at PD2 due to Omicron variant was 73.8% (95% CI: 53.9; 85.9). This was lower than that observed only accounting for those cases with confirmed sequencing available.

In Naïve participants, the VE (1-IRR) PD2 following sensitivity analysis was 27.6% (95% CI: - 47.3; 65.3) with 15 in the Vaccine Group and 21 in the Placebo Group.

Delta (B.1.617.2) variant

For the Delta variant, the number of cases was limited.

In all participants regardless of prior infectious status, the VE (1-IRR) PD1 was 43.6% (95% CI: 121.8; 87.9) with 4 cases in the Vaccine Group and 7 in the Placebo Group and the VE PD2 was 100% (no case in the Vaccine Group and 5 in the Placebo Group).

In Non-Naïve participants, the VE (1-IRR) PD1 was 80.3% (95% CI: -75.9; 99.6) with 1 case in the Vaccine Group and 5 in the Placebo Group and 100% (95% CI: -48.8; 100.0) at PD2 (no case in the Vaccine Group and 4 in the Placebo Group).

In Naïve participants, at PD1, there were 2 cases in the Vaccine Group and 1 case in the Placebo Group; at PD2, there was only one case in the Placebo Group.

Unknown variants and sequencing not producing valid results

For cases with unknown variant results, the VE (1-IRR) PD 2 was 34.6% (95% CI: -28.3; 67.5) in all participants regardless of prior infectious status, with 16 cases in the Vaccine Group and 24 in the Placebo Group. In Non-Naïve participants the VE (1-RR) PD2 was 41.1% (95% CI: -26.6; 73.7) with 12 cases in the Vaccine Group and 20 in the Placebo Group. In Naïve participants, at PD2 the number of unknown variant results was the same in the Vaccine Group and the Placebo Group with 4 cases in each group.

For the sequencing that did not produce valid results because testing failed to produce a valid sequence, the VE (1-IRR) PD2 was 82.2% (95% CI: 18.3; 98.1) in all participants (2 cases in the Vaccine Group and 11 in the Placebo Group) and 75.4% (95% CI: -23.0; 97.5) in Non-Naïve participants (2 cases in the Vaccine Group and 8 in the Placebo Group). In Naïve participants, at PD2, there were no cases of variants that did not produce valid results in the Vaccine Group and 3 in the Placebo Group.

Efficacy against Severe COVID-19 by Variants

The overall number of severe disease cases was very limited which either precluded to estimate the VE by variant or lead to a point of estimate of 100% for the VE with only 1 case in the Placebo Group and no case in the Vaccine Group.

Descriptive Efficacy – Subgroup Analyses

This section presents results for exploratory efficacy with the analysis of the prevention of symptomatic COVID-19 by subgroups.

The CDC-defined COVID-19 subgroups analysis was similar to that of symptomatic COVID-19. For other endpoints (hospitalized symptomatic COVID-19, death associated with symptomatic COVID-19, severe COVID-19, and symptomatic COVID-19 with severity of moderate or worse), given the small number of or lack of cases in some of these subgroups, the comparison across subgroups is limited.

Efficacy against symptomatic COVID-19 in All Participants regardless of prior SARS-CoV-2 infection by subgroups

Vaccine efficacy against symptomatic COVID-19 by age groups in all participants regardless of prior SARS-CoV-2 infection is presented in Table 5.10. With fewer cases and a wider 95% CI, the youngest age group 18 to 25 years presented a lower VE than the 18-59 years age group (VE [1- IRR] PD2 of 67.3% [95% CI: 49.7; 79.3]) that accounted for most of participants. The older age groups presented a limited number of participants at risk and cases, which precluded a definitive conclusion.

Table 48: Vaccine efficacy (1-IRR) against symptomatic COVID-19 by age group - mFAS-PD2 (All participants regardless of baseline SARS-CoV-2 status)

Age group	Vaccine Group (N=5736)				Placebo Group (N=5680)				Vaccine Efficacy	
	Cases/ Episodes	1000 PYR	IR (95% CI)	Subjects at risk	Cases/ Episodes	1000 PYR	IR (95% CI)	Subjects at risk	%	(95% CI)
18-25 years	8	0.138	57.811 (24.96 ; 113.91)	1265	15	0.139	108.154 (60.53 ; 178.38)	1284	46.5	(-34.3 ; 80.4)
18-59 years	29	0.572	50.695 (33.95 ; 72.81)	5000	87	0.561	155.054 (124.19 ; 191.26)	4980	67.3	(49.7 ; 79.3)
≥ 60 years	3	0.032	92.978 (19.17 ; 271.72)	311	2	0.032	62.963 (7.63 ; 227.45)	307	-47.7	(-1668.0 ; 83.1)
≥ 65 years	2	0.015	131.432 (15.92 ; 474.78)	141	1	0.016	61.521 (1.56 ; 342.77)	155	-113.6	(-12504.0 ; 88.9)

Abbreviations: CI, confidence interval; IR, incidence rate; PYR, person-years at risk
Cases: number of participants with at least one symptomatic COVID-19 episode from 14 days post-injection 2 in the analysis population. IR: cases per 1000 PYR. Subjects at risk: subjects with censor date on or after 14 days post-injection 2 in the analysis population.

For a description of VE and CI calculation see Section 3.3.2.

Source: modified from Section 8, Table 8.153B

A summary of VE against symptomatic COVID-19 after the 2nd dose (mFAS-PD2) by sex, country, race/ethnicity, and high-risk medical condition in all participants regardless of baseline SARS-CoV-2 status was provided:

- The VE in males was higher when compared to females (70.0% [95% CI: 43.0; 85.2] versus 59.7% [95% CI: 30.0; 77.7]).
- There was no case of symptomatic COVID-19 in Uganda and one case in the Placebo Group in Ghana. In other countries, the VE was 44.0% (95% CI: -3.3; 70.5) in Mexico, 61.1% (95% CI: -70.4; 93.5) in Colombia, 57.7% (95% CI: -85.4; 92.9) in Kenya, 79.6% (95% CI: 50.0; 93.1) in India, and 85.7% (95% CI: 37.8; 98.4) in Nepal.

- The VE was 81.1% (95% CI: 59.3; 92.3) in Asian participants and 63.4% (95% CI: -52.6; 93.7) in Black or African American participants. In White participants, there was no case of symptomatic COVID-19, but these participants accounted for only 0.6% of the overall mFAS-PD 2 analysis set.
- In participants aged 18 to 59 years and with risk factors for severe COVID-19, the VE was 66.2% (95% CI: 28.2; 85.3) and comparable to that observed in participants without risk factors for severe COVID-19 in that age group (i.e., VE: 68.0% [95% CI: 45.5; 82.0]). In participants aged ≥65 years with risk factors for COVID-19, the VE was not calculated as there was only one case in the Vaccine group and no case in the Placebo Group.

Efficacy against symptomatic COVID-19 in Non-Naïve participants by subgroups

The VE (1-IRR) of 18-59 years age group that accounted for most of participants was 74.1% (95% CI: 54.6; 86.1) and was similar to the point estimate of VE in the youngest age group (18 to 25 years). The older age groups presented a limited number of participants at risk and cases, which precluded a definitive conclusion.

A summary of VE against symptomatic COVID-19 after the 2nd dose (mFAS-PD2 Non-Naïve- D01/D22) by sex, country, race/ethnicity, and high-risk medical condition in Non-Naïve participants was presented:

- The VE in males and females was comparable.
- There was no case of symptomatic COVID-19 in Uganda and one case in the Placebo Group in Ghana. In other countries, the VE was 66.6% (95% CI:11.2; 89.2) in Mexico, 82.5% (95% CI: -56.7; 99.6) in Colombia, 83.1% (95% CI: -38.9; 99.6) in Kenya, 79.7% (95% CI: 50.2; 93.1) in India, and 60.4% (95% CI: -141.7; 96.2) in Nepal.
- The VE was 76.1% (95% CI: 47.3; 90.5) in Asian participants and 85.8% (95% CI: -10.5; 99.7) in Black or African American participants. In White participants, there was no case of symptomatic COVID-19, but these participants accounted for only a small proportion of the overall study population.
- In participants aged 18 to 59 years and with risk factors for severe COVID-19, the VE was 71.9% (95% CI: 20.5; 91.9) and comparable to that observed in participants without risk factors for severe COVID-19 in that age group (i.e., VE: 75.1% [95% CI: 50.9; 88.4]). In participants aged ≥65 years with risk factors for severe COVID-19, the VE was not calculated as there was no case versus only one case in the Placebo Group for those without risk factors for severe COVID-19.

Efficacy against symptomatic COVID-19 in Naïve Participants by subgroups

The VE (1-IRR) of 18-59 years age group that accounted for most of participants was 41.9% (95% CI: -20.5; 73.1). With fewer cases in the 18-25 year age group, estimates of VE were imprecise. The older age groups presented a limited number of participants at risk and cases, which precluded a definitive conclusion.

A summary of VE against symptomatic COVID-19 by sex, race/ethnicity, and high-risk medical condition in naïve participants at the second injection was presented:

- The VE in males was higher when compared to females (42.0% [95% CI: -92.7; 84.7] versus 25.1% [95% CI: -84.9; 70.6]).
- Overall, when looking at country level, there were few cases of symptomatic COVID-19 in Naïve participants. There was no case in Uganda, Ghana or India. In Mexico and Colombia, the

number of cases was the same in the Vaccine Group and the Placebo Group, i.e., 11 cases per group and 2 cases per group, respectively. In Kenya, there were 2 cases in the Vaccine Group and 1 case in the Placebo Group. In Nepal, the VE was 100.0% (95% CI: 39.9; 100.0) with no case in the Vaccine Group and 8 in the Placebo Group.

- In Asian participants, the VE was 100.0% [95% CI: 37.4; 100.0]) with all 8 cases in the Placebo Group. In Black or African American participants, the case count was very limited and similar in both the Vaccine Group and the Placebo Group. In White participants, there was no case of symptomatic COVID-19, but these participants accounted for only 0.9% of the overall mFAS-PD2 Naïve-D01+D22 analysis set.
- In participants aged 18 to 59 years and with risk factors for severe COVID-19, the VE was 41.6% (95% CI: -102.4; 85.0) and comparable to that observed in participants without risk factors for severe COVID-19 in that age group (i.e., VE: 41.4% [95% CI: -49.6; 78.7]). In participants aged ≥ 65 years with risk factors for severe COVID-19, the VE was not calculated as there was only one case in the Vaccine group.

- **Summary of main immunogenicity results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 49: Summary of immunogenicity for trials

Title: Immunogenicity and reactogenicity following a booster dose of COVID-19 mRNA vaccine (Pfizer-BioNtech) and two adjuvanted sub-unit vaccines (SP/GSK) administered as a booster dose in adults who received two doses of Pfizer-BioNTech mRNA vaccine as a primary vaccination: a randomized, multicentre, single-blind trial- COVIBOOST			
Study identifier	VAT00013 EudraCT: 2021-004550-33 Clinical Trial No.: NCT05124171		
Design	Phase III randomized, single-blinded, multicentre design		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable not applicable
Hypothesis	Superiority and Non-inferiority (post hoc analysis)		
Treatments groups	Comirnaty (tozinameran) group		Single booster dose (30 µg) N=82
	VidPrevtyn Beta group		Single booster dose (5 µg), N=80
	CoV2 preS dTM-AS03 (D614) group		Single booster dose of CoV2 preS dTM-AS03 (5 µg D614), N=85
Endpoints and definitions - <u>Post-hoc analyses results based on a validated assay</u>	Primary endpoint	GMT ratio between VidPrevtyn Beta and Comirnaty vaccines	To compare the neutralising antibody titres against Omicron BA.1 strain 28 days after booster vaccination between the groups receiving VidPrevtyn Beta and Comirnaty vaccines

	Secondary endpoints	Difference of seroresponse rate (defined as the percentage of participants with a 4-fold or greater rise in serum neutralisation titre at D28 relative to baseline) between VidPrevtyn Beta and Comirnaty vaccines against Omicron BA.1 strain GMT ratio between VidPrevtyn Beta and Comirnaty vaccines against D614 strain Difference of seroresponse rate VidPrevtyn Beta and Comirnaty vaccines against D614 strain	To compare the seroresponse rate against Omicron BA.1 strain 28 days after booster vaccination between the groups receiving VidPrevtyn Beta and Comirnaty vaccines To compare the post-boosting neutralising antibody titres and seroresponse rate against the wild-type D614G strain 28 days after booster vaccination between the groups receiving the VidPrevtyn Beta and Comirnaty vaccines
	Exploratory endpoints	GMT with log10 transformation within a booster group at D15 and D28. GMT ratio and confidence interval between 2 booster groups of the 3 pairs specified above at D15 and D28 Seroresponse rate of each booster group at D15 and D28 Difference of seroresponse rate and confidence interval between 2 booster groups of the 3 pairs specified above at D15 and D28	To assess post-booster neutralising antibody GMT ratios between the 3 pairs of boosters vaccines by variant (BA.1, D614G, BA.4/BA.5) To assess post-booster differences of seroresponse rates between the 3 pairs of booster vaccines by variant
Database lock	09 May 2022 (interim)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Revised Per protocol analysis set at D28		

Descriptive statistics and estimate variability	<table><tr><th></th><th colspan="3">CoV2 preS dTM-AS03 (B.1.351) booster (N=54)</th><th colspan="3">Pfizer/BioNTech booster (N=60)</th><th colspan="3">CoV2 preS dTM-AS03 (B.1.351) / Pfizer/BioNTech booster</th></tr><tr><th>Strain Readout</th><th>M</th><th>GMT</th><th>(95% CI)</th><th>M</th><th>GMT</th><th>(95% CI)*</th><th>GMT ratio</th><th>(95% CI)*</th><th>Superiority†</th></tr><tr><td>B.1.1.529 (Omicron BA.1)</td><td>54</td><td>1327.5</td><td>(1005.0 ; 1753.4)</td><td>58</td><td>524.0</td><td>(423.3 ; 648.6)</td><td>2.53</td><td>(1.80 ; 3.57)</td><td>Yes</td></tr></table> N: number of participants in Revised PPAS Monogram at D28 M: number of participants available for the endpoint * 2-sided 95% CI is based on the student t-distribution of logarithmic transformation of the individual titers. † Superiority is concluded if the lower limit of the 2-sided 95% CI of the GMT ratio > 1.2 SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram
Effect estimate per comparison	The neutralising Ab GMTR against Omicron BA.1 variant strain of VidPrevtyn Beta relative to Comirnaty was 2.53 (95% CI: 1.80; 3.57) which meets the superiority criterion of lower limit of the 2-sided 95% CI of GMTR > 1.2.
Analysis description	**Secondary analysis and exploratory analysis**
	The difference of neutralising seroresponse rate against Omicron BA.1 variant strain between VidPrevtyn Beta and Comirnaty was 3.8 (95% CI: -3.9; 12.8) which meets the non-inferiority criterion of lower limit of the 2-sided 95% CI of the difference > -10%. The neutralising Ab GMTR against D614G strain of VidPrevtyn Beta relative to Comirnaty was 1.43 (95% CI: 1.06; 1.94) which does not meet the superiority criterion of lower limit of the 2-sided 95% CI of GMTR > 1.2. The difference of neutralising seroresponse rate against D614G strain between VidPrevtyn Beta and Comirnaty was 3.0 (95% CI: -6.9; 12.8) which meets the non-inferiority criterion of lower limit of the 2-sided 95% CI of the difference > -10%. VidPrevtyn Beta booster vaccine induced 2.5-fold higher neutralising antibody titres against Omicron BA.4/5 than those induced by Comirnaty booster in the fully validated Monogram PsVN assay. Furthermore, the neutralising seroresponse rates observed with the VidPrevtyn Beta at D28 was higher than those observed with Comirnaty, irrespective of the variant tested. For Omicron BA.4/BA.5, 98% (95% CI: 89.1; 99.9) of participants who received the VidPrevtyn Beta booster vaccine showed at least a 4-fold rise in neutralising antibody titres from D0 to D28 versus 85.5% (95% CI: 73.3; 93.5) of participants with the Comirnaty booster vaccine. The difference of seroresponse rate between VidPrevtyn Beta and Comirnaty booster vaccine was 12.5 (95% CI: 1.4; 24.2).

Title: Immunogenicity and Safety of SARS-CoV-2 Recombinant Protein Vaccines with AS03 Adjuvant in Adults 18 Years of Age and Older as a Primary Series and Immunogenicity and Safety of a Booster Dose of SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (two Monovalent and one Bivalent)		
Study identifier	VAT00002 – Supplemental Booster Cohort 2	
Design	Phase III, randomised, open-label (Supplemental Cohort 1 and Supplemental Cohorts Comparator Group), modified double-blind (Supplemental Cohort 2), multi-centre study conducted in previously-vaccinated adults 18 years of age and older to evaluate the safety, reactogenicity, and immunogenicity of a booster dose of a CoV2 preS dTM-AS03 vaccine formulation (one of two monovalent or a bivalent) administered by intramuscular (IM) route 4 to 10 months after receiving primary vaccination	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months not applicable not applicable
Hypothesis	Superiority and Non-inferiority	

Treatments groups	Previously vaccinated mRNA, adenovirus-vectored or protein (CoV2 preS dTM-AS03 [D614]) groups		Single booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine, N=705
Endpoints and definitions	Co-Primary endpoints	Individual serum neutralising titre at D01 and D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups. Individual serum neutralising titre at D01 and D15 against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group. Individual serum neutralising titre against the D614G strain at D36 (Comparator Group)	To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is superior to that observed immediately before booster.
	Secondary endpoint with hypothesis testing	Individual serum neutralising titre at D01 and D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine intervention Groups. Individual serum neutralising titre against the D614 strain at D36 (Comparator Group) Individual serum neutralising titre at D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine intervention Groups Individual serum neutralising titre at D36 against the B.1.351 variant for the Comparator Group. Seroresponse rate, defined as a 4-fold or greater rise in serum neutralisation titre (post/pre) at D15 relative to D01, against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine Intervention Groups. Seroresponse rate, defined as a 4-fold or greater rise in serum neutralisation titre [post/pre] against the D614G strain at D36 relative	To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine induces an immune response that is superior to that observed immediately before booster. To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine induces an immune response against the B.1.351 variant at D15 that is superior to that against the B.1.351 variant at D36 in the Comparator Group. To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a

		to D01 (Comparator Group).	two-dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals.
	Secondary descriptive endpoints	Individual serum neutralising titre at D01 and D15 against the D614G strain and to the B.1.351 variant in each Intervention Group Individual serum neutralisation titre fold-rise post-vaccination relative to D01 at D15 against the D614G strain and to the B.1.351 variant in each Intervention Group ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralisation titre [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain and to the B.1.351 variant in each study Intervention Group Seroresponse rate, defined as a 4-fold or greater rise in serum neutralisation titre [post/pre] at D15 relative to D01, against the D614G strain and to the B.1.351 variant in each study Intervention Group	To describe, in adults previously vaccinated with an mRNA-, adenovirus-vectored or protein COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine
Database lock	13 May 2022		
Results and Analysis			

Analysis description	**Primary Analysis**
Analysis population and time point description	Per protocol analysis set at D15 for booster arms (PPAS Naïve at D01+ D22) and at D36 for Comparator in aged 18-55 years old

Descriptive statistics and estimate variability	

	Pfizer Primed MV (B.1.351) (N=279)			Comparator (N=331)				Pfizer Primed MV (B.1.351) / Comparator			
Strain Readout	M	GMT	(95% CI)	Strain Readout	M	GMT	(95% CI)	Strain comparison	GMT ratio	(98.3% CI)	Non-inferiority*
B.1.351	279	7172	(6363 ; 8083)	D614G	302	3658	(3123 ; 4286)	B.1.351 vs D614G	1.96	(1.54 ; 2.50)	Yes

M: number of participants with available data; N: number of participants in PPAS for Booster Group or PPAS Naive at D01+D22 for Comparator Group
2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers
2-sided 98.3% CI is based on the Welch's t-distribution of logarithmic transformation of the individual titers for GMT ratio between two groups.
Antilog transformations were applied to the results.
* Non-inferiority on GMTs is concluded if the lower limit of the 2-sided 98.3% CI of the ratio of GMTs between groups is > 0.667.
Prior prime vaccination: Pfizer = Pfizer/BioNTech
MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for both strains

	Pfizer Primed MV (B.1.351) Post-booster / Pre-booster				
Strain Readout	N	M	Geometric mean (of Individual Ratio)	(98.3% CI)	Superiority*
B.1.351	279	256	35.41	(26.71 ; 46.95)	Yes

M: number of participants with available data in both post-booster and pre-booster; N: number of participants in PPAS
2-sided 98.3% CI is based on the Student t-distribution of logarithmic transformation of the individual titers.
Antilog transformations were applied to the results.
* Superiority is concluded if the lower limit of the 2-sided 98.3% CI of the fold rise on post-booster versus pre-booster > 2.
Prior prime vaccination: Pfizer = Pfizer/BioNTech
MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351)
SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for both strains

Effect estimate per comparison	The neutralising Ab geometric mean titre ratio (GMTR) of MV CoV2 preS dTM-AS03 (B.1.351) vaccine booster dose in Pfizer/BioNTech primed participants aged 18-55 years at D15 to the 2 dose primary series in the Comparator Group at D36 was 1.96 (98.3% confidence interval [CI]: 1.54; 2.50), which meets the non-inferiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 0.667. The geometric mean of individual ratio of post-booster neutralising Ab GMTs at D15 relative to pre-booster neutralising Ab GMTs in Pfizer/BioNTech primed participants aged 18-55 years at D01 was 35.41 (98.3% CI: 26.71; 46.95), which meets the superiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 2.
Analysis description	**Secondary analysis with hypothesis testing**
	The neutralising Ab GMTR of MV CoV2 preS dTM-AS03 (B.1.351) vaccine booster dose in mRNA primed participants at D15 to the 2-dose primary series in the Comparator Group at D36 was 2.06 (98.3% CI: 1.62; 2.61) in 18-55 years old, which meets the non-inferiority criterion of lower limit of the 2 sided 98.3% CI of GMTR > 0.667. The geometric mean of individual ratio of post booster neutralising Ab GMTs at D15 relative to pre-booster neutralising Ab GMTs at D01 was 34.19 (98.3% CI: 26.58; 43.98) in 18-55 years old, which meets the superiority criterion of lower limit of the 2 sided 98.3% CI of GMTR > 2. The neutralising Ab GMTR against B.1.351 strain of 5 µg of MV CoV2 preS dTM-AS03 (B.1.351) vaccine booster dose in Pfizer/BioNTech primed participants at D15 compared to the 2-dose primary series in the Comparator Group at D36 was 17.36 (98.3% CI: 13.39; 22.50) in 18-55 years old, which meets the superiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 1.5. The differences of the seroresponse rate against B.1.351 strain in Pfizer/BioNTech primed and mRNA primed participants following a booster dose of MV CoV2 preS

	dTM-AS03 (B.1.351) vaccine versus seroresponse rate against D614G strain in Comparator Group were -16.58% (98.3% CI: -22.99; -11.01) and -17.07% (98.3% CI: -22.79; -11.86) in 18-55 years old, respectively, not meeting the non-inferiority criterion of the lower limit of 2-sided 98.3% CI of the difference of seroresponse between groups > -10%.
Analysis description	**Secondary descriptive analysis**
	Overall, a meaningful boosting effect of either a single dose of MV CoV2 preS dTM-AS03 (B.1.351) booster vaccine against D614G and B.1.351 variant strains is observed irrespective of the priming vaccine/platform and the age group. At D15, neutralising Ab GMTs against D614G strain after MV CoV2 preS dTM-AS03 (B.1.351) booster vaccines in all participants (≥ 18 years of age) increased by about 14-fold in mRNA primed group and more than 28-fold in adenovirus-vectored primed group. Against B.1.351 strain and at D15, neutralising Ab GMTs increased by 39-fold in mRNA primed group and more than 72-fold in adenovirus-vectored primed group after MV CoV2 preS dTM-AS03 (B.1.351) booster vaccine. The neutralising Ab seroresponse rate (participants with ≥ 4-fold rise in neutralising Ab titres) against both strains tested was high across all priming platform groups (> 76% of participants).

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

VAT00013

VAT000013, a randomized, single-blind, multicentre, investigator-sponsored French Phase III study, is currently ongoing. The study features an intuitive, clear-cut design: Participants 18 years of age and older who have been previously vaccinated with Pfizer/BioNTech's primary vaccine series were randomly assigned to one of three treatment arms corresponding to each booster group (i.e. mRNA booster, VidPrevtyn Beta (B.1.35.1 strain) or VidPrevtyn (D614 strain)). VAT00013 was not designed as a pivotal study. For a pivotal trial, planned sample size was small, with only 300 participants in total. In accordance with the intended target population, half should include older people ≥65 years. Due to limited recruitment in this population, the enrolment cap in the ≥65 years group was removed during study conduct. In terms of the intended therapeutic indication, this limits the validity of the study results for this patient group. Individuals with immunodeficiencies or autoimmune diseases were excluded, which also limits the validity of the study results for this patient group.

The sample size calculation is acceptable and could be reproduced. The study assumptions, however, were not satisfied in the study, resulting in lower proportions, a lower sample size per group (approximately 80 subjects), and wider confidence intervals (approximately 10%). However, this is not considered to have a major impact on the trial conclusions.

Post-hoc analyses were determined retrospectively to allow comparison of the superiority of an

approved mRNA vaccine against Omicron BA.1 for the scope of this application, showing an improvement in neutralising antibody responses to clinically relevant circulating variants of concern (VoC) and a non-inferior seroresponse rate in comparison to the approved Comirnaty vaccine. As the Omicron variant was the prevalent circulating VoC, the primary objective was denoted on comparisons of neutralising antibody responses against Omicron BA.1. Exploratory objectives also include analyses for BA.4/BA.5, Beta and Delta, which is acknowledged. The original protocol-defined primary analysis compares the proportion of participants with at least 10-fold increase in neutralising antibodies between baseline and D15 among the 3 study arms. For post-hoc-analyses, the latest available timepoint for antibody responses used were the D28 post-booster samples, also providing information on the durability of antibody responses.

In addition, a conditional secondary objective assesses neutralising antibodies against D614G strain to demonstrate non-inferiority against the parental monovalent D614 vaccine.

The chosen objectives and endpoints are of relevance to conclude on the benefit/risk and to inform vaccination recommendations.

The most important limitation of this study was that the primary analysis of neutralising antibodies was performed with a Microneutralisation Assay (MNA) that was not validated. This critical issue was resolved by performing a re-analysis of the samples using a validated Monogram PsVN. It is noted that not all samples could be re-analysed in the validated Monogram PsVN assays as participants needed to be re-consented to this analysis. Eventually, 86% and 89% of the analysis sets of VidPrevtyn Beta and Comirnaty, respectively, were re-analysed, translating into 54 samples in VidPrevtyn Beta group and 60 samples in the Comirnaty group.

The applicant provided a comparison of the demographics in these analyses stratified to gender, age category and age (mean; min; max). Overall the demographics are comparable between these analyses. A stress test was also performed in order to exclude a bias from non-tested samples. The data was provided and considered acceptable.

There was a discussion on the comparably low number of participants in this study VAT00013, in particular in the elderly population. This age group is furthered studied in 2 ongoing studies. One of these studies is an ancillary study to VAT00013. Additional results in particular in the elderly population would become available by Q1 2023 (**REC**).

There were no data on immunocompromised individuals in study VAT00013. As immunogenicity/efficacy data in the immunocompromised individuals might be different from those observed in the overall population, the Applicant should provide immunogenicity and safety data on this population from the two planned independent studies (VAT00027 and VAT00028) as soon as results are available (**REC**).

VAT00002 - Supplemental Phase III Cohort 2

As part of an amendment to the original VAT00002 study, Supplemental Phase III Cohorts have been incorporated into the study. All parts of study VAT00002 are ongoing. The key Booster Cohort 2 results presented include data for the primary safety objectives collected up to the data extraction date (13 May 2022), and the primary and some secondary immunogenicity objectives collected up to D15 (14 days post booster-injection). Also presented are the Comparator Group results for the primary and secondary immunogenicity objectives collected up to D36 (i.e. 14 days post-dose 2 of the primary schedule of D614 strain). It is highlighted that VidPrevtyn (D614 strain) for primary series is not approved.

Supplemental Phase III cohorts of study VAT00002 have a parallel, randomized, modified double-blind design for Booster Cohort 2.Two booster vaccine options were evaluated in the Booster Cohort 2:

VidPrevtyn Beta, and a bivalent version of VidPrevtyn Beta with the same amount of total antigen but in addition to the beta strain it also contains the original strain.

The study design is per se adequate to assess the nAB immune response of a booster dose of VidPrevtyn Beta after priming with 2 different COVID-19 vaccine platforms, i.e. after priming with either 2 mRNA or 2 Ad-vector COVID-19 vaccines. Moreover, a homologous protein booster was also assessed. The limitation of the study design is, that the nAB immune response after a booster dose of VidPrevtyn Beta is only assessed in comparison to SARS-CoV-2 seronegative individuals in a comparator group that has received 2 doses of 10µg of the VidPrevtyn (D614 strain) which is not approved for primary schedule. The co-primary objectives in VAT00002 were to demonstrate non-inferiority of the immune response against strain B.1.351 on day 15 post booster dose, to the immune response against the D614G strain induced by a 2-dose 10 µg primary series of VidPrevtyn (D614 strain) vaccine on day 36, and superiority to the immune response against B.1.351 observed immediately before booster. A comparator arm to compare the immune response induced by VidPrevtyn Beta as a booster dose with that induced by a booster dose of an approved COVID-19 vaccine was not implemented in VAT00002.

Efficacy data and additional analyses

VAT00013

Study VAT00013 met the primary objective. The Applicant performed key analyses from the study report including immunogenicity at D15 and D28 with the revised Per protocol population tested with MNA, with the exclusion of 6 screening failures, which initially were include. The neutralising Ab geometric mean titre ratio (GMTR) against Omicron BA.1 variant strain of VidPrevtyn Beta vaccine relative to Comirnaty, using the validated Monogram PsVN was 2.53 (95% confidence interval [CI]: 1.80; 3.57) which meets the superiority criterion.

Non-inferiority of the sero-response rate (D28/D0) against SARS-CoV-2 Omicron BA.1 could be demonstrated with SRR difference of 3.8 (95% CI -3.9; 12.8). Therefore, the conditional secondary objective 2 has been met.

Superiority of the GMT ratio against SARS-CoV-2 D614G could not be demonstrated with GMTR 1.43 (95% CI 1.06; 1.94) as the lower bound of the CI was not >1.2 . Therefore, the conditional co-secondary objective 3 was not met. Though not pre-specified, non-inferiority of the GMT ratio against SARS-CoV-2 D614G would be given.

Non-inferiority of the sero-response rate against SARS-CoV-2 D614G could be demonstrated with SRR difference of 3.0 (95% CI -6.9; 12.8).

GMTs against BA.4-5 with a validated Monogram PsVN assay were also provided. Booster vaccinations with Vidprevtyn Beta and Comirnaty resulted in GMTs of 925 and 370, respectively. This translates to a GMTR of 2.5 (95% CI 1.7; 3.67) which would meet the superiority criterion (lower bound of 95% CI >1.2) once it would have been pre-specified. Therefore, a substantially better increase of nAB titres against SARS-CoV-2 Omicron BA.4-5 after booster vaccination with Vidprevtyn Beta as compared to Comirnaty can be noted.

Only 6 participants older than 65 years of age were recruited. As such, it is questionable whether the results can be extrapolated to the elderly population with regard to the intended indication. VAT00002 study included more participants from this age group, moreover the applicant initiated 2 studies in the elderly to assess safety and immunogenicity of VidPrevtyn Beta.

VAT00002 - Supplemental Phase III Cohort 2

The two co-primary immunogenicity objectives were met. VidPrevtyn Beta used as a booster

demonstrated in adults (18-55 years of age) previously vaccinated with Comirnaty that induces an immune response against B.1.351 strain at D15 that is non-inferior to the immune response against D614G strain induced by a 2-dose 10 µg primary series of VidPrevtyn (D614) vaccine in naïve individuals at day 36 and superior to that observed immediately before booster.

The descriptive analysis of GMTs and GMTRs indicates a notable increase of nABs after a booster dose of the VidPrevtyn Beta against both the D614 and the B.1.351 strains irrespective of priming vaccine/priming platform in both age cohorts. The proportion of elderly is limited to 140 subjects (10.5%). The increase is higher for GMTs against D614G than that against B.1.351. In contrast GMTRs were higher against the B.1.351 strain. It is of importance, that baseline GMTs against the B.1.351 strain were lower compared to baseline antibody titres against the D614 strain. Different baseline titres against different strains in the different intervention groups are most likely due to a different extent by priming vaccination and in addition to natural infection before booster (i.e. between D1 and booster). The intervention group participants reflect the "real-world" primed population with baseline immunity induced by either vaccination or natural infection. The numbers and proportions of participants with unrecognized prior SARS-CoV-2 infection in the intervention cohorts (booster cohorts) is currently not known. This is a weakness of the study conduct. Unrecognised SARS-CoV-2 infections previous to booster could alter the immune response to the booster vaccination. An analysis stratified by previous SARS-CoV-2 infection status prior to booster vaccination is considered of importance to estimate the boosting effect of the vaccine alone. The Applicant has retrospectively evaluated the baseline samples of booster arms for the presence of antibodies to SARS-CoV-2 nucleoprotein. The testing has been performed but the analysis of responses stratified by baseline anti-nucleoprotein serostatus is ongoing at the time of this submission and will be provided as soon as it is available (**REC**).

All 3 booster vaccines, i.e. VidPrevtyn Beta (B.1.351), Bivalent VidPrevtyn Original/Beta (D614+B.1.531) and VidPrevtyn (D614) induced notable increases in neutralising titres to all Omicron subvariants in younger and older adults primed with Comirnaty on D15, when compared to pre-boost level. GMTs tended to be lower in the older age cohort. A direct and systematically comparison of the immune response against each Omicron subvariant (BA.1; BA.2; BA.4) for the 3 formulations was not performed. Comparison of the three formulations in light of the data presented is impeded by the fact that the assessment of immunogenicity was performed in different laboratories. Moreover, the subset of participants for the evaluation is small, and the baseline Ab levels are different against the different substrains and different in each booster vaccine group. The difference in baseline antibody titres is likely due to some individuals being infected prior to booster administration. No immunogenicity data assessing the nAB immune response against Omicron subvariants are available for priming vaccines different from Comirnaty.

The descriptive immunogenicity data, i.e., GMTRs on day 15 and GMTRs D15/D0 indicate a robust booster immune response in the older population, though in a limited sample size with regard to subjects 65 years of age and older.

This study is however supportive as the Comparator used was not an approved COVID-19 vaccine.

The monovalent and bivalent vaccine formulations were not directly compared. The immunogenicity profile that derives from the neutralising antibody response however appears to be broadly comparable.

VAT0008 Stage 2

This study was a randomized, modified double-blind, placebo-controlled design, conducted in adults 18 years of age and older to evaluate the efficacy, safety, and immunogenicity of a primary series of 2 injections of 10 µg antigen dose (5 µg antigen per strain) of the bivalent VidPrevtyn Original/Beta (D614 and B.1.351. strains) administered 21 days apart by intramuscular (IM) route.

Initially it was planned that participants who were SARS-CoV-2 non-naïve as determined by a rapid serodiagnostic test at baseline were to be capped to a maximum of approximately 30% of the total study population (up to ~1633 participants/arm in Stage 2). The rapid serodiagnostic test turned out to be less sensitive than expected and in turn numerous SARS-CoV-2 pre-infections were determined at a subsequent testing. The applicant argues that due to a change in the global epidemiological data and the change in the primary endpoint to the overall population regardless of prior SARS-CoV-2 infection, the cap of 30% of SARS-CoV-2 non-naïve was removed. Out of the 13,002 randomised participants, 12,924 (99.4%) were included in the Full Analysis Set (FAS). As a result of not detecting prior SARS-CoV-2 infection at baseline and/or removing the enrolment cap for non-naïve participants only 1176 participants were naïve at D01, and only 683 participants (5.3%) were naïve at D01 and Day22 in the FAS.

In mFAS-PD2 the participants predominant race was Black or African American (44.4%), followed by Asian (41.9%), American Indian or Alaska Native (4.8%), and White (0.6%). This does not reflect the racial demographics in the EU. Nevertheless, there are no known differences in vaccine efficacy in different ethnicities, the presented racial demographics do not prevent the use of these results.

There were imbalances in the demographics for sex (1.4-fold more male than female) and age (mean age about 36 years; only 2.6% of participants ≥65 years).

Depending on age strata, the median follow-up post-dose 2 was between 54 to 58 days.

Study VAT0008 Stage 2 could not demonstrate efficacy in mFAS-PD2 Naïve D01+D22 as the lower bound of CI was negative for protection against infection (VE 9.6%, 95% CI -16.4; 29.9) and against symptomatic COVID-19 disease (VE 30.9%, 95% CI -39.9; 66.7%).

Study VAT0008 Stage 2 demonstrated efficacy in the population of previously SARS-CoV-2 infected participants with 75.9% VE (95% CI 62.7; 84.9) in mFAS-PD1 Non-Naïve (first vaccination dose) and 75.1% VE (95% CI 56.3; 86.6) in mFAS-PD2 Non-Naïve (second vaccination dose). The limited follow-up time of 21 days in mFAS-PD1 Non-Naïve (first vaccination dose) needs to be considered.

Notably, VE after the first vaccination dose and after the second vaccination dose is comparable but not increased. One could speculate that in such setting the vaccination shares similarity to a booster vaccination dose after prior infection, indicating that the increase in efficacy from mFAS-PD2 Naïve D01+D22 to mFAS-PD2 Non-Naïve needs to be attributed to prior SARS-CoV-2 infection rather than the capability of the bivalent CoV2 preS dTM-AS03 (5 µg D614 + 5 µg B.1.351) vaccine to provide protection as a primary vaccination series. Comparison of neutralising antibody (nAB) GMTs after the first and the second vaccination doses could gain more insight addressing the question whether the second dose is substantially increasing nAB GMTs or not.

Failure to demonstrate efficacy in mFAS-PD1 Non-Naïve against moderate or worse COVID-19 disease, or severe COVID-19 disease was impacted by the low number of events.

Breakthrough infections were mostly due to infection with SARS-CoV-2 Omicron variant followed in frequency by SARS-CoV-2 Delta variant as expected from the prevalence of these variants at the time of study conduct. However, with introduction of the bivalent CoV2 preS dTM-AS03 (5 µg D614 + 5 µg B.1.351) vaccine the applicant is providing results from a variant adapted vaccine meant to protect against emerging variants.

Although there is no intended booster vaccination in study VAT0008 Stage 2, the analysis sets mFAS-PD1 Non-Naïve and mFAS-PD2 Non-Naïve share a similarity to a booster vaccination as vaccinations are done in previously SARS-CoV-2 infected participants. Therefore, immunogenicity results from these analysis sets could be comparable to results from booster vaccinations. Given the short follow-up time of 21 days for mFAS-PD1 Non-Naïve for demonstrating VE, mFAS-PD2 Non-Naïve would be considered

the appropriate analysis set for comparison of nAB GMTs.

The protocol for VAT0008 Stage 2 lists additional secondary endpoints that have not been addressed in the brief CSR, including immunogenicity analyses. Comparing nAB GMTs from mFAS-PD2 Non-Naïve to those from VAT0013 or VAT0002 (Supplemental Phase III Cohort 2) could be a possibility to infer efficacy from VAT0008 Stage 2 to an expectation of effectiveness in VAT0013. For this purpose, nAB GMTs against SARS-CoV-2 Omicron variant BA.4/BA.5 after booster vaccination with CoV2 preS dTM-AS03 (B.1.351) vaccine are deemed most relevant and should be compared to nAB GMTs against SARS-CoV-2 Omicron variant BA.4/BA.5 from mFAS-PD2 Non-Naïve participants.

No immunogenicity results for VAT0008 Stage 2 are available. The applicant is in the process of testing these samples and do not expect to have this data before the end of 2022 (**REC**).

In conclusion, results from study VAT0008 Stage 2 cannot be compared to results from VAT0002 or VAT0013 and can therefore not be considered supportive to draw any conclusion on effectiveness of CoV2 preS dTM-AS03 (B.1.351) vaccine as a booster vaccination up until relevant immunogenicity results from VAT008 Stage 2 become available.

2.5.7. Conclusions on the clinical efficacy

In VAT00013 study, the immunogenicity of the VidPrevtyn Beta given as a single booster dose in Comirnaty primed participants was compared to VidPrevtyn (D614) non-approved booster vaccine and the Comirnaty (containing D614 strain) approved booster vaccine. Study VAT00013 met the primary objective and it is accepted to infer efficacy as a booster by an immunogenicity bridge.

For VAT0002 the descriptive analysis of GMTs and GMTRs indicates a notable increase of nABs after a booster dose of the VidPrevtyn Beta against both the D614 and the B.1.351 strain irrespective of priming vaccine/priming platform (i.e. mRNA or adenoviral-vector vaccines).

Study VAT0008 Stage 2 demonstrated efficacy in the population of previously SARS-CoV-2 infected participants with 75.9% VE (95% CI 62.7; 84.9) in mFAS-PD1 Non-Naïve (first vaccination dose) and 75.1% VE (95% CI 56.3; 86.6) in mFAS-PD2 Non-Naïve (second vaccination dose). Study VAT0008 Stage 2 could not demonstrate efficacy in mFAS-PD2 Naïve D01+D22. In view of lack of immunogenicity data from VAT00008, results from study VAT0008 Stage 2 cannot be compared to results from VAT0002 or VAT0013 and can therefore not be considered supportive to draw any conclusion on efficacy of VidPrevtyn Beta.

The CHMP considers the following measures necessary to address the clinical efficacy issues

- To support the lack of data in the elderly, the applicant should provide immunogenicity and safety data on this population from two currently ongoing studies (ancillary study VAT00013 and NIH-initiated study) as soon as results are available (by 31 March 2022)
- Immunogenicity results (nAB GMTs) against D614G and VOCs, in particular against SARS-CoV-2 Omicron variants BA.4/BA.5, from participants in study VAT0008 Stage 2 should be provided. The analysis sets mFAS-PD1 Non-Naïve and mFAS-PD2 Non-Naïve are considered the most appropriate sets for comparison. Data from the naïve population should also be provided (31 March 2022).
- To support the lack of data in immunocompromised individuals, the Applicant should provide immunogenicity and safety data on this population from the two planned studies (VAT00027 and VAT00028) as soon as results are available (by 31 December 2023).

2.5.8. Clinical safety

The applicant has provided results from the following studies:

- VAT00002* Supplemental Phase III Cohort 2: a single booster dose of 5 µg of CoV2 preS dTMAS03 (B.1.351) vaccine or 5 µg CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine given to participants previously primed with heterologous (mRNA and Ad-vector COVID-19 vaccines) or priming vaccines/platforms (Sanofi's protein COVID19 vaccine). The safety database lock was 13 May 2022.
- Study VAT00008 – Stage 2: primary vaccination with 2 injections of either 10 µg CoV2 preS dTM-AS03 (D614 + B.1.351) or placebo administered 21 days apart. Data cut-off date was 15 March 2022.
- Study VAT00013: summary of safety data from participants previously primed with Pfizer/BioNTech vaccine, receiving a single booster dose of 5 µg of CoV2 preS dTM-AS03 (B.1.351) vaccine. Data were collected up to 28 days after administration of the booster dose.
- Interim data from VAT00002 Supplemental Phase III Cohort 1 and study VAT0008 – stage 1 concerning VidPrevtyn (D614)

2.5.8.1. Patient exposure

VAT00002 - Supplemental Phase III Cohort 2

In VAT00002 Booster group, there was a total of 705 participants who received a single booster injection of Beta Monovalent (5 µg B.1.351) vaccine. Of these 610 participants completed ≥ 2 months safety follow-up after the last injection. A total of 621 participants received a single booster injection of bivalent (2.5 µg D614 + 2.5 µg B.1.351) vaccine. Of these 546 participants completed ≥ 2 months safety follow-up after the last injection. Patient exposure to the booster injection according to the primary series administration is presented in the table below.

Table 50: Exposure to a booster dose of CoV2 preS dTM-AS03 (B.1.351) or (D614 + B.1.351) vaccines in VAT00002 – Supplemental Phase III Cohort 2

	VAT00002 - Supplemental Phase III Cohort 2					
	Pfizer/ BioNTech N=378 (MV) N=378 (BV) n (%)	Moderna N=112 (MV) N=108 (BV) n (%)	Oxford University/ AstraZeneca N=101 (MV) N=101 (BV) n (%)	J&J/ Janssen N=38 (MV) N=38 (BV) n (%)	Protein Primed* N=78 (MV) n (%)	All Booster N=707 (MV) N=625 (BV) n (%)
Number (%) of exposed participants to a single booster dose of CoV2 preS dTM-AS03 (5 µg B.1.351) or (2.5 µg D614 + 2.5 µg B.1.351)						
MV (B.1.351)	378 (100)	111 (99.1)	100 (99.0)	38 (100)	78 (100)	**705 (99.7)**
BV (D614 + B.1.351)	375 (99.2)	108 (100)	100 (99.0)	38/38 (100)	N/A	**621 (99.4)**
Number (%) of participants with at least 2 months of safety follow up after booster injection						
MV (B.1.351)	324 (85.7)	99 (89.2)	76 (76.0)	37 (97.4)	74 (94.9)	**610 (86.5)**
BV (D614 + B.1.351)	331 (88.3)	100 (92.6)	78 (78.0)	37 (97.4)	N/A	**546 (87.9)**
Study duration (days)	180					
Mean participant duration in days (SD)	144 (30.9)					
Median safety follow-up in days	145					

Abbreviations: BV, bivalent; MV, monovalent.

N: number of participants randomized in each group

n: number of participants fulfilling the item listed

*Participants previously vaccinated with CoV2 preS dTM-AS03 (D614) vaccine in VAT00002 - Original Phase II Cohort and then boosted with a single dose of 5 µg of CoV2 preS dTM-AS03 (B.1.351) vaccine in VAT00002 Phase III Supplemental Cohort 2

Source: modified from 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Section 8, Table 8.1, Table 8.5 and Table 8.15.

VAT00008 – Stage 2

There was a total of 5788 participants who received 2 injections of 10 µg of CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine administered 21 days apart. The data analysis cut-off date was 15 March 2022, and at that timepoint safety follow up past dose two for the SafAS was at least 1 month for 4327 participants (66.9%) and at least 2 months for 2731 participants (42.2%).

Table 51: Exposure to a 2-injection primary series of CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine or placebo in VAT00008 – Stage 2

	VAT00008 – Stage 2	
Number (%) of participants exposed to	**10 µg CoV2 preS dTM-AS03 (D614 + B.1.351) N=6472 (SafAS) n (%)**	**Placebo N=6450 (SafAS) n (%)**
Dose 1*	6472 (99.4)	6450 (99.4)
Dose 2*	5788 (88.9)	5755 (88.7)
Number (%) of participants with at least 2 months of safety follow up after last injection	2731 (42.2)	2722/6450 (42.2)
Study duration (days)	148	
Median follow-up in days	85	

*Number of randomized participants in vaccine group: 6512; Number of randomized participants in placebo group: 6490

N: number of participants injected in each group.

n: number of participants fulfilling the item listed.

Source: 5.3.5.1 VAT00008 Stage 2 Brief Interim CSR, Section 8, Table 8.3B, Table 8.134B, and Table 8.149B.

Summary of exposure to CoV2 preS dTM AS03 (B.1.351) Vaccine

In total 7798 participants received at least 1 dose of CoV2 preS dTM AS03 (B.1.351) containing vaccine as following:

- 705 participants received a single booster dose of 5 µg of MV CoV2 preS dTM AS03 (B.1.351) vaccine.
- 621 participants received a single booster dose of 5 µg of BV CoV2 preS dTM AS03 (D614+B.1.351) vaccine.
- 6472 participants received at least 1 dose of 10 µg CoV2 preS dTM AS03 (D614+B.1.351) vaccine as a primary series.

Regarding the age stratification: (96.2%) participants were in the 18-64 years age group, (3.1%) were in the 65-74 years age group, (0.6%) in the 75-84 years age group, and 10 (0.1%) were in the >=85 years age group.

VAT00013

There were 247 participants enrolled, randomized, and vaccinated as following: 85 participants in CoV2 preS dTM-AS03 (D614) booster group, 80 participants in CoV2 preS dTM-AS03 (B.1.351) booster group, and 82 participants in Pfizer/BioNTech booster group and all were included in analysis for safety. The participants who received a single booster injection of 5 µg of CoV2 preS dTM-AS03 (B.1.351) vaccine, all of them completed 28 days of safety follow up after the booster administration.

Safety analysis set

The safety set parameters were similar in the Studies VAT00002 - Supplemental Phase III Cohort 2 and VAT00008 – Stage 2, presented in the table below.

Table 52: VAT00002 – Supplemental Phase III Cohort 2 and VAT00008 – Stage 2: Safety endpoints and time windows for collection

Safety Parameter	Adverse events or reactions collected	Collection Window
Immediate events/reactions	Unsolicited injection site* and systemic adverse events (AEs)/adverse reactions (ARs)	Within 30 minutes after vaccination
Reactogenicity†:		
Solicited injection site reactions	Injection site pain, injection site erythema, and injection site swelling	Within 7 days after vaccination (D01 to D08)
Solicited systemic reactions	Fever, headache, malaise, myalgia, arthralgia, chills	Within 7 days after vaccination (D01 to D08)
Unsolicited non-serious AEs/ARs	Any other AE that occurred within 21 days of any vaccination and that did not correspond to one of the reactions prelisted	Within 21 days after any vaccination
Adverse events of special Interest (AESI)	See Section 8.1 for the list of AESIs	Throughout the study period
Medically-attended adverse events (MAAEs)	Any MAAE (All including related)	Throughout the study period
SAEs	Any SAE (All including related)	Throughout the study period, including the collection of SAEs related to study procedures before the first study intervention administration (eg, SAEs related to blood sampling).
Deaths	Any death	Throughout the study period
AEs leading to discontinuation	Any AE leading to discontinuation (serious and non-serious)	Throughout the study period

* Immediate unsolicited injection site reactions were collected in VAT00008 study only

† In VAT00008, solicited reactions (ie, injection site reactions and solicited systemic reactions) and unsolicited non-serious AEs/ARs were collected in the reactogenicity subset.

Source: 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Appendix 1 Clinical study protocol and VAT00008 Stage 2 Brief Interim CSR, Appendix 1 Clinical study protocol.

The safety data from the 3 studies: VAT00002 – Supplemental Phase III Cohort 2, VAT00008 – Stage 2, and VAT00013 will not be pooled due to the difference in the safety data collection methods.

Demographics of VAT00002 – Supplemental Phase III Cohort 2 is displayed in the below table.

Table 53: Demographics and baseline characteristics of the safety population, study VAT00002 Supplemental Cohort 2 Booster Groups

Prior Prime Vaccination	Pfizer Primed		Moderna Primed		AZ Primed		J&J Primed		Protein Primed	All Booster	
Booster Vaccine Received Characteristics	MV (B.1.351) (N=378)	BV (D614+B.1.351) (N=375)	MV (B.1.351) (N=111)	BV (D614+B.1.351) (N=108)	MV (B.1.351) (N=100)	BV (D614+B.1.351) (N=100)	MV (B.1.351) (N=38)	BV (D614+B.1.351) (N=38)	MV (B.1.351) (N=78)	MV (B.1.351) (N=705)	BV (D614+B.1.351) (N=621)
Sex: female n/M (%)	208/378 (55.0)	198/375 (52.8)	60/111 (54.1)	64/108 (59.3)	42/100 (42.0)	48/100 (48.0)	19/38 (50.0)	20/38 (52.6)	38/78 (48.7)	367/705 (52.1)	330/621 (53.1)
Sex: male n (n/M (%)	170/378 (45.0)	177/375 (47.2)	51/111 (45.9)	44/108 (40.7)	58/100 (58.0)	52/100 (52.0)	19/38 (50.0)	18/38 (47.4)	40/78 (51.3)	338/705 (47.9)	291/621 (46.9)
Age (years) mean (SD)	40.6 (14.0)	40.6 (13.9)	44.6 (15.8)	46.6 (13.9)	51.7 (11.8)	51.2 (13.3)	47.1 (12.0)	47.4 (12.6)	65.9 (11.5)	46.0 (15.8)	43.7 (14.3)
Age (years) median	40.0	39.0	42.0	47.0	51.0	52.0	47.0	47.5	64.0	47.0	43.0
Age (years) min, max	18.0; 83.0	18.0; 76.0	19.0; 75.0	18.0; 77.0	26.0; 77.0	20.0; 80.0	24.0; 70.0	19.0; 73.0	23.0; 93.0	18.0; 93.0	18.0; 80.0
Age 18 through 55 years (M)	318	315	78	76	64	64	28	28	4	492	483
Age 18 through 59 years (M)	338	329	86	84	73	74	33	30	9	539	517
Age 18 through 64 years (M)	361	352	96	95	85	86	35	36	40	617	569
Age ≥ 56 years (M)	60	60	33	32	36	36	10	10	74	213	138
Age ≥ 60 years (M)	40	46	25	24	27	26	5	8	69	166	104
Age ≥ 65 years (M)	17	23	15	13	15	14	3	2	38	88	52
Race: American Indian or Alaska Native n/M (%)	5/378 (1.3)	6/375 (1.6)	6/111 (5.4)	2/108 (1.9)	0/100	0/100	4/38 (10.5)	2/38 (5.3)	14/78 (17.9)	29/705 (4.1)	10/621 (1.6)
Race: Asian n/M (%)	12/378 (3.2)	13/375 (3.5)	1/111 (0.9)	3/108 (2.8)	4/100 (4.0)	7/100 (7.0)	2/38 (5.3)	2/38 (5.3)	2/78 (2.6)	21/705 (3.0)	25/621 (4.0)
Race: Black or African American n/M (%)	54/378 (14.3)	60/375 (16.0)	16/111 (14.4)	32/108 (29.6)	3/100 (3.0)	2/100 (2.0)	16/38 (42.1)	10/38 (26.3)	2/78 (2.6)	91/705 (12.9)	104/621 (16.7)
Race: Native Hawaiian or Other Pacific Islander n/M (%)	2/378 (0.5)	1/375 (0.3)	0/111	0/108	0/100	0/100	1/38 (2.6)	0/38	0/78	3/705 (0.4)	1/621 (0.2)
Race: White n/M (%)	247/378 (65.3)	239/375 (63.7)	78/111 (70.3)	61/108 (56.5)	91/100 (91.0)	86/100 (86.0)	15/38 (39.5)	21/38 (55.3)	37/78 (47.4)	468/705 (66.4)	407/621 (65.5)
Race: Multiracial	6/378 (1.6)	6/375 (1.6)	3/111 (2.7)	1/108 (0.9)	0/100	1/100 (1.0)	0/38	0/38	1/78 (1.3)	10/705 (1.4)	8/621 (1.3)
Race: Not reported n/M (%)	44/378 (11.6)	48/375 (12.8)	1/111 (0.9)	6/108 (5.6)	1/100 (1.0)	2/100 (2.0)	0/38	2/38 (5.3)	0/78	46/705 (6.5)	58/621 (9.3)
Ethnicity: Hispanic or Latino n/M (%)	38/378 (10.1)	44/375 (11.7)	15/111 (13.5)	13/108 (12.0)	7/100 (7.0)	6/100 (6.0)	4/38 (10.5)	8/38 (21.1)	39/78 (50.0)	103/705 (14.6)	71/621 (11.4)
Ethnicity: Not Hispanic or Latino n/M (%)	248/378 (65.6)	262/375 (69.9)	93/111 (83.8)	90/108 (83.3)	76/100 (76.0)	76/100 (76.0)	31/38 (81.6)	29/38 (76.3)	39/78 (50.0)	487/705 (69.1)	457/621 (73.6)
Race: Unknown n/M (%)	8/378 (2.1)	2/375 (0.5)	6/111 (5.4)	3/108 (2.8)	1/100 (1.0)	2/100 (2.0)	0/38	1/38 (2.6)	22/78 (28.2)	37/705 (5.2)	8/621 (1.3)
Ethnicity: Not reported n/M (%)	86/378 (22.8)	66/375 (17.6)	1/111 (0.9)	4/108 (3.7)	14/100 (14.0)	15/100 (15.0)	1/38 (2.6)	0/38	0/78	102/705 (14.5)	85/621 (13.7)

N: number of enrolled participants; n: number of participants fulfilling the item listed; M: number of participants randomized in each vaccine and subgroup; SD, standard deviation
Prior prime vaccination: Pfizer = Pfizer/BioNTech, Moderna = Moderna, AZ = Oxford University/AstraZeneca, J&J = Johnson & Johnson/Janssen, Protein = CoV2 preS dTM-AS03 (D614) vaccine
Booster vaccine received: MV (B.1.351) = CoV2 preS dTM-AS03 (5 µg B.1.351), BV (D614 + B.1.351) = CoV2 preS dTM-AS03 (2.5 µg D614 + 2.5 µg B.1.351)
Source: modified from Section 8, Table 8.16

Overall, in the SafAS, the proportion of participants with at least one high-risk medical condition was comparable across the mRNA platform primed groups and the Oxford/AstraZeneca primed groups (ranging from 50% of participants in the monovalent boosted-Oxford/AstraZeneca primed group to 62.2% of the monovalent boosted-Moderna primed group). Participants in the J&J/Janssen primed groups (78.9% in the bivalent boosted group, 84.2% in the monovalent boosted group) and the Protein primed group (80.8%) had higher proportions of participants with at least 1 high-risk medical condition. The most common high-risk medical condition was obesity, 36.5% and 34.8% in the MV and BV booster groups, respectively. Overall, the most common (> 5% of participants) high-risk medical conditions after obesity were smoking (18,7%, 20.1%), hypertension/high blood pressure (20.4%, 16.1%), and type 2 diabetes mellitus (9.8%, 5.0%) in MV and BV booster groups, respectively.

In study VAT00008 – stage 2, the proportion of participants was well balanced across vaccine and placebo groups. The proportion of males was higher compared to females. The mean age was 36.1 (12.8) years, and similar in both treatment groups. Approximately 94% of participants were aged between 18 and 59 years. Mostly of the participants were SARS-CoV-2 non-naïves at baseline for both

treatment groups. The most common high-risk medical conditions (≥ 5% of participants) were smoking, obesity, and immunocompromised state from other causes. Overall, the proportion of participants having risk factors for severe COVID-19 was similar between treatment groups.

Table 54: Demographics of the safety population - SafAS

Characteristics	Vaccine Group N=6472 n (%)	Placebo Group N=6450 n (%)	Total N=12924* n (%)
Sex: male	3789 (58.5)	3751 (58.2)	7542* (58.4)
Sex: female	2683 (41.5)	2699 (41.8)	5382 (41.6)
Age (years) mean (SD)	36.1 (13.0)	36.0 (12.9)	36.1 (12.9)
Age (years) median	34.0	34.0	34.0
Age (years) min, max	18.0 ; 93.0	18.0 ; 93.0	18.0 ; 93.0
Age 18 through 59 years	6078 (93.9)	6067 (94.1)	12147* (94.0)
Age 18 through 64 years	6306 (97.4)	6255 (97.0)	12563* (97.2)
Age ≥60 years	394 (6.1)	383 (5.9)	777 (6.0)
Age ≥65 years	166 (2.6)	195 (3.0)	361 (2.8)
Age ≥75 years	37 (0.6)	51 (0.8)	88 (0.7)
Race: American Indian or Alaska Native	408 (6.3)	402 (6.2)	811† (6.3)
Race: Asian	2562 (39.6)	2567 (39.8)	5129 (39.7)
Race: Black or African American	2873 (44.4)	2854 (44.2)	5727 (44.3)
Race: Native Hawaiian or Other Pacific Islander	1 (<0.1)	2 (<0.1)	3 (<0.1)
Race: White	36 (0.6)	38 (0.6)	74 (0.6)
Race: Multiracial	5 (<0.1)	6 (<0.1)	11 (<0.1)
Race: Not reported	95 (1.5)	82 (1.3)	177 (1.4)
Ethnicity: Hispanic or Latino	1056 (16.3)	1051 (16.3)	2109† (16.3)
Ethnicity: Not Hispanic or Latino	5381 (83.1)	5372 (83.3)	10753 (83.2)
Ethnicity: Not reported	15 (0.2)	13 (0.2)	28 (0.2)

Abbreviations: SD, standard deviation

N=number of participants in the specified group. This value is used as the denominator for percentage calculations. n=number of participants with the specified characteristic

*Two participants received a vaccine at V1 but whether they received the vaccine, or the placebo is unknown. Therefore, there is a difference of 2 participants in the total number of participants of the SafAS.

†One of the 2 participants who had a missing information about the vaccine/placebo actually received was American Indian or Alaska Native. For the other participant, the race was unknown although the ethnicity was Hispanic or Latino.

Source: Modified from Section 8, Table 8.11B

In study VAT00013, 247 participants were enrolled: 85 participants in CoV2 preS dTM-AS03 (D614) booster group, 80 participants in CoV2 preS dTM-AS03 (B.1.351) booster group, and 82 participants in Pfizer/BioNTech booster group. The mean age of participants was similar between vaccine groups. There were less females than males in the two booster groups while in Group 1 (Pfizer/BioNTech booster vaccine group), the gender proportion was balanced. The interval between the second dose of the primary series and the booster dose was 174 days (approximately 5.8 months) and was comparable across groups. The most common high-risk medical conditions associated with increased risk of severe COVID-19 (≥ 4.5%) were smoking, obesity, and hypertension.

2.5.8.2. Adverse events

Study VAT00002 - Supplemental Phase III Cohort 2

Solicited local ARs

In study VAT00002- Phase III, within 7 days after a booster injection 77.1% in the MV (B.1.351) vaccine groups and 78.4% participants in the BV (D614 + B.1.351) vaccine group experienced at least one local ARs, of which 3.3% and 1.9%, respectively, were of Grade 3 intensity.

The most common reported local AR was 'Pain' experienced by 76.2% and 77.8%, respectively, of all Booster Group participants, 2.9% and 1.8%, respectively, were of Grade 3 intensity, followed by swelling and erythema. The majority of solicited injection site reactions were of Grade 1 or 2 intensities, occurred within 3 days and resolved spontaneously within 1 to 3 days. All Grade 3 solicited injection site reactions for both vaccine groups occurred within 3 days.

Regarding age groups, more participants aged 18-55 years experienced solicited injection site reactions (83.1% and 84.3% for MV and BV vaccines, respectively) than those ≥56 years of age (63.2% and 58.0% for MV and BV vaccines, respectively).

An overview of all local solicited ARs and the grade 3 ARs are summarized in the table below:

Table 55: Study VAT00002 – Supplemental Phase III Cohort 2: Frequency of solicited injection site reactions within 7 days after a single booster dose with MV CoV2 preS dTM-AS03 (B.1.351) or BV CoV2 preS dTM-AS03 (D614 + B.1.351) in adults 18 years of age and older by priming vaccine platform

VAT00002 - Supplemental Phase III Cohort 2													
		mRNA Primed						Ad-vector Primed					
		MV (B.1.351) (N=489)			BV (D614 + B.1.351) (N=483)			MV (B.1.351) (N=138)			BV (D614 + B.1.351) (N=138)		
Participants experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
General disorders and administration site conditions													
Local reactions	Any	382/477	80.1	(76.2 ; 83.6)	377/478	78.9	(74.9 ; 82.4)	106/138	76.8	(68.9 ; 83.6)	106/138	76.8	(68.9 ; 83.6)
	Grade 3	15/477	3.1	(1.8 ; 5.1)	6/478	1.3	(0.5 ; 2.7)	4/138	2.9	(0.8 ; 7.3)	6/138	4.3	(1.6 ; 9.2)
Injection Site Pain	Any	378/477	79.2	(75.3 ; 82.8)	375/478	78.5	(74.5 ; 82.1)	104/138	75.4	(67.3 ; 82.3)	104/138	75.4	(67.3 ; 82.3)
	Grade 3	14/477	2.9	(1.6 ; 4.9)	6/478	1.3	(0.5 ; 2.7)	4/138	2.9	(0.8 ; 7.3)	5/138	3.6	(1.2 ; 8.3)
Injection Site Erythema	Any	30/477	6.3	(4.3 ; 8.9)	23/478	4.8	(3.1 ; 7.1)	9/138	6.5	(3.0 ; 12.0)	12/138	8.7	(4.6 ; 14.7)
	Grade 3	1/477	0.2	(0 ; 1.2)	0/478	0	(0 ; 0.8)	0/138	0	(0 ; 2.6)	1/138	0.7	(0 ; 4.0)
Injection Site Swelling	Any	44/477	9.2	(6.8 ; 12.2)	29/478	6.1	(4.1 ; 8.6)	8/138	5.8	(2.5 ; 11.1)	8/138	5.8	(2.5 ; 11.1)
	Grade 3	0/477	0	(0 ; 0.8)	0/478	0	(0 ; 0.8)	0/138	0	(0 ; 2.6)	0/138	0	(0 ; 2.6)
		Protein Primed*						All Booster (All Priming Platforms)					
		MV (B.1.351) (N=78)						MV (B.1.351) (N=705)			BV (D614 + B.1.351) (N=621)		
Participants experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**				**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
General disorders and administration site conditions													
Local reactions	Any	46/78	59.0	(47.3 ; 70.0)				534/693	77.1	(73.7 ; 80.1)	483/616	78.4	(74.9 ; 81.6)
	Grade 3	4/78	5.1	(1.4 ; 12.6)				23/693	3.3	(2.1 ; 4.9)	12/616	1.9	(1.0 ; 3.4)
Injection Site Pain	Any	46/78	59.0	(47.3 ; 70.0)				528/693	76.2	(72.8 ; 79.3)	479/616	77.8	(74.3 ; 81.0)
	Grade 3	2/78	2.6	(0.3 ; 9.0)				20/693	2.9	(1.8 ; 4.4)	11/616	1.8	(0.9 ; 3.2)
Injection Site Erythema	Any	2/78	2.6	(0.3 ; 9.0)				41/693	5.9	(4.3 ; 7.9)	35/616	5.7	(4.0 ; 7.8)
	Grade 3	1/78	1.3	(0 ; 6.9)				2/693	0.3	(0 ; 1.0)	1/616	0.2	(0 ; 0.9)
Injection Site Swelling	Any	3/78	3.8	(0.8 ; 10.8)				55/693	7.9	(6.0 ; 10.2)	37/616	6.0	(4.3 ; 8.2)
	Grade 3	1/78	1.3	(0 ; 6.9)				1/693	0.1	(0 ; 0.8)	0/616	0	(0 ; 0.6)

N: number of participants injected in each group. n: number of participants experiencing the endpoint listed in the first column. M: number of participants with available data for the relevant endpoint.

Solicited systemic ARs

In the MV (B.1.351) or BV (D614 + B.1.351) vaccines groups within 7 days after a booster injection, 60.0% and 64.8% of participants, respectively, experienced at least one solicited systemic AR, of which 6.9% and 6.3%, respectively, were of Grade 3 intensity. The most frequently reported solicited systemic reactions in the MV and BV vaccines' all Booster Groups were headache (41.4% and 43.0% of participants), myalgia (37.8% and 41.9%), and malaise (33.0% and 33.1%). The majority of solicited systemic reactions were of Grade 1-2 and occurred within 3 days. The majority of Grade 3 systemic ARs occurred within the first 4 days after vaccination and lasted between 1-3 days.

Regarding the age groups: more participants aged 18-55 years experienced solicited systemic ARs (66.1% and 69.2% for MV and BV vaccines, respectively) than those ≥ 56 years of age (45.9% and 49.3% for MV and BV vaccines, respectively). The rates were comparable in frequency in each Booster Group with younger adults reporting more solicited systemic reactions than older adults.

The table below summarizes systemic reactions following a 5-µg single booster dose of MV (B.1.351) or BV (D614 + B.1.351) vaccines by priming vaccine platform in adults 18 years of age.

Table 56: Study VAT00002 – Supplemental Phase III Cohort 2: Frequency of solicited systemic reactions within 7 days after a single booster dose with MV CoV2 preS dTM-AS03 (B.1.351) or BV CoV2 preS dTM-AS03 (D614 + B.1.351) in adults 18 years of age and older by priming vaccine platform

VAT00002 - Supplemental Phase III Cohort 2													
		mRNA Primed						Ad-vector Primed					
		MV (B.1.351) (N=489)			BV (D614 + B.1.351) (N=483)			MV (B.1.351) (N=138)			BV (D614 + B.1.351) (N=138)		
Participants experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited systemic reactions	Any	305/477	63.9	(59.5 ; 68.3)	307/478	64.2	(59.7 ; 68.5)	75/138	54.3	(45.7 ; 62.8)	92/138	66.7	(58.1 ; 74.5)
	Grade 3	37/477	7.8	(5.5 ; 10.5)	28/478	5.9	(3.9 ; 8.4)	7/138	5.1	(2.1 ; 10.2)	11/138	8.0	(4.0 ; 13.8)
Fever	Any	16/472	3.4	(1.9 ; 5.4)	22/476	4.6	(2.9 ; 6.9)	3/134	2.2	(0.5 ; 6.4)	7/137	5.1	(2.1 ; 10.2)
	Grade 3	2/472	0.4	(0.1 ; 1.5)	2/476	0.4	(0.1 ; 1.5)	0/134	0	(0 ; 2.7)	1/137	0.7	(0 ; 4.0)
Myalgia	Any	190/477	39.8	(35.4 ; 44.4)	194/478	40.6	(36.1 ; 45.1)	45/138	32.6	(24.9 ; 41.1)	64/138	46.4	(37.9 ; 55.1)
	Grade 3	9/477	1.9	(0.9 ; 3.6)	13/478	2.7	(1.5 ; 4.6)	2/138	1.4	(0.2 ; 5.1)	5/138	3.6	(1.2 ; 8.3)
Malaise	Any	161/477	33.8	(29.5 ; 38.2)	154/478	32.2	(28.0 ; 36.6)	43/138	31.2	(23.6 ; 39.6)	50/138	36.2	(28.2 ; 44.8)
	Grade 3	14/477	2.9	(1.6 ; 4.9)	14/478	2.9	(1.6 ; 4.9)	6/138	4.3	(1.6 ; 9.2)	5/138	3.6	(1.2 ; 8.3)
Headache	Any	211/477	44.2	(39.7 ; 48.8)	201/478	42.1	(37.6 ; 46.6)	56/138	40.6	(32.3 ; 49.3)	64/138	46.4	(37.9 ; 55.1)
	Grade 3	20/477	4.2	(2.6 ; 6.4)	10/478	2.1	(1.0 ; 3.8)	0/138	0	(0 ; 2.6)	6/138	4.3	(1.6 ; 9.2)
Chills	Any	96/477	20.1	(16.6 ; 24.0)	95/478	19.9	(16.4 ; 23.7)	27/138	19.6	(13.3 ; 27.2)	35/138	25.4	(18.3 ; 33.5)
	Grade 3	10/477	2.1	(1.0 ; 3.8)	6/478	1.3	(0.5 ; 2.7)	2/138	1.4	(0.2 ; 5.1)	2/138	1.4	(0.2 ; 5.1)
Arthralgia	Any	146/477	30.6	(26.5 ; 35.0)	143/478	29.9	(25.8 ; 34.2)	35/138	25.4	(18.3 ; 33.5)	41/138	29.7	(22.2 ; 38.1)
	Grade 3	10/477	2.1	(1.0 ; 3.8)	10/478	2.1	(1.0 ; 3.8)	0/138	0	(0 ; 2.6)	2/138	1.4	(0.2 ; 5.1)
		Protein Primed*						All Booster (All Priming Platforms)					
		MV (B.1.351) (N=78)						MV (B.1.351) (N=705)			BV (D614 + B.1.351) (N=621)		
Participants experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**				**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited systemic reactions	Any	36/78	46.2	(34.8 ; 57.8)				416/693	60.0	(56.3 ; 63.7)	399/616	64.8	(60.9 ; 68.5)
	Grade 3	4/78	5.1	(1.4 ; 12.6)				48/693	6.9	(5.2 ; 9.1)	39/616	6.3	(4.5 ; 8.6)
Fever	Any	3/75	4.0	(0.8 ; 11.2)				22/681	3.2	(2.0 ; 4.9)	29/613	4.7	(3.2 ; 6.7)
	Grade 3	0/75	0	(0 ; 4.8)				2/681	0.3	(0 ; 1.1)	3/613	0.5	(0.1 ; 1.4)
Myalgia	Any	27/78	34.6	(24.2 ; 46.2)				262/693	37.8	(34.2 ; 41.5)	258/616	41.9	(38.0 ; 45.9)
	Grade 3	4/78	5.1	(1.4 ; 12.6)				15/693	2.2	(1.2 ; 3.5)	18/616	2.9	(1.7 ; 4.6)
Malaise	Any	25/78	32.1	(21.9 ; 43.6)				229/693	33.0	(29.5 ; 36.7)	204/616	33.1	(29.4 ; 37.0)
	Grade 3	3/78	3.8	(0.8 ; 10.8)				23/693	3.3	(2.1 ; 4.9)	19/616	3.1	(1.9 ; 4.8)
Headache	Any	20/78	25.6	(16.4 ; 36.8)				287/693	41.4	(37.7 ; 45.2)	265/616	43.0	(39.1 ; 47.0)
	Grade 3	1/78	1.3	(0 ; 6.9)				21/693	3.0	(1.9 ; 4.6)	16/616	2.6	(1.5 ; 4.2)
Chills	Any	15/78	19.2	(11.2 ; 29.7)				138/693	19.9	(17.0 ; 23.1)	130/616	21.1	(17.9 ; 24.5)
	Grade 3	2/78	2.6	(0.3 ; 9.0)				14/693	2.0	(1.1 ; 3.4)	8/616	1.3	(0.6 ; 2.5)
Arthralgia	Any	18/78	23.1	(14.3 ; 34.0)				199/693	28.7	(25.4 ; 32.2)	184/616	29.9	(26.3 ; 33.7)
	Grade 3	3/78	3.8	(0.8 ; 10.8)				13/693	1.9	(1.0 ; 3.2)	12/616	1.9	(1.0 ; 3.4)

N: number of participants injected in each group; n: number of participants experiencing the endpoint listed in the first column; M: number of participants with available data for the relevant endpoint.
* Participants previously vaccinated with CoV2 preS dTM-AS03 (D614) vaccine as a primary series in VAT00002 - Original Phase II Cohort and then boosted with a single dose of 5 µg of CoV2 preS dTM-AS03 (B.1.351) vaccine in VAT00002 Phase III Supplemental Cohort 2.
Prior prime vaccination platform: mRNA = all mRNA (Pfizer/BioNTech, Moderna), Ad-vector = all adenovirus-vectored (Oxford University/AstraZeneca, Johnson & Johnson/Janssen), Protein = CoV2 preS dTM-AS03 (D614).
Source: modified from 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Section 8, Table 8.32 and Table 8.40.

Participants without a high-risk medical condition reported a higher frequency of (local and systemic) solicited AEs (89.8%) than participants with such conditions (78.2%).

Study VAT00008 – Stage 2

Solicited local ARs

Overall, the frequency of solicited injection site ARs after any injection was higher in BV (D614 + B.1.351) vaccine group compared to placebo (46.7% vs. 26.8%, respectively). Lower frequencies of these events were reported after the 2nd injection compared to the 1st dose in the vaccine group (31.7% versus 35.6% participants). In the Placebo Group these ARs were similar after the 1st and 2nd dose (17.1% and 16.7% participants). Pain was the most frequently reported ARs in the vaccine group (46.2%) compared to placebo group (26.6%), followed by swelling (4.9% versus 0.5%, respectively) and erythema (1.9% versus 0.3%).

Most of the solicited local AR were of Grade 1- 2 intensity in both groups and Grade 3 events were 4.1% in the vaccine group vs 1.8% in the placebo group. In both groups, after any injection, most reactions started within 3 days and resolved spontaneously after 1 to 3 days.

An overview of the frequencies of solicited injection site reactions within 7 days after each study injection in participants 18 years of age and older is presented in the table below.

Table 57: Study VAT00008 – Stage 2: Frequency of solicited injection site reactions within 7 days after any dose and after dose 1 and dose 2 with BV CoV2 preS dTM-AS03 (D614 + B.1.351) in adults 18 years of age and older

			VAT00008 – Stage 2					
			BV (D614 + B.1.351) 10 µg + AS03 N=2433			Placebo N=2418		
Participants experiencing at least one:		Maximum intensity	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited injection site reactions	After any injection	Any	1130/2419	46.7	(44.7 ; 48.7)	645/2403	26.8	(25.1 ; 28.7)
		Grade 3	98/2419	4.1	(3.3 ; 4.9)	43/2403	1.8	(1.3 ; 2.4)
	Post-dose 1	Any	862/2419	35.6	(33.7 ; 37.6)	412/2403	17.1	(15.7 ; 18.7)
		Grade 3	58/2419	2.4	(1.8 ; 3.1)	30/2403	1.2	(0.8 ; 1.8)
	Post-dose 2	Any	720/2270	31.7	(29.8 ; 33.7)	376/2258	16.7	(15.1 ; 18.3)
		Grade 3	54/2270	2.4	(1.8 ; 3.1)	20/2258	0.9	(0.5 ; 1.4)
Injection Site Pain	After any injection	Any	1118/2419	46.2	(44.2 ; 48.2)	639/2403	26.6	(24.8 ; 28.4)
		Grade 3	96/2419	4.0	(3.2 ; 4.8)	43/2403	1.8	(1.3 ; 2.4)
	Post-dose 1	Any	846/2418	35.0	(33.1 ; 36.9)	407/2403	16.9	(15.5 ; 18.5)
		Grade 3	57/2418	2.4	(1.8 ; 3.0)	30/2403	1.2	(0.8 ; 1.8)
	Post-dose 2	Any	710/2270	31.3	(29.4 ; 33.2)	374/2258	16.6	(15.1 ; 18.2)
		Grade 3	53/2270	2.3	(1.8 ; 3.0)	20/2258	0.9	(0.5 ; 1.4)
Injection Site Erythema	After any injection	Any	47/2419	1.9	(1.4 ; 2.6)	8/2403	0.3	(0.1 ; 0.7)
		Grade 3	1/2419	<0.1	(0 ; 0.2)	0/2403	0	(0 ; 0.2)
	Post-dose 1	Any	31/2419	1.3	(0.9 ; 1.8)	6/2403	0.2	(0.1 ; 0.5)
		Grade 3	1/2419	<0.1	(0 ; 0.2)	0/2403	0	(0 ; 0.2)
	Post-dose 2	Any	22/2269	1.0	(0.6 ; 1.5)	2/2258	<0.1	(0 ; 0.3)
		Grade 3	0/2269	0	(0 ; 0.2)	0/2258	0	(0 ; 0.2)
Injection Site Swelling	After any injection	Any	118/2419	4.9	(4.1 ; 5.8)	13/2403	0.5	(0.3 ; 0.9)
		Grade 3	3/2419	0.1	(0 ; 0.4)	0/2403	0	(0 ; 0.2)
	Post-dose 1	Any	74/2419	3.1	(2.4 ; 3.8)	9/2403	0.4	(0.2 ; 0.7)
		Grade 3	1/2419	<0.1	(0 ; 0.2)	0/2403	0	(0 ; 0.2)
	Post-dose 2	Any	66/2269	2.9	(2.3 ; 3.7)	4/2258	0.2	(0 ; 0.5)
		Grade 3	2/2269	<0.1	(0 ; 0.3)	0/2258	0	(0 ; 0.2)

N: number of participants injected in each group
n: number of participants experiencing the endpoint
M: number of participants with available data for the relevant endpoint
Source: modified from 5.3.5.1 VAT00008 Stage 2 Brief Interim CSR, Section 8, Table 8.30B, 8.33B, 8.34B, 8.38B, 8.39B, and 8.40B.

Solicited systemic ARs

Overall, the frequency of solicited systemic ARs after any injection was higher in BV (D614 + B.1.351) vaccine group compared to placebo group, respectively (45.5% versus 34.2%). In the vaccine group, a comparable proportion of participants reported solicited systemic reactions after the 1st and 2nd injections (33.8% and 30.4% participants, respectively). Participants reported headache, malaise, myalgia, arthralgia, and chills at a similar frequency after each injection. The frequency of fever was low (≤4.5%) and was comparable after the 1st and 2nd injections. Most of the solicited systemic reactions were of Grade 1 and Grade 2 intensity in the vaccine and placebo groups. The proportion of participants in the vaccine group who reported Grade 3 solicited systemic reactions was comparable between the 1st and 2nd injections (4.3% and 4.0%participants, respectively). The proportion of participants reporting Grade 3 fever was ≤ 0.8%. In both groups, after any injection, most reactions started within 3 days and resolved spontaneously after 1 to 3 days.

Table 58: Study VAT00008 – Stage 2: Frequency of solicited systemic reactions within 7 days after any dose and after dose 1 and dose 2 with BV CoV2 preS dTM-AS03 (D614 + B.1.351) in adults 18 years of age and older.

			VAT00008 – Stage 2					
			BV (D614 + B.1.351) 10 µg + AS03 N=2433			Placebo N=2418		
Participants experiencing at least one:		Maximum intensity	n/M	%	(95% CI)	n/M	%	(95% CI)
	After any injection	Any	1100/2420	45.5	(43.5 ; 47.5)	823/2403	34.2	(32.4 ; 36.2)
Solicited systemic reactions		Grade 3	172/2420	7.1	(6.1 ; 8.2)	109/2403	4.5	(3.7 ; 5.4)
	Post-dose 1	Any	818/2420	33.8	(31.9 ; 35.7)	560/2403	23.3	(21.6 ; 25.0)
		Grade 3	104/2420	4.3	(3.5 ; 5.2)	75/2403	3.1	(2.5 ; 3.9)
	Post-dose 2	Any	690/2271	30.4	(28.5 ; 32.3)	520/2259	23.0	(21.3 ; 24.8)
		Grade 3	91/2271	4.0	(3.2 ; 4.9)	52/2259	2.3	(1.7 ; 3.0)
Fever	After any injection	Any	180/2386	7.5	(6.5 ; 8.7)	139/2369	5.9	(5.0 ; 6.9)
		Grade 3	25/2386	1.0	(0.7 ; 1.5)	27/2369	1.1	(0.8 ; 1.7)
	Post-dose 1	Any	106/2367	4.5	(3.7 ; 5.4)	63/2348	2.7	(2.1 ; 3.4)
		Grade 3	10/2367	0.4	(0.2 ; 0.8)	10/2348	0.4	(0.2 ; 0.8)
	Post-dose 2	Any	94/2221	4.2	(3.4 ; 5.2)	89/2206	4.0	(3.3 ; 4.9)
		Grade 3	17/2221	0.8	(0.4 ; 1.2)	20/2206	0.9	(0.6 ; 1.4)
Myalgia	After any injection	Any	605/2419	25.0	(23.3 ; 26.8)	426/2403	17.7	(16.2 ; 19.3)
		Grade 3	71/2419	2.9	(2.3 ; 3.7)	45/2403	1.9	(1.4 ; 2.5)
	Post-dose 1	Any	412/2418	17.0	(15.6 ; 18.6)	258/2403	10.7	(9.5 ; 12.0)
		Grade 3	38/2418	1.6	(1.1 ; 2.2)	34/2403	1.4	(1.0 ; 2.0)
	Post-dose 2	Any	364/2270	16.0	(14.5 ; 17.6)	258/2258	11.4	(10.1 ; 12.8)
		Grade 3	39/2270	1.7	(1.2 ; 2.3)	17/2258	0.8	(0.4 ; 1.2)
Malaise	After any injection	Any	666/2419	27.5	(25.8 ; 29.4)	504/2403	21.0	(19.4 ; 22.7)
		Grade 3	75/2419	3.1	(2.4 ; 3.9)	52/2403	2.2	(1.6 ; 2.8)
	Post-dose 1	Any	454/2417	18.8	(17.2 ; 20.4)	306/2403	12.7	(11.4 ; 14.1)
		Grade 3	43/2417	1.8	(1.3 ; 2.4)	40/2403	1.7	(1.2 ; 2.3)
	Post-dose 2	Any	410/2270	18.1	(16.5 ; 19.7)	317/2258	14.0	(12.6 ; 15.5)
		Grade 3	39/2270	1.7	(1.2 ; 2.3)	20/2258	0.9	(0.5 ; 1.4)
Headache	After any injection	Any	795/2419	32.9	(31.0 ; 34.8)	635/2403	26.4	(24.7 ; 28.2)
		Grade 3	98/2419	4.1	(3.3 ; 4.9)	57/2403	2.4	(1.8 ; 3.1)
	Post-dose 1	Any	553/2418	22.9	(21.2 ; 24.6)	418/2403	17.4	(15.9 ; 19.0)
		Grade 3	55/2418	2.3	(1.7 ; 3.0)	42/2403	1.7	(1.3 ; 2.4)
	Post-dose 2	Any	503/2270	22.2	(20.5 ; 23.9)	379/2258	16.8	(15.3 ; 18.4)
		Grade 3	50/2270	2.2	(1.6 ; 2.9)	21/2258	0.9	(0.6 ; 1.4)
Chills	After any injection	Any	428/2419	17.7	(16.2 ; 19.3)	297/2403	12.4	(11.1 ; 13.7)
		Grade 3	63/2419	2.6	(2.0 ; 3.3)	30/2403	1.2	(0.8 ; 1.8)
	Post-dose 1	Any	282/2418	11.7	(10.4 ; 13.0)	185/2403	7.7	(6.7 ; 8.8)
		Grade 3	32/2418	1.3	(0.9 ; 1.9)	18/2403	0.7	(0.4 ; 1.2)
	Post-dose 2	Any	254/2269	11.2	(9.9 ; 12.6)	166/2258	7.4	(6.3 ; 8.5)
		Grade 3	35/2269	1.5	(1.1 ; 2.1)	12/2258	0.5	(0.3 ; 0.9)
Arthralgia	After any injection	Any	556/2419	23.0	(21.3 ; 24.7)	393/2403	16.4	(14.9 ; 17.9)
		Grade 3	77/2419	3.2	(2.5 ; 4.0)	46/2403	1.9	(1.4 ; 2.5)
	Post-dose 1	Any	390/2418	16.1	(14.7 ; 17.7)	260/2403	10.8	(9.6 ; 12.1)
		Grade 3	44/2418	1.8	(1.3 ; 2.4)	34/2403	1.4	(1.0 ; 2.0)
	Post-dose 2	Any	326/2270	14.4	(12.9 ; 15.9)	229/2258	10.1	(8.9 ; 11.5)
		Grade 3	36/2270	1.6	(1.1 ; 2.2)	20/2258	0.9	(0.5 ; 1.4)

N: number of participants injected in each group. n: number of participants experiencing the endpoint. M: number of participants with available data for the relevant endpoint
Source: modified from 5.3.5.1 VAT00008 Stage 2 Brief Interim CSR, Section 8, Table 8.30B, 8.33B, 8.34B, 8.53B, 8.54B, and 8.55B.

Headache was the most frequently reported solicited systemic reaction after any injection in the vaccine group (32.9%) and placebo group (26.4%) followed by malaise (27.5 % in the vaccine and 21.0% in the placebo group), myalgia (25% in the vaccine group and 17.7% in the placebo group) and arthralgia (23 % in the vaccine group and 16.4% in the placebo group). Grade 3 headache, malaise, myalgia, arthralgia, and chills were reported at similar frequencies, ranging from 1.3% to 2.3%. There was no increase overall in reporting of grade 3 solicited systemic reactions after the second dose (4.3% versus 4%). The majority of solicited systemic reactions occurred within 3 days and resolved spontaneously within 1 to 3 days). 1.0% of participants or less per solicited reaction and per study group had systemic reactions still ongoing at D09 after any injection. The applicant has responded to questions raised for the D164 variant that "as unblinding was performed at treatment level and not at individual participant level it is not possible to assign individually events to the vaccine or placebo groups". That the unblinding is not performed down to individual level hampers the current safety evaluation also for the BV vaccine evaluated in VAT0008 stage 2 as it is not possible for most cases to identify which AE with narrative belonged to vaccinated or placebo group.

Study VAT00013

Solicited local ARs

In study VAT00013, within 7 days after a booster injection of MV (B.1.351) vaccine, in total 64 participants (80%) experienced at least one local AE. The most common reported local ARs were: pain as injection site reaction (77.5%), followed by edema or swelling (16.3), redness (11.3%) and itching (6.3%).

Table 59: Study VAT00013: Frequency of solicited injection site AEs within 7 days after a single booster dose with MV CoV2 preS dTM-AS03 (B.1.351) in adults ≥ 18 years of age

VAT00013	
Variable	CoV2 preS dTM-AS03 (B.1.351) N=80 n (%)
At least one local AE between D0 and D7	64 (80.0)
Pain	62 (77.5)
Grade 1	47 (58.8)
Grade 2	13 (16.3)
Grade 3	2 (2.5)
Redness	9 (11.3)
Grade 0	4 (5.0)
Grade 1	5 (6.3)
Grade 2	0 (0)
Grade 3	0 (0)
Edema or swelling	13 (16.3)
Grade 0	4 (5.0)
Grade 1	7 (8.8)
Grade 2	1 (1.3)
Grade 3	1 (1.3)
Itching	5 (6.3)
Mild	5 (6.3)
Moderate	0 (0)
Severe	0 (0)

Two scales were used for the classification of solicited AEs: 1) modified FDA scale (2007) (grade 0, grade 1, grade 2, grade 3, grade 4) and 2) WHO scale if the solicited AE was not present in the FDA scale (mild, moderate, severe).
The following solicited AEs were classified with the FDA scale: Pain, Swelling, Edema, redness
The following solicited AEs were classified with the WHO scale: Itching.
Source: modified from 5.3.5.1 VAT00013 Interim CSR, Table 14

Solicited systemic ARs

In study VAT00013, within 7 days after a booster injection of MV (B.1.351) vaccine, in total 50 (62.5%) participants presented at least one systemic AE. The most frequent systemic AEs reported in (40%) participants were asthenia/malaise, followed by headache (33.8%) and myalgia (23.8%).

Table 60: VAT00013 - Study VAT00013: Frequency of solicited systemic events within 7 days after a single booster dose with MV CoV2 preS dTM-AS03 (B.1.351) in adults ≥ 18 years of age

VAT00013	
Variable	CoV2 preS dTM-AS03 (B.1.351) N=80 n (%)
At least one solicited AE between D0 and D7	71 (88.8)
At least one systemic AE between D0 and D7	50 (62.5)
Asthenia or malaise	
No	48 (60.0)
Grade 0	1 (1.3)
Grade 1	20 (25.0)
Grade 2	9 (11.3)
Grade 3	2 (2.5)
Arthralgia	
No	76 (95.0)
Grade 1	2 (2.5)
Grade 2	2 (2.5)
Grade 3	0 (0)
Headaches	
No	53 (66.3)
Grade 1	17 (21.3)
Grade 2	6 (7.5)
Grade 3	4 (5.0)
Fever	
No	80 (100)
Grade 1	0 (0)
Grade 2	0 (0)
Grade 3	0 (0)
Chills	
No	70 (87.5)
Grade 1	9 (11.3)
Grade 2	1 (1.3)
Grade 3	0 (0)
Lymphadenopathy	
No	77 (96.3)
Grade 1	2 (2.5)
Grade 2	0 (0)
Grade 3	1 (1.3)
Myalgia	
No	61 (76.3)
Grade 1	11 (13.8)
Grade 2	7 (8.8)
Grade 3	1 (1.3)
Nausea	
No	76 (95.0)
Grade 1	3 (3.8)
Grade 2	1 (1.3)
Grade 3	0 (0)
Vomiting	
No	80 (100)
Grade 2	0 (0)
Diarrhea	
No	75 (93.8)
Mild	4 (5.0)
Moderate	1 (1.3)
Severe	0 (0)
Pain in the extremities	
No	77 (96.3)
Mild	2 (2.5)
Severe	1 (1.3)
Insomnia	
No	74 (92.5)
Mild	5 (6.3)
Moderate	0 (0)
Severe	1 (1.3)

Two scales were used for the classification of solicited AEs: 1) modified FDA scale (2007) (grade 0, grade 1, grade 2, grade 3, grade 4) and 2) WHO scale if the solicited AE was not present in the FDA scale (mild, moderate, severe).
The following solicited AEs were classified with the FDA scale: Arthralgia, Asthenia or Malaise, Headache, Fever, Chills, Lymphadenopathy, Myalgia, Nausea, Vomiting.
The following solicited AEs were classified with the FDA scale: Diarrhoea, Pain in the extremities, Insomnia.
Source: modified from 5.3.5.1 VAT00013 Interim CSR, Table 14

Study VAT00002 - Supplemental Phase III Cohort 2

Unsolicited AEs and ARs

There were no reports of immediate unsolicited AEs including unsolicited ARs after the booster injection of MV CoV2 preS dTM-AS03 (B.1.351) or BV CoV2 preS dTM-AS03 (D614 + B.1.351) vaccines.

Within 21 days after the booster injection of MV CoV2 preS dTM-AS03 (B.1.351) or BV CoV2 preS dTM-AS03 (D614 + B.1.351) vaccines, the overall proportion of participants who experienced at least one unsolicited AE was 23.1% and 24.8% respectively, with Grade 3 unsolicited AEs being 2.4% and 3.1%, respectively. The most frequently reported unsolicited AEs for the MV and BV vaccine groups were cough (4.4% and 5.3%, respectively), fatigue (4.1% and 3.7%, respectively), rhinorrhoea (3.7% and 3.5%, respectively), and headache (3.4% for both groups).

Participants 18-55 years of age experienced more unsolicited AEs (27.2%) than those aged ≥56 years (13.6%). The rates were comparable in frequency in each monovalent booster group with younger adults reporting more unsolicited AEs than older adults which was also observed for Grade 3 unsolicited AEs.

Participants without a high-risk medical condition reported a higher frequency of unsolicited AEs (28.3%) than participants with such conditions (19.5%).

Table 61: Study VAT00002 – Supplemental Phase III Cohort 2: Frequency of unsolicited AEs within 21 days after a single booster dose with MV CoV2 preS dTM-AS03 (B.1.351) or BV CoV2 preS dTM-AS03 (D614 + B.1.351) in ≥ 1.0% adults 18 years of age and older by priming vaccine platform

VAT00002 - Supplemental Phase III Cohort 2														
	mRNA Primed				Ad-vector Primed				Protein Primed		All Booster (All Priming Platforms)			
	MV (B.1.351) (N=489)		BV (D614 + B.1.351) (N=483)		MV (B.1.351) (N=138)		BV (D614 + B.1.351) (N=138)		MV (B.1.351) (N=78)		MV (B.1.351) (N=705)		BV (D614 + B.1.351) (N=621)	
Participants experiencing at least one:	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)
Blood and lymphatic system disorders														
Lymphadenopathy	4/489	0.8 (0.2 ; 2.1)	3/483	0.6 (0.1 ; 1.8)	1/138	0.7 (0 ; 4.0)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	5/705	0.7 (0.2 ; 1.6)	5/621	0.8 (0.3 ; 1.9)
Ear and labyrinth disorders														
Tinnitus	0/489	0 (0 ; 0.8)	0/483	0 (0 ; 0.8)	1/138	0.7 (0 ; 4.0)	0/138	0 (0 ; 2.6)	1/78	1.3 (0 ; 6.9)	2/705	0.3 (0 ; 1.0)	0/621	0 (0 ; 0.6)
Gastrointestinal disorders														
Abdominal pain	3/489	0.6 (0.1 ; 1.8)	5/483	1.0 (0.3 ; 2.4)	2/138	1.4 (0.2 ; 5.1)	0/138	0 (0 ; 2.6)	0/78	0 (0 ; 4.6)	5/705	0.7 (0.2 ; 1.6)	5/621	0.8 (0.3 ; 1.9)
Diarrhoea	8/489	1.6 (0.7 ; 3.2)	12/483	2.5 (1.3 ; 4.3)	3/138	2.2 (0.5 ; 6.2)	0/138	0 (0 ; 2.6)	0/78	0 (0 ; 4.6)	11/705	1.6 (0.8 ; 2.8)	12/621	1.9 (1.0 ; 3.4)
Nausea	11/489	2.2 (1.1 ; 4.0)	9/483	1.9 (0.9 ; 3.5)	2/138	1.4 (0.2 ; 5.1)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	13/705	1.8 (1.0 ; 3.1)	11/621	1.8 (0.9 ; 3.1)
Noninfective gingivitis	0/489	0 (0 ; 0.8)	0/483	0 (0 ; 0.8)	0/138	0 (0 ; 2.6)	0/138	0 (0 ; 2.6)	1/78	1.3 (0 ; 6.9)	1/705	0.1 (0 ; 0.8)	0/621	0 (0 ; 0.6)
General disorders and administration site conditions														
Chills	3/489	0.6 (0.1 ; 1.8)	5/483	1.0 (0.3 ; 2.4)	2/138	1.4 (0.2 ; 5.1)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	5/705	0.7 (0.2 ; 1.6)	7/621	1.1 (0.5 ; 2.3)
Fatigue	25/489	5.1 (3.3 ; 7.5)	17/483	3.5 (2.1 ; 5.6)	4/138	2.9 (0.8 ; 7.3)	6/138	4.3 (1.6 ; 9.2)	0/78	0 (0 ; 4.6)	29/705	4.1 (2.8 ; 5.9)	23/621	3.7 (2.4 ; 5.5)
Influenza like illness	0/489	0 (0 ; 0.8)	1/483	0.2 (0 ; 1.1)	0/138	0 (0 ; 2.6)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	0/705	0 (0 ; 0.5)	3/621	0.5 (0.1 ; 1.4)
Injection site pruritus	5/489	1.0 (0.3 ; 2.4)	5/483	1.0 (0.3 ; 2.4)	0/138	0 (0 ; 2.6)	1/138	0.7 (0 ; 4.0)	0/78	0 (0 ; 4.6)	5/705	0.7 (0.2 ; 1.6)	6/621	1.0 (0.4 ; 2.1)
Malaise	4/489	0.8 (0.2 ; 2.1)	6/483	1.2 (0.5 ; 2.7)	1/138	0.7 (0 ; 4.0)	1/138	0.7 (0 ; 4.0)	1/78	1.3 (0 ; 6.9)	6/705	0.9 (0.3 ; 1.8)	7/621	1.1 (0.5 ; 2.3)
Non-cardiac chest pain	1/489	0.2 (0 ; 1.1)	0/483	0 (0 ; 0.8)	0/138	0 (0 ; 2.6)	3/138	2.2 (0.5 ; 6.2)	0/78	0 (0 ; 4.6)	1/705	0.1 (0 ; 0.8)	3/621	0.5 (0.1 ; 1.4)
Pyrexia	1/489	0.2 (0 ; 1.1)	3/483	0.6 (0.1 ; 1.8)	1/138	0.7 (0 ; 4.0)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	2/705	0.3 (0 ; 1.0)	5/621	0.8 (0.3 ; 1.9)
Infections and infestations														
COVID-19	7/489	1.4 (0.6 ; 2.9)	8/483	1.7 (0.7 ; 3.2)	1/138	0.7 (0 ; 4.0)	0/138	0 (0 ; 2.6)	0/78	0 (0 ; 4.6)	8/705	1.1 (0.5 ; 2.2)	8/621	1.3 (0.6 ; 2.5)
Gastroenteritis	1/489	0.2 (0 ; 1.1)	3/483	0.6 (0.1 ; 1.8)	0/138	0 (0 ; 2.6)	0/138	0 (0 ; 2.6)	1/78	1.3 (0 ; 6.9)	2/705	0.3 (0 ; 1.0)	3/621	0.5 (0.1 ; 1.4)
Lower respiratory tract infection	0/489	0 (0 ; 0.8)	0/483	0 (0 ; 0.8)	0/138	0 (0 ; 2.6)	0/138	0 (0 ; 2.6)	1/78	1.3 (0 ; 6.9)	1/705	0.1 (0 ; 0.8)	0/621	0 (0 ; 0.6)
Nasopharyngitis	1/489	0.2 (0 ; 1.1)	1/483	0.2 (0 ; 1.1)	1/138	0.7 (0 ; 4.0)	2/138	1.4 (0.2 ; 5.1)	2/78	2.6 (0.3 ; 9.0)	4/705	0.6 (0.2 ; 1.4)	3/621	0.5 (0.1 ; 1.4)
Pharyngitis	12/489	2.5 (1.3 ; 4.2)	9/483	1.9 (0.9 ; 3.5)	4/138	2.9 (0.8 ; 7.3)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	16/705	2.3 (1.3 ; 3.7)	11/621	1.8 (0.9 ; 3.1)
Upper respiratory tract infection	3/489	0.6 (0.1 ; 1.8)	3/483	0.6 (0.1 ; 1.8)	0/138	0 (0 ; 2.6)	0/138	0 (0 ; 2.6)	2/78	2.6 (0.3 ; 9.0)	5/705	0.7 (0.2 ; 1.6)	3/621	0.5 (0.1 ; 1.4)
Urinary tract infection	3/489	0.6 (0.1 ; 1.8)	0/483	0 (0 ; 0.8)	0/138	0 (0 ; 2.6)	0/138	0 (0 ; 2.6)	1/78	1.3 (0 ; 6.9)	4/705	0.6 (0.2 ; 1.4)	0/621	0 (0 ; 0.6)
Injury, poisoning and procedural complications														
Lower limb fracture	0/489	0 (0 ; 0.8)	0/483	0 (0 ; 0.8)	0/138	0 (0 ; 2.6)	0/138	0 (0 ; 2.6)	1/78	1.3 (0 ; 6.9)	1/705	0.1 (0 ; 0.8)	0/621	0 (0 ; 0.6)
Musculoskeletal and connective tissue disorders														
Arthralgia	5/489	1.0 (0.3 ; 2.4)	2/483	0.4 (0.1 ; 1.5)	1/138	0.7 (0 ; 4.0)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	6/705	0.9 (0.3 ; 1.8)	4/621	0.6 (0.2 ; 1.6)
Back pain	6/489	1.2 (0.5 ; 2.7)	3/483	0.6 (0.1 ; 1.8)	1/138	0.7 (0 ; 4.0)	1/138	0.7 (0 ; 4.0)	0/78	0 (0 ; 4.6)	7/705	1.0 (0.4 ; 2.0)	4/621	0.6 (0.2 ; 1.6)
Myalgia	8/489	1.6 (0.7 ; 3.2)	4/483	0.8 (0.2 ; 2.1)	2/138	1.4 (0.2 ; 5.1)	1/138	0.7 (0 ; 4.0)	0/78	0 (0 ; 4.6)	10/705	1.4 (0.7 ; 2.6)	5/621	0.8 (0.3 ; 1.9)
Pain in extremity	0/489	0 (0 ; 0.8)	2/483	0.4 (0.1 ; 1.5)	0/138	0 (0 ; 2.6)	3/138	2.2 (0.5 ; 6.2)	0/78	0 (0 ; 4.6)	0/705	0 (0 ; 0.5)	5/621	0.8 (0.3 ; 1.9)
Nervous system disorders														
Ageusia	0/489	0 (0 ; 0.8)	2/483	0.4 (0.1 ; 1.5)	0/138	0 (0 ; 2.6)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	0/705	0 (0 ; 0.5)	4/621	0.6 (0.2 ; 1.6)
Anosmia	0/489	0 (0 ; 0.8)	2/483	0.4 (0.1 ; 1.5)	0/138	0 (0 ; 2.6)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	0/705	0 (0 ; 0.5)	4/621	0.6 (0.2 ; 1.6)
Dizziness	1/489	0.2 (0 ; 1.1)	2/483	0.4 (0.1 ; 1.5)	1/138	0.7 (0 ; 4.0)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	2/705	0.3 (0 ; 1.0)	4/621	0.6 (0.2 ; 1.6)
Headache	17/489	3.5 (2.0 ; 5.5)	20/483	4.1 (2.5 ; 6.3)	7/138	5.1 (2.1 ; 10.2)	1/138	0.7 (0 ; 4.0)	0/78	0 (0 ; 4.6)	24/705	3.4 (2.2 ; 5.0)	21/621	3.4 (2.1 ; 5.1)
Trigeminal neuralgia	0/489	0 (0 ; 0.8)	0/483	0 (0 ; 0.8)	0/138	0 (0 ; 2.6)	0/138	0 (0 ; 2.6)	1/78	1.3 (0 ; 6.9)	1/705	0.1 (0 ; 0.8)	0/621	0 (0 ; 0.6)
Respiratory, thoracic and mediastinal disorders														
Cough	21/489	4.3 (2.7 ; 6.5)	25/483	5.2 (3.4 ; 7.5)	8/138	5.8 (2.5 ; 11.1)	8/138	5.8 (2.5 ; 11.1)	2/78	2.6 (0.3 ; 9.0)	31/705	4.4 (3.0 ; 6.2)	33/621	5.3 (3.7 ; 7.4)
Dyspnoea	1/489	0.2 (0 ; 1.1)	1/483	0.2 (0 ; 1.1)	1/138	0.7 (0 ; 4.0)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	2/705	0.3 (0 ; 1.0)	3/621	0.5 (0.1 ; 1.4)
Nasal congestion	11/489	2.2 (1.1 ; 4.0)	9/483	1.9 (0.9 ; 3.5)	5/138	3.6 (1.2 ; 8.3)	4/138	2.9 (0.8 ; 7.3)	1/78	1.3 (0 ; 6.9)	17/705	2.4 (1.4 ; 3.8)	13/621	2.1 (1.1 ; 3.6)
Oropharyngeal pain	15/489	3.1 (1.7 ; 5.0)	5/483	1.0 (0.3 ; 2.4)	5/138	3.6 (1.2 ; 8.3)	4/138	2.9 (0.8 ; 7.3)	0/78	0 (0 ; 4.6)	20/705	2.8 (1.7 ; 4.3)	9/621	1.4 (0.7 ; 2.7)
Rhinorrhoea	19/489	3.9 (2.4 ; 6.0)	20/483	4.1 (2.5 ; 6.3)	6/138	4.3 (1.6 ; 9.2)	2/138	1.4 (0.2 ; 5.1)	1/78	1.3 (0 ; 6.9)	26/705	3.7 (2.4 ; 5.4)	22/621	3.5 (2.2 ; 5.3)
Skin and subcutaneous tissue disorders														
Blister	0/489	0 (0 ; 0.8)	0/483	0 (0 ; 0.8)	0/138	0 (0 ; 2.6)	0/138	0 (0 ; 2.6)	1/78	1.3 (0 ; 6.9)	1/705	0.1 (0 ; 0.8)	0/621	0 (0 ; 0.6)
Rash	4/489	0.8 (0.2 ; 2.1)	1/483	0.2 (0 ; 1.1)	0/138	0 (0 ; 2.6)	2/138	1.4 (0.2 ; 5.1)	0/78	0 (0 ; 4.6)	4/705	0.6 (0.2 ; 1.4)	3/621	0.5 (0.1 ; 1.4)
Vascular disorders														
Peripheral venous disease	0/489	0 (0 ; 0.8)	0/483	0 (0 ; 0.8)	0/138	0 (0 ; 2.6)	0/138	0 (0 ; 2.6)	1/78	1.3 (0 ; 6.9)	1/705	0.1 (0 ; 0.8)	0/621	0 (0 ; 0.6)

N: number of participants in each group; n: number of participants experiencing the endpoint; M: number of participants with available data for the relevant endpoint

Prior prime vaccination platform: mRNA = mRNA. Ad-vector = adenovirus-vectored

Source: modified from 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Section 8, Table 8.51.

Within 21 days after the booster injection of VidPrevtyn Beta or BV CoV2 preS dTM-AS03 (D614 + B.1.351) vaccines, the overall proportion of participants who experienced at least one unsolicited AR was 7.1% and 7.9%, respectively. The most frequently reported unsolicited AR for the MV and BV vaccine groups was fatigue (2.0% and 1.4%, respectively). Thereafter followed for the MV vaccine nausea (1.3%), injection site pruritus (0.7%), lymphadenopathy (0.6%) and diarrhoea (0.6%). For the BV vaccine followed injection site pruritus (1.0%), nausea (0.8%) and lymphadenopathy (0.8%).

4/705 (0.6%) and 2/621 (0.3%) in the MV and BV booster groups, respectively reported grade 3 unsolicited ARs.

Most unsolicited AEs and ARs occurred mainly within 3 days after injection, were mainly of Grade 1 or Grade 2 intensity, and resolved within 7 days or less. Nevertheless, 4/705 (0.6%) and 7/621 (1.1%) participants in the MV and BV vaccine groups respectively, had ARs with duration of 8 days of more.

As regards duration of grade 3 unsolicited AEs, 8/705 (1.1%) and 6/621 (1.0%) in the MV and BV booster groups reported an event with duration 8 days or more. For unsolicited ADRs 1/705 (0.1%) and 0/621 in the MV and BV booster groups, had a duration of 8 days or more.

Most grade 3 unsolicited AEs resolved within 7 days following injection in both the MV and BV vaccine groups. 8/705 (1.1%) and 6/621 (1.0%) in the MV and BV booster groups reported a grade 3 event with duration 8 days or more. The duration of most grade 3 unsolicited ARs was 1-3 days. For unsolicited ARs 1/705 (0.1%) and 0/621 in the MV and BV booster groups, had a duration of 8 days or more.

No participant in the booster groups had an AE/AR that lead to discontinuation.

Medically Attended Adverse Events (MAAE)

In the MV (B.1.351) booster group, 23 participants reported 27 MAAEs up to 21 days after booster injection, The proportion of participants was highest in the mRNA platform primed groups (15 participants, 17 MAAEs), followed by the Protein primed group (5 total participants, 7 total MAAEs), and the Ad-vector platform primed groups (3 total participants, 3 total MAAEs). "Infections and infestations" was the SOC in which the highest number of participants (11) reported a total of 11 MAAEs. Three participants experienced in total 5 MAAEs that were assessed as related to the investigational product. The related events were all recovered/resolved. The MAAEs considered related were tinnitus, arthralgia, myalgia, headache and eczema.

In the BV (D614 + B.1.351) Booster Groups, 20 participants (all in the mRNA platform primed groups) reported 36 MAAEs up to 21 days after booster. The group that reported the highest number of MAAEs was the Pfizer/BioNTech primed group with 16 participants reporting 32 total MAAEs. Overall, "Infections and infestations" was the SOC in which the highest number of participants (10) reported a total of 11 MAAEs. One participant, in the Moderna primed group, experienced 1 MAAE (serum sickness-like reaction) that was assessed as related to the investigational product. The related event resolved.

Adverse events of special interest according to study protocol

The list of AESI used in the clinical study diverged significantly from the list of AESIs that will be used post-marketing.

AESIs according to the clinical study protocol include anaphylactic reactions, generalized convulsion, myocarditis, pericarditis, thrombocytopenia, thrombosis with Thrombocytopenia Syndrome and pIMDs (potential immune-mediated diseases). A listing of pIMDs of special interest was made available.

The Applicant reported:

- One protein-primed participant receiving MV (B.1.351) booster experienced trigeminal neuralgia that was assessed as unrelated to the study vaccine by the investigator. Outcome: resolving

  The participant presented with neuralgia and tinnitus one day after booster injection. The symptoms started after a dental procedure. A neurologist diagnosed the patient with trigeminal neuralgia. It was reported that the event was probably due to aging (age above 75) and a maxillofacial problem. The patient's medical history included neuralgia in the face treated with pregabalin without improvement.

- One case of anaphylaxis in the BV (B.1.351 + D614) booster group was reported as an AESI. This case was considered not related (allergic reaction to egg 5 months after vaccination).

No pIMDs were reported for the MV and BV vaccine.

AESIs according to the RMP list that will be used postmarketing: Guillain-Barre syndrome, acute disseminated encephalomyelitis transversal myelitis, bell's palsy, narcolepsy, acute aseptic arthritis, rheumatoid arthritis, type 1 diabetes, (idiopathic) thrombocytopenia, microangiopathy (including thrombotic microangiopathy), heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis/pericarditis, single organ cutaneous vasculitis, disseminated intravascular coagulation, venous thromboembolism (including pulmonary embolism and deep vein thrombosis), haemorrhagic stroke, ischemic stroke, cerebral venous sinus thrombosis, thrombotic thrombocytopenia syndrome, thrombotic thrombocytopenia purpura, acute liver injury, acute kidney injury including glomerulonephritis, generalized convulsion, meningoencephalitis, acute respiratory distress syndrome, erythema multiforme, chilblain – like lesions, anosmia, ageusia, anaphylaxis, multisystem inflammatory syndrome, death (any cause), Coronavirus disease – 201/VAED, subacute thyroiditis, autoimmune thyroiditis, acute pancreatitis, autoimmune pancreatitis, Kawasaki's disease, appendicitis and eye disorders.

- 27 participants reported AESI from the RMP list in the MV (B.1.351) group (3.8%). None of them were assessed as related.
- 29 participants reported AESI form the RMP list in the BV (D614+B.1.351) group (4.7%). One of them was considered as related, a non-serious case of chilblains in a 20-29-year-old. He experienced chilblains (Grade 1) 21 days after vaccination. The participant recovered from the event after 13 days without any action taken.

In both groups, the most frequently reported events were COVID-19 (19 out 21 in the MV (B.1.351) vaccine. group, 22 out 27 in the BV (D614 + B.1.351) vaccine group).

Study VAT00008 – Stage 2

Unsolicited AEs and ARs

There were 11 immediate unsolicited AEs reported by a total of 11 participants (4 in the BV CoV2 preS dTM-AS03 [D614 + B.1.351] vaccine group and 7 in the placebo group) after any injection. Eight participants reported immediate unsolicited AEs after the first injection, and 3 participants after the second injection. All immediate unsolicited AEs were non-serious events. Four (< 0.1%) participants in the vaccine group and 6 (< 0.1%) participants in the placebo group reported immediate events that were assessed as related to the vaccine/procedure. No event was of Grade 3 intensity.

Within 21 days after any injection, the proportion of participants who reported at least 1 unsolicited AE was 6.3% for the vaccine group and 8.1% for the placebo group. No participants reported Grade 3 unsolicited AEs within this time period. The proportion of participants who reported at least 1 unsolicited AE after the first injection was 4.0% in the vaccine group and 4.7% in the placebo group. The proportion of participants who reported at least 1 unsolicited AE after the second injection was 3.4% in the vaccine group and 4.4% in the placebo group.

Participants ≥ 65 years of age (9.6% for the vaccine group and 9.2% in the placebo group) reported unsolicited AEs more frequently than participants 18 to 64 years of age (6.1% for the vaccine group and 8.0% for the placebo group).

Within 21 days after any injection, the proportion of participants who reported at least 1 unsolicited AE was slightly higher in naïve participants in both the vaccine and placebo groups (7.8% and 10.8%, respectively) compared to non-naïve participants (6.3% and 7.8%, respectively).

Among participants with a high-risk medical condition, those in the vaccine group reported a slightly lower frequency of unsolicited AEs than participants in the placebo group (7.7% and 10.4%, respectively). Across both study intervention groups, participants without a high-risk medical condition reported a lower frequency of unsolicited AEs than those with a high-risk medical condition.

When comparing the unsolicited AE frequencies from VAT0008 stage 2 BV (D614 + B.1.135) primary vaccination indication to the MV booster (B.1.135) in VAT0002 supplemental phase III cohort 2 the frequencies where much lower in the primary vaccination scheme in VAT00008 in line with what was also seen for MV D164 vaccine that was evaluated in VAT0008 stage one. Difference in study design (placebo versus no use of placebo group), difference in serostatus and differences in participating countries (different geographical regions) may have played a role for the observed discrepancies.

The reporting frequencies of AE varied for different races in VAT0008 for vaccinated and placebo recipients respectively: Asian participants (0.8% and 2%), Black or African American participants (8.8% and 10.7%), American Indian or Alaska Native participants (5.9% and 16.7%) and White participants (50% and 35.7%).

The same tendency is seen for VAT0008 stage 2 that the AE frequency in the white population is much higher than for the other races as seen for VAT00008 stage 1. However, only a small number of white participants was included in VAT0008 stage 1 and 2.

The frequency of participants reporting unsolicited ARs within 21 days after any injection was low, with 19 (0.8%) participants in the vaccine group experiencing 28 unsolicited ARs and 16 (0.7%) participants in the placebo group experiencing 25 unsolicited ARs.

Table 62: Study VAT00008 – Stage 2: Frequency of unsolicited adverse reactions within 21 days after any injection with CoV2 preS dTM-AS03 (D614 + B.1.351) in adults 18 years of age and older

	VAT00008 - Stage 2							
	BV (D614 + B.1.351) 10 µg + AS03 (N=2433)				Placebo (N=2418)			
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n ARs**	**n/M**	**%**	**(95% CI)**	**n ARs**
General disorders and administration site conditions								
Local reactions								
Injection site erythema	1/2433	<0.1	(0 ; 0.2)	1	0/2418	0	(0 ; 0.2)	0
Injection site pain	2/2433	<0.1	(0 ; 0.3)	2	0/2418	0	(0 ; 0.2)	0
Injection site swelling	1/2433	<0.1	(0 ; 0.2)	1	0/2418	0	(0 ; 0.2)	0
Systemic reactions								
Fatigue	1/2433	<0.1	(0 ; 0.2)	1	0/2418	0	(0 ; 0.2)	0
Eye disorders								
Vision blurred	1/2433	<0.1	(0 ; 0.2)	1	0/2418	0	(0 ; 0.2)	0
Gastrointestinal disorders								
Diarrhoea	1/2433	<0.1	(0 ; 0.2)	1	1/2418	<0.1	(0 ; 0.2)	1
Nausea	1/2433	<0.1	(0 ; 0.2)	1	0/2418	0	(0 ; 0.2)	0
Vomiting	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1
Immune system disorders								
Anaphylactic reaction	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1
Infections and infestations								
Nasopharyngitis	1/2433	<0.1	(0 ; 0.2)	1	1/2418	<0.1	(0 ; 0.2)	2
Suspected COVID-19	11/2433	0.5	(0.2 ; 0.8)	19	6/2418	0.2	(0.1 ; 0.5)	6
Metabolism and nutrition disorders								
Decreased appetite	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1
Musculoskeletal and connective tissue disorders								
Arthralgia	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	2
Back pain	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1
Nervous system disorders								
Ageusia	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1
Anosmia	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1
Dizziness	0/2433	0	(0 ; 0.2)	0	4/2418	0.2	(0 ; 0.4)	4
Headache	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1
Respiratory, thoracic and mediastinal disorders								
Cough	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1
Oropharyngeal pain	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1
Skin and subcutaneous tissue disorders								
Pruritus	0/2433	0	(0 ; 0.2)	0	1/2418	<0.1	(0 ; 0.2)	1

n: number of participants experiencing the endpoint. M: number of participants with available data for the relevant age group
n ARs: number of ARs
Source: modified from 5.3.5.1 VAT00008 Stage 2 Brief Interim CSR, Section 8, Table 8.80B

Medically attended adverse events (MAAEs)

Up to the analysis cut-off date, the proportion of participants who reported at least 1 MAAE was similar in both treatment groups. A total of 751 participants (366 in the Vaccine Group and 385 in the Placebo Group) reported 1121 MAAEs (560 in the Vaccine Group and 561 in the Placebo Group). Among these, 18 participants reported at least 1 MAAE assessed as related to study intervention (11 in the Vaccine Group, 7 in the Placebo Group). No related MAAE was assessed as serious.

Related MAAE was 13 in the vaccine group and 8 in the Placebo Group.

Table 63: Related MAAEs up to analysis cut-off date, by system organ class and preferred term - SafAS - Stage 2

	Vaccine	Placebo
All	**13**	**8**
Injection site pain	2	2
Drug hypersensitivity	2	
Arthralgia	1	
Myalgia	2	
Dizziness	1	
Headache	3	3
Nasal congestion	1	
Pruritus	1	
Eye pruritus		1
Diarrhoea		2

There was one case of heavy menstrual bleeding reported in the vaccinated group in VAT0008 stage 2 that was medically attended evaluated to be not related. The case described a woman in her 30s that experienced heavy menstrual bleeding 10 days after first vaccine dose, and the event lasted for approximately 2 months and required medical attention and medication. Heavy menstrual bleeding is newly identified as an ADR after vaccination with two other COVID-19 vaccines (Comirnaty and Spikevax). As the mechanisms is still not clear this could potentially be relevant for Vidprevtyn Beta also. However, the data from the clinical studies is too limited to draw any conclusion and the applicant has been asked to follow heavy menstrual bleedings in summary safety reports.

Adverse events of special interest according to study protocol

The list of AESI used in the clinical study diverged significantly from the list of AESIs that will be used post-marketing.

AESIs include anaphylactic reactions, generalized convulsion, myocarditis, pericarditis, thrombocytopenia, thrombosis with Thrombocytopenia Syndrome and pIMDs (potential immune-mediated diseases). A listing of pIMDs of special interest was made available.

Up to the analysis cut-off date, when the AESI list according to the clinical study protocol was used, a total of 2 participants (1 [< 0.1%] in the BV CoV2 preS dTM-AS03 [D614 + B.1.351] vaccine group and 1 [< 0.1%] in the placebo group) reported a total of 3. 2 AESIs were reported in 1 participant (alcoholic seizure and seizure) and alcoholic seizure was reported for another participant. None of the AESIs were assessed as related to the study intervention.

There were no potentially immune-mediated medical conditions or diseases (pIMDs) reported.

AESIs according to the RMP list that will be used postmarketing: Guillain-Barre syndrome, acute disseminated encephalomyelitis transversal myelitis, bell's palsy, narcolepsy, acute aseptic arthritis, rheumatoid arthritis, type 1 diabetes, (idiopathic) thrombocytopenia, microangiopathy (including thrombotic microangiopathy), heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis/pericarditis, single organ cutaneous vasculitis, disseminated intravascular coagulation, venous thromboembolism (including pulmonary embolism and deep vein thrombosis), haemorrhagic stroke, ischemic stroke, cerebral venous sinus thrombosis, thrombotic thrombocytopenia syndrome, thrombotic thrombocytopenia purpura, acute liver injury, acute kidney injury including glomerulonephritis, generalized convulsion, meningoencephalitis, acute respiratory distress syndrome,

erythema multiforme, chilblain – like lesions, anosmia, ageusia, anaphylaxis, multisystem inflammatory syndrome, death (any cause), Coronavirus disease – 201/VAED, subacute thyroiditis, autoimmune thyroiditis, acute pancreatitis, autoimmune pancreatitis, Kawasaki's disease, appendicitis and eye disorders.

For primary vaccination 103 participants reported an AESIs: 1 acute respiratory distress, 80 COVID-19 related cases, 13 conjunctivitis, 4 arthritis, 2 conjunctivitis allergic, 2 seizure, 1 eye pain, 1 Lacrimation increased, and 1 vision blurred. AESIs was reported by 99 participants in the placebo group: 1 Hepatic failure, anaphylactic reaction, 93 COVID-19 cases, 1 diabetes mellitus, 2 arthritis, 1 Azotaemia, 5 conjunctivitis, 3 conjunctivitis allergic, 1 eye pain, 2 Lacrimation increased, 1 eye pruritus, 1 hordeolum. One case of vision blurred, and 19 cases of suspected COVID-19 was listed as related.

Study VAT00013

Unsolicited AEs and ARs

Unsolicited adverse events were collected within 28 days after MV CoV2 preS dTM-AS03 (B.1.351) booster vaccination. 29 (36.3%) participants reported at least 1 unsolicited AE, and in total 40 unsolicited AE were reported for (B.1.351). The unsolicited AEs were of Grade 1 / Grade 2 intensity or mild / moderate intensity.

Table 64: Study VAT00013: Unsolicited adverse events by preferred term for the three groups

Preferred terms	Pfizer/BioNTech	MV CoV2 preS dTM-AS03 (5 µg B.1.351)	MV CoV2 preS dTM-AS03 (5 µg D614)	Total
Cough	1	1	5	7
Rhinitis	2	1	3	6
Oropharyngeal pain	2	1	2	5
Odynophagia		3	1	4
Rhinorrhea			4	4
Abdominal pain upper		2	1	3
Back pain	1	1	1	3
Dyspepsia	1	1	1	3
Eczema	2	1		3
Gastroenteritis	2	1		3
Influenza like illness		2	1	3
Pyrexia	1	1	1	3
Abdominal pain		1	1	2
Bronchitis	1	1		2
Conjunctivitis			2	2
Dysmenorrhea	1		1	2
Dyspnea	1		1	2
Feeling hot	1		1	2
Food poisoning	2			2
Hemorrhoids	1	1		2
Hot flush		2		2
Injection site hemorrhage	1	1		2
Ligament sprain	1		1	2
Limb discomfort	1	1		2
Nasopharyngitis		2		2
Paresthesia	1	1		2
Vertigo	1		1	2
Total	46	40	40	126

There were 14 AEs evaluated as related to MV CoV2 preS dTM-AS03 (B.1.351) booster vaccination, all of them were mild to moderate, 13 recovered within 6 days, and one case of hypertension, starting 5 days post booster administration, was reported as ongoing at D28.

14 events assessed as related to the MV CoV2 preS dTM-AS03 (D614) booster vaccine, all of them were mild to moderate, 12 recovered within 10 days, and 2 events were reported as unchanged at D28 (Moderate neck pain case starting 2 days post booster administration and moderate musculoskeletal pain starting 13 days post booster administration).

15 events assessed as related to the Pfizer/BioNTech booster vaccine, all were mild to moderate and most of them resolved within 10 days.

Table 65: VAT00013 - Unsolicited events reported within 28 days after a single booster dose with MV CoV2 preS dTM-AS03 (B.1.351) in adults 18 years of age and older, by system organ class and preferred term

SOC/PT	Number of events
Eye disorders	**1**
Eye pain	1
Gastrointestinal disorders	**11**
Abdominal discomfort	1
Abdominal pain	1
Abdominal pain upper	2
Dyspepsia	1
Gastrooesophageal reflux disease	1
Glossitis	1
Haemorrhoids	1
Odynophagia	3
General disorders and administration site conditions	**4**
Influenza like illness	2
Injection site haemorrhage	1
Pyrexia	1
Infections and infestations	**8**
Bronchitis	1
Gastroenteritis	1
Hordeolum	1
Nasopharyngitis	2
Rhinitis	1
Tonsillitis	1
Tonsillitis bacterial	1
Musculoskeletal and connective tissue disorders	**3**
Back pain	1
Limb discomfort	1
Pain in extremity	1
Nervous system disorders	**2**
Hypoaesthesia	1
Paraesthesia	1
Reproductive system and breast disorders	**2**
Menstrual disorder	1
Premenstrual pain	1
Respiratory, thoracic and mediastinal disorders	**3**
Cough	1
Nasal inflammation	1
Oropharyngeal pain	1
Skin and subcutaneous tissue disorders	**2**
Acne	1
Eczema	1
Vascular disorders	**4**
Haematoma	1
Hot flush	2
Hypertension	1
Total	**40**

Medically attended adverse events (MAAEs)

Medically attended AEs (MAAEs) were not specifically reported as such during this study, as described in the clinical study protocol. Four events required generalist physician contact, however none of the non-serious AEs led to hospitalization.

Cases evaluated to be related for B.1.351 booster was Hypertension, abdominal discomfort, nasal inflammation grade 1, hot flush x 2, premenstrual pain, eczema, Pyrexia, pain in the extremity, Injection site haemorrhage, Haematoma, paresthesia, Hypoaesthesia, menstrual disorder.

Cases evaluated to be related for D614 booster: Dry mouth, cough, Influenza like illness, Rhinorrhoea, Oropharyngeal pain, withdrawal bleed, Dizziness, Vertigo, Odynophagia, pyrexia, neck pain, feeling hot, musculoskeletal pain, and nasal dryness.

Cases evaluated to be related for Pfizer-BioNTech vaccine: Cough, Blepharospasm, foreign body sensation in eyes, lymphopenia, blepharitis, vaginal haemorrhage, injection site haemorrhage, menstruation delayed, paraesthesia, hyperhidrosis, feeling hot, pyrexia, chest discomfort, Heavy menstrual bleeding, and Gastroenteritis.

Adverse events of special interest

For VAT00013 two AESI were reported: 1 related case of "flare-up of rheumatoid arthritis" and one case of "mild eye pain", assessed as not related by the investigator.

Pooled safety analyses

The Applicant presents the following pooled treatment groups for the pooled safety analysis:

a) 5µg MV(B.1.351) Booster: all participants receiving one injection of 5 µg CoV2 preS dTM-AS03 MV(B.1.351) antigen in Study VAT00002 Supplemental Cohort 2 Main Arms (Exploratory Arms excluded)

b) 5µg BV(D614+B.1.351) Booster: all participants receiving one injection of 5 µg CoV2 preS dTM-AS03 BV(D614+B.1.351) antigen in Study VAT00002 Supplemental Cohort 2 Main Arms

c) Pooled Booster: all participants receiving one injection of 5 µg CoV2 preS dTM-AS03 MV (B.1.351) or BV(D614+B.1.351) antigen in Study VAT00002 Supplemental Cohort 2 Main Arms

d) 10µg BV(D614+B.1.351): all participants receiving at least one injection of 10 µg CoV2 preS dTM-AS03 BV(D614+B.1.351) antigen as primary series in Study VAT00008 Stage 2

e) Total B.1.351 Vaccine: a combined group of all participants receiving at least one injection of CoV2 preS dTM-AS03 vaccine as a booster of 5µg MV (B.1.351) or 5µg BV (D614+B.1.351) antigen in Study VAT00002 Supplemental Cohort 2 Main Arms or as primary series of 10 µg CoV2 preS dTM-AS03 BV(D614+B.1.351) antigen in Study VAT00008 Stage 2

f) Placebo: the group of participants receiving at least one injection of placebo over the course of Study VAT00008 Stage 2

VAT00013 has not been included in any pool based on the following reasons:

- solicited reactions follow up time were not the same, 21 days for VAT00002 and VAT00008 versus 28 days in VAT000013,
- self-reported diary cards were not used in VAT00013.
- For VAT00002 and VAT00008 the FDA scale was used for registering solicited AEs. VAT00013 also used the FDA scale, but it was supplemented with the WHO scale for symptoms not

present in the FDA scale. Accordingly, the list of solicited symptoms was more comprehensive for this study.

Based on the differences above the applicant has not used the safety data from VAT00013 to support the safety profile described in the SmPC.

In VAT00008, reactogenicity (solicited reactions and unsolicited adverse events up to 21 days after vaccination) was only captured in the reactogenicity subset (n=2433) which is a subset of the Safety Analysis Set (SafAS).In VAT00002 reactogenicity was captured in the entire SafAS. Interpretation of results compared across the pooled treatment groups needs to take this study design into account. When using the complete SafAS when pooling data from VAT00008 and VAT00002, frequencies of AEs will be underestimated.

A total of 7798 participants received at least 1 dose of a vaccine containing CoV2 preS dTM AS03 (B.1.351) in a monovalent or bivalent formulation.

Among these participants:

- 705 participants received a single booster dose of 5 µg MV CoV2 preS dTM AS03 (B.1.351) vaccine. Safety follow up time was at least 2 months for 610 participants.
- 621 participants received a single booster dose of 5 µg BV CoV2 preS dTM AS03 (D614+B.1.351) vaccine. Safety follow up time was at least 2 months for 546 participants.
- 6472 participants received at least 1 dose of 10 µg BV CoV2 preS dTM AS03 (D614+B.1.351) vaccine as a primary series. Safety follow up time was at least 2 months for 2731 of the participants.

In addition, 6450 participants who received placebo during the VAT00008 Stage 2 study are included in the analysis, and of them 2722 have been followed for at least two months after the last injection.

After injection and up to the data cut-off date, the number of participants who reported at least 1 AE in the Total B.1.351 Vaccine group and the Placebo group was as follows: a total of 2808 (36.0%) participants in the Total B.1.351 Vaccine group and a total of 1300 (20.2%) participants in the Placebo group. In the 10 µg BV (D614+B.1. 351) Primary Series group, the number of participants who reported at least 1 AE was 1682 (26.0%).

In the Pooled Booster MV (B.1.351) + BV (D614+B.1.351) group, the number of participants who reported at least 1 AE was 1126 (84.9%). This consisted of 592 (84.0%) participants in the 5 µg MV (B.1.351) Booster group and 534 (86.0%) in the 5 µg BV (D614+B.1.351) Booster group.

Overall, adverse events were reported at similar rates between the two booster groups (5 µg MV (B.1.351) Booster group and 5 µg BV (D614+B.1.351) Booster group). Individual system organ classes (SOC) were also reported at similar rates between the two booster groups. As expected, the most frequently reported SOCs in MV and BV groups were those that contained PTs associated with solicited reactions, i.e., General disorders and administration site conditions (MV: 559 participants (79.3%); BV: 501 participants (80.7%)), Musculoskeletal and connective tissue disorders (MV: 322 participants (45.7%); BV: 307 participants (49.4%)), and Nervous system disorders (MV: 301 participants (42.7%); BV: 277 participants (44.6%)).

As regards related adverse events (adverse reactions), the number of participants who reported at least 1 Adverse Reaction (AR) in the Total B.1.351 Vaccine group and the Placebo group was as follows: a total of 2602 (33.4%) participants in the Total B.1.351 Vaccine group and a total of 1049 (16.3%) participants in the Placebo group. In the Pooled Booster MV (B.1.351) + BV (D614+B.1.351) group, the number of participants who reported at least 1 AR was 1102 (83.1%). This consisted of 576 (81.7%) participants in the 5 µg MV (B.1.351) Booster group and 526 (84.7%) in the 5 µg BV

(D614+B.1.351) Booster group. In the 10 µg BV (D614+B.1. 351) Primary Series group, the number of participants who reported at least 1 AR was 1500 (23.2%).

Overall, adverse reactions were reported at similar rates between the two booster groups (5 µg MV (B.1.351) Booster group and 5 µg BV (D614+B.1.351) Booster group). Individual system organ classes (SOC) of ARs were also reported at similar rates between the two booster groups. These included General disorder and administration site conditions (MV: 558 participants (79.1%); BV: 499 participants (80.4%)), Musculoskeletal and connective tissue disorders (MV: 310 participants (44.0%); BV: 299 participants (48.1%)), and Nervous system disorders (MV: 287 participants (40.7%); BV: 267 participants (43.0%)).

Differences in AE reporting frequencies between studies VAT00002 Supplemental Phase III Cohort 2 and VAT00008 stage 2.

Table 66: Summary safety table for Studies VAT00002 – Supplemental Phase III Cohort 2 and VAT00008 – Stage 2 after any injection up to data cut-off date

Safety Parameter	VAT00002 – Supplemental Phase III Cohort 2		VAT00008 - Stage 2	
	MV (B.1.351) N=705 n/M (%)	BV (D614 + B.1.351) N=621 n/M (%)	BV (D614 + B.1.351) N=6472 (SafAS) N=2433 (RSafAS) n/M (%)	Placebo N=6450 (SafAS) N=2418 (RSafAS) n/M (%)
Deaths	0/705 (0)	0/621 (0)	4/6472 (<0.1)	6/6450 (<0.1)
Related	0/705 (0)	0/621 (0)	0/6472 (0)	0/6450 (0)
Not related	0/705 (0)	0/621 (0)	4/6472 (<0.1)	6/6450 (<0.1)
Withdrawn from study	8/707 (1.1)	2/625 (0.3)	131 (2.0)	141 (2.2)
Discontinued study due to AE	0/705 (0)	0/621 (0)	5/6472 (<0.1)	5/6450 (<0.1)
Any solicited AR	575/693 (83.0)	524/616 (85.1)	1398/2420 (57.8)	983/2403 (40.9)
Any solicited local AR	534/693 (77.1)	483/616 (78.4)	1130/2419 (46.7)	645/2403 (26.8)
Any solicited local AR – Grade 3	23/693 (3.3)	12/616 (1.9)	98/2419 (4.1)	43/2403 (1.8)
Any solicited systemic AR	416/693 (60.0)	399/616 (64.8)	1100/2420 (45.5)	823/2403 (34.2)
Any solicited systemic AR – Grade 3	48/693 (6.9)	39/616 (6.3)	172/2420 (7.1)	109/2403 (4.5)
Any unsolicited AE within 21 days of vaccination	163/705 (23.1)	154/621 (24.8)	154/2433 (6.3)	196/2418 (8.1)
Any unsolicited AE within 21 days of vaccination – Grade 3	17/705 (2.4)	19/621 (3.1)	14/2433 (0.6)	18/2418 (0.7)
Any SAE	8/705 (1.1)	9/621 (1.4)	30/6472 (0.5)	26/6450 (0.4)
Related SAE	0/705 (0)	1/621 (0.2)	0/6472 (0)	0/6450 (0)
Any AESI	1/705 (0.1)	0/621 (0)	1/6472 (<0.1)	1/6450 (<0.1)
Related AESI	0/705 (0)	0/621 (0)	0/6472 (0)	0/6450 (0)

Abbreviations: AE, adverse event; AESI: adverse event of special interest; AR, adverse reaction; RSafAS, reactogenicity safety analysis set; SAE, serious adverse event; SafAS, safety analysis set.

N: number of participants in the treatment group for the analysis set

n: number of participants with specified adverse event type

M: number of participants with available data for the relevant endpoint (for solicited AEs) and for corresponding subgroup for unsolicited AEs

Source: modified from 5.3.5.1 VAT00002 Supplemental Cohort 2 Brief CSR, Section 8, Table 8.8, Table 8.28, Table 8.32, Table 8.47, Table 8.63, and Table 8.81; 5.3.5.1 VAT00008 Stage 2 Brief Interim CSR, Section 8, Table 8.30B, Table 8.68B, Table 8.86B, Table 8.96B, and Table 8.149B.

There is a high discrepancy in the frequencies of adverse event reported in VAT0008 stage 2 reactogenicity subset compared to VAT0002 Supplemental Cohort 2. This is in line with what was seen for the parental vaccine MV (D614) in that frequencies of adverse events were much lower in VAT0008 stage 1 compared to VAT00002 Supplemental Cohort 1 especially for unsolicited AEs. It is unknown if the large difference in reporting frequencies of AEs is caused by differences in; previous COVID-19 infection status, differences in AE reporting between geographical regions, differences in study design, booster vaccination versus primary vaccination or bivalent versus monovalent formulation. All these uncertainties make the data from VAT0008 difficult to use without introducing some bias.

Calculation of frequencies of adverse reactions in section 4.8 of the SmPC is based on the 705 participants receiving 5 µg MV (B.1.351) vaccine. For a sample size of 705 participants, it is only possible to estimate frequencies of common ADRs (frequency (≥1/100)).

The safety profile observed with the MV (B.1.351) booster group is similar to the safety profile observed in the larger safety dataset of participants having received beta-containing formulations of the vaccine (N=3759). This extended safety dataset consists of both booster cohorts (MV and BV) and the reactogenicity subset of VAT00008 stage 2.

Table 67: Frequencies of adverse reactions calculated based on the Vidprevtyn Beta safety database (n=705) and based on an extended safety database with pooled beta containing vaccines (n=3759)

		Submitted SmPC section[1]	Supportive analysis (not to be included in the SmPC)	
MedDRA System Organ Class	**Adverse reaction**	**VidPrevtyn Beta safety database (N=705)**	**Extended safety database with pooled Beta containing vaccines (N=3759*)**	**Extended safety database with pooled monovalent D614 vaccine (N=4161**)**
Blood and lymphatic system disorders	Lymphadenopathy	Uncommon (0.6%)	Uncommon (0.2%)	Uncommon (0.3%)
Nervous system disorders	Headache	Very common (40.7%)	Very common (35.8%)	Very common (39.1%)
Gastrointestinal disorders	Nausea	Common (1.3%)	**Uncommon (0.4%)**	**Uncommon (0.9%)**
	Diarrhoea	Uncommon (0.6%)	Uncommon (0.2%)	Uncommon (0.2%)
Musculoskeletal and connective tissue disorders	Myalgia Arthralgia	Very common (37.2%) Very common (28.2%)	Very common (29.9%) Very common (25.0%)	Very common (37.6%) Very common (28.4%)
General disorders and administration site conditions	Malaise Chills Injection site pain	Very common (32.5%) Very common (19.6%) Very common (74.9%)	Very common (29.2%) Very common (18.5%) Very common (56.6%)	Very common (36.3%) Very common (21.3%) Very common (60.6%)
	Fever Fatigue Injection site swelling Injection site erythema	Common (3.1%) Common (2.0%) Common (7.8%) Common (5.8%)	Common (6.1%) **Uncommon (0.6%)** Common (5.6%) Common (3.3%)	**Very common (10.6%)** Common (2.1%) Common (8.4%) Common (7.3%)
	Injection site pruritus Injection site bruising Injection site warmth	Uncommon (0.7%) Uncommon (0.1%) Uncommon (0.3%)	Uncommon (0.3%) Uncommon (<0.1%) Uncommon (<0.1%)	**Common (1.2%)** Uncommon (0.2%) Uncommon (0.1%)

[1] The percentages displayed here are slightly different from the percentages presented in the SmPC since all events (solicited and unsolicited) were pooled together, reported to the complete population, while the percentages presented in the SmPC reflect the number of events reported in the population who documented the absence or the presence of the same event.

* VAT00002 Cohort 2 and the reactogenicity subset of VAT00008 stage 2 (all participants reporting solicited reaction and unsolicited reactions up to 21 days post each injection).

** VAT00002 Cohort 1 and 2 and the reactogenicity subset of VAT00008 Stage 1 (all participants reporting solicited reaction and unsolicited reactions up to 21 days post each injection). Source: Appendix 9, Table 5

In general, most of the ADRs are reported with higher frequencies in the Vidprevtyn Beta safety set than in the extended safety database set of pooled Beta containing vaccines (n=3759). Pooling of data from Booster and primary vaccination introduces uncertainty in the frequency estimates. Frequencies of adverse reactions in section 4.8 of the SmPC is therefore based on the Vidprevtyn Beta booster safety database.

Cardiac related AEs in the pooled dataset for Vidprevtyn Beta

There are no reported events of pericarditis or myocarditis in the studies evaluated. In the pooled MV (B.1.351) and BV (D614+B.1.351) booster group from VAT00002, there were in the SOC cardiac disorders registered 10 AE (4 angina pectoris, 1 atrial fibrillation, 2 palpitations and 3 tachycardia). One case of palpitation was evaluated as related to the study-vaccine. There were in addition 2 cases

of chest discomfort, 2 cases of chest pain where one was related (MV B.1.351) and 4 cases of "non-cardiac chest pain" where one was related (MV B.1.351).

For the BV (D614+B.1.351) primary vaccination group from VAT0008 stage 2, there were in the SOC cardiac disorders reported, one case of Rheumatic heart disease registered in the vaccine group and 1 angina pectoris in the placebo group. There were also one related case of hypertension in the vaccine- and 1 related case of hypertension in the Placebo-group. There were in addition 4 cases of "non-cardiac chest pain" in the vaccine group versus 2 in the placebo-group where none was evaluated to be related.

Pooled safety interim data from VAT00002 Supplemental Phase III Cohort 1 and VAT00008 stage 1

Interim data from another ongoing cohort, VAT00002 Supplemental Phase III Cohort 1 (n= 803) and interim data from VAT00008 stage 1 (5061 vaccinated, and 5078 in placebo group) investigating boosting and primary vaccination with the parental vaccine (D614) was evaluated in the context of VidPrevtyn (D614) aiming to be used for primary immunisation and booster. Except for differing antigens, this vaccine has the same composition, including adjuvant (AS03). As supportive, the applicant provided the full dataset for all ages and pool data from the VAT00008 and VAT00002 studies for the (D614) variant as this information is also considered relevant for evaluation of safety of the booster vaccine MV (B.1.351).

The Applicant has provided a new data cut (May 2022). The applicant has provided pooled data for heterologous booster (n=671), homolog booster (n=132), pooled booster (n=803), primary series (n=6109) and total MV(D614) Vaccine (n=6916). Imbalances have been observed between vaccinated and placebo (primary vaccination) on PT and SOC level for adverse events reported.

For instance, for nervous system disorders there were imbalances seen for primary vaccination for related AEs for both paraesthesia (4 (0.1%) in vaccine group versus 0 in Placebo) and dizziness (11(0.3%) in vaccine group versus 1 (less than 0.1%) in placebo). These are known ADR for other COVID-19 vaccines. The applicant initially identified dizziness and swelling face would have been listed as ADRs in the SmPC for the D614 however these AR are not listed for VidPrevtyn Beta, intended to be used as a booster only.

For the SOC skin and subcutaneous tissue disorders there is an imbalance on the SOC level for primary vaccination where 14 (0.4%) reported related AE in the SOC after vaccination versus 2 (less than 0.1%) in Placebo. Related events of Pruritus and rash was reported by 3 and 4 participants versus 0 in Placebo.

For related AEs there were 4 (0.1%) cases of Insomnia in the primary vaccination group versus 0 in Placebo.

According to the applicant no additional adverse reaction is identified, when compared to the list of adverse reactions listed in the MV (B.1.351) booster vaccine SmPC.

Based on the data presented the applicant should in the monthly reports have special monitoring on dizziness, swelling face/angioedema and paraesthesia as these are adverse reactions that are seen for the D614 variant, and it is plausible that can be adverse reactions for the MV (B.1.351) booster that can manifest when more individuals are vaccinated.

2.5.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

VAT00002- Supplemental Phase III Cohort 2

In the monovalent (B.1.351) Booster Groups, a total of 8 participants reported 8 SAEs, assessed as not related to the study vaccine.

In the bivalent (D614 + B.1.351) Booster Groups: 9 participants (6 Pfizer/BioNTech primed, 1 Moderna primed, and 2 J&J/Janssen primed) reported a total of 10 SAEs.

One participant, primed with the Moderna vaccine in the 18-55 years age group, experienced 1 SAE (Serum sickness-like reaction). The event was assessed as related to the study vaccine by the Investigator and unrelated by the sponsor. The narrative shows a time of onset, 11 days, that makes it likely to be related, and no alternative causes were reported. The outcome of the SAE was reported as resolved.

The other SAEs reported for the BV booster was assessed as not related to the study vaccine.

VAT00008- Stage 2

Until the data cut of March 2022 there were 30 participants (0.5%) in the bivalent (D614 + B.1.351) group that reported an SAE compared to 26 (0.4%) in placebo. In total there was 85 SAE, 44 were in the vaccine group and 41 in placebo, and none were related to study intervention.

The frequency of SAEs was lower in the 18 to 59 years age group compared to the ≥60 years age group, both in the Vaccine and the Placebo Groups. The frequency of SAEs was comparable in the Vaccine Group compared to the Placebo Group.

One participant in the Vaccine Group reported an SAE of hypertensive crisis that was assessed as not related to the investigational product. Time to onset of the event was 86 days after the second study vaccination.

No SAEs were reported for thromboembolic events, myocarditis/ pericarditis, anaphylactic shock/shock and narcolepsy.

VAT00013

Three SAEs were recorded for this study, one in each group:

- In the group receiving MV B.1.351 one participant showed Arthralgia, Myalgia and pain in the extremities 5 days after the vaccination as a flare-up of a known rheumatoid arthritis. The event is considered related and the participant is also considered to have been erroneously included in the study. The event is resolved after hospitalization and corticosteroid therapy.
- The second related SAE in a subject of the MV D614 group was a case of appendicitis 15 days after the vaccination. The report attributes this also causally to the vaccination as an inflammation of a lymphatic organ.
- The case in the Comirnaty group is malaise with loss of consciousness. It occurred 45 days post vaccination and 3 days after a "sleeve gastrectomy" in a 20-29-year-old obese and hypothyroid person supplemented with levothyroxine. Due to the possible linkage of thromboembolic events with that vaccine the seen spleen infarct is considered possibly related to the vaccination although this specific gastrectomy also has it as a rare event.

Deaths

In studies VAT00002 -Supplemental Phase III Cohort 2 and VAT00013, there were no deaths reported in participants who received the MV (B.1.351) or the BV MV (D614 + B.1.351).

In Stage 2 of study VAT00008, a total of 10 participants died, 4 in the Vaccine Group and 6 in the Placebo Group. None of the deaths were reported as related to the study vaccine.

The fatal cases in the vaccine group regarding the reported PT were:

- Chronic kidney disease in a 30-39-year-old participant, on haemodialysis for more than 6 years at the time of the event. Worsening of chronic renal failure reported, time to onset was more than 3 months after second study vaccination.
- Acute respiratory distress syndrome in a 50-59-year-old participant 42 days after the second injection of study intervention. The cause of death was reported as severe pneumonia. A PCR test for COVID-19 was negative.
- Angioedema in a 40-49-year-old participant with ongoing medical history of HIV (under antiretroviral treatment) and goiter. The participant became very ill 43 days after receiving the first injection of study intervention and within 1-2 hours after taking a single dose of carbimazole and propranolol and died. The suspected cause of death was angioedema to carbimazole.
- Fatal wound in a participant 21 days post vaccination

2.5.8.4. Laboratory findings

Laboratory results are available for a Phase 1 study (VAT00001), but not for the Phase 2/3 trials. This is acceptable. No Grade 2 or 3 events were seen for the following laboratory measurements: AP, ALT, AST, Neutrophils, Leukocytes, Lymphocytes, Eosinophils, Sodium – Hyponatremia, Potassium – Hyperkalaemia, Creatinine.

2.5.8.5. Safety in special populations

Pregnancy and lactating women

Up to the analysis cut-off date of VAT00008 – stage 2, 49 participants reported a pregnancy. 24/49 pregnancies are ongoing, 3/49 pregnancies reported a normal delivery, 1/49 with unknown pregnancy outcome and 1/49 participant did not receive vaccine or placebo.

Overall, 20/49 cases reporting early pregnancy termination:

- 6 were induced, elective abortions
- 1 was an ectopic pregnancy
- 6 had a reported spontaneous abortion with underlying cause or confounding factors
- 7 had reported spontaneous abortion with no underlying cause or information was not supplied

Four of the 13 abnormal pregnancy terminations included cases where the participant had taken herbal concoction (2 cases), cannabis abuse/HIV (1 participant) and a traffic accident (1 case). For the remaining 9 cases limited information is available. The study is still blinded, and it is unclear how many cases are after vaccination.

The number of spontaneous abortion cases from VAT000008 stage 2 is considered compatible with background incidence. Also, some of the reported abortion cases had underlying causes or confounding factors reported. Based on the available data, no safety concern is identified in pregnant women population according to the applicant.

The applicant has three studies that will evaluate safety in pregnant participants and infants (VAT0006, VAT0007 and VAT00012).

Elderly Population

In VAT00002 booster cohort 2, there were 88 participants in the MV (B.1.351) and 52 participants in the BV (B.1.351+D614) booster groups ≥ 65 years. 14 participants in the MV and four in the BV were ≥ 75 years. The MV group also included nine participants ≥ 80 years and three participants ≥ 85 years. There were no participants ≥ 80 years in the BV group.

Frequencies of AEs have been presented separately for patients 18-55 years and age ≥ 56 years. In general, the younger age group reported a higher frequency of solicited and unsolicited events than the older group.

In the pooled MV and BV Booster group the frequency of any AE (solicited and unsolicited) in age group 18-64 was 1034/1192 (86.7%). Corresponding frequencies in the age group 65-74 years were 77/113 (68.1%) and in age group 75-84 years 13/18 (72.2%).

For the monovalent booster group, elderly participants in general reported fewer AEs than younger participants, frequency 85.1%, 75,8% and 76.9% in the age groups 18-64, 65-74 and 75-84, respectively. There are some indications that elderly participants report more vascular disorders than younger participants (frequency 4.5% and 0.5% in age groups 65-74 and 18-64, respectively). Numbers are small.

No fatal case and no increase of SAEs were observed in the vaccine groups, when compared to placebo groups, in any of the age groups.

Table 68: VAT00002 Booster Cohort 2 - Number and Percentage of Participants with Specific Events after First Injection up to Data Cut-off by Age Group- SafAS

Participants experiencing at least one:	18-64 years		65-74 years		75-84 years		>= 85 years	
	n/N	%	n/N	%	n/N	%	n/N	%
Any AE (solicited and unsolicited)	530/623	85.1	50/66	75.8	10/13	76.9	2/3	66.7
Any SAEs	6/623	1.0	1/66	1.5	1/13	7.7	0/3	0
Fatal	0/623	0	0/66	0	0/13	0	0/3	0
Hospitalization/ prolongation of hospitalization	6/623	1.0	1/66	1.5	0/13	0	0/3	0
Life threatening	1/623	0.2	0/66	0	0/13	0	0/3	0
Disability/incapacity	0/623	0	0/66	0	0/13	0	0/3	0
Other (medically significant)	1/623	0.2	0/66	0	1/13	7.7	0/3	0
AE leading to study discontinuation	0/623	0	0/66	0	0/13	0	0/3	0
Specific SOC/PT								
SOC Psychiatric disorders	2/623	0.3	0/66	0	0/13	0	0/3	0
SOC Nervous system disorders	287/623	46.1	12/66	18.2	2/13	15.4	0/3	0
SMQ Accidents and injuries	11/623	1.8	1/66	1.5	0/13	0	0/3	0
SOC Cardiac disorders	7/623	1.1	0/66	0	0/13	0	0/3	0
SOC Vascular disorders	3/623	0.5	3/66	4.5	1/13	7.7	0/3	0
SMQ Cerebrovascular disorders	1/623	0.2	0/66	0	0/13	0	0/3	0
SOC Infections and infestations	71/623	11.4	5/66	7.6	3/13	23.1	0/3	0
SMQ Anticholinergic syndrome	0/623	0	0/66	0	0/13	0	0/3	0
PT Quality of life decreased, Impaired quality of life	0/623	0	0/66	0	0/13	0	0/3	0
Combined events (PT: Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia; HLGT: Fractures)	3/623	0.5	1/66	1.5	0/13	0	0/3	0

n: number of participants experiencing the endpoint, N: total number of participants in the corresponding age group, SOC: system organ class, PT: preferred term, SafAS: safety analysis set
SAE: serious AE, SOC: system organ class, PT: preferred term, HLGT: high level group term, SMQ: standard MedDRA query
Reactogenicity events were observed in the entire SafAS of Study VAT02 Supplemental Cohort 2.
Date of study data cutoff: VAT02 Supplemental Cohort 2 (13May2022)
Analysis includes the events with the onset or end dates before the first authorized/approved COVID-19 vaccination
Source: modified from Appendix 5 to these responses, Table 8

Immunocompromised population

In Study VAT00002 Cohort 2 around 1.6% of the participants were immunocompromised and in Study VAT00008 Stage 2, immunocompromised subjects represented 5.1% of the participants. Use in immunocompromised individuals is included as missing information into the RMP.

2.5.8.6. Safety related to drug-drug interactions and other interactions

No interaction studies have been performed. Concomitant administration of VidPrevtyn Beta with other vaccines has not been studied.

VAT00002 – Supplemental Phase III Cohort 2 and VAT00008 stage 2

In VAT00002 Supplemental Phase III Cohort 2 and VAT00008 stage 2 study protocols reportable medications are defined. Their use is collected in the CRF from the day of each initial study vaccination to the end of the solicited and unsolicited follow-up periods. Reportable medications include medications that may affect the interpretation of safety data (e.g., an antipyretic or analgesic that could have reduced the intensity or frequency of an adverse event) or may interfere with the development or measurement of the immune response (e.g., the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain bioassays).

Category 1 medications include those impacting or that may have an impact on the evaluation of the safety (e.g., antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], anticoagulants, antithrombotic).

In VAT00002, in the MV (B.1.351) booster group 221/705 (31.3%) took category 1 medication within 7 days following vaccination. The corresponding number in the BV (B.1.351 + D614) group was 193/621 (31.1%).

In VAT00008 stage 2, the vaccinated group there were 6.4% that used reportable medications within 7 days after any study vaccination versus 5.1% in placebo. Category 1 medication that might have an impact on the safety evaluation was used by 6.1% in the vaccinated group and 4.6% in placebo.

VAT00013

No data have been submitted.

2.5.8.7. Discontinuation due to adverse events

VAT00002 – Supplemental Phase III Cohort 2

No participants in the MV (B.1.351) or BV (B.1.351 + D614) booster groups, reported an AE leading to study discontinuation.

VAT00008- Stage 2

The proportion of participants who discontinued the study due to an AE was the same between treatment groups respectively 5 (< 0.1%) participants in the Vaccine Group and 5 (< 0.1%) participants in the Placebo Group; all AEs were assessed as not related to the study intervention. In the Vaccine Group, the PTs of the AEs leading to discontinuation were fatal wound, chronic kidney disease, acute respiratory distress syndrome, angioedema, and diabetic foot.

VAT00013

Three participants discontinued VAT00013 and none of them was due to an AE.

2.5.8.8. Post marketing experience

There are no post-marketing data of the vaccine.

2.5.9. Discussion on clinical safety

The safety of the VidPrevtyn Beta is mainly based on interim data from the study VAT00002 Supplemental Phase III Cohort 2, and the safety profile in the SmPC is based on this data. Included in this cohort where 705 participants boosted with VidPrevtyn Beta and 621 participants boosted with the 5 µg BV CoV2 preS dTM-AS03 (B.1.351 + D614) vaccine in a blinded manner.

An investigator-led study (VAT00013) provides some supportive data where participants previously primed with Comirnaty received a single booster dose of VidPrevtyn Beta (80 participants) or VidPrevtyn (D614) booster (74 participants) or Comirnaty (80 participants) in a blinded manner. Participants were followed for 28 days post vaccination.

Also included in the dataset as supportive, interim data from the study VAT00008 stage 2 which is a randomized placebo-controlled study investigating primary vaccination with two doses of 10 µg BV (B.1.351 + D614) administered 21 days apart. In the reactogenicity subset 2433 vaccinated and 2418 placebo participants were included. In the Safety Analysis Set (SafAS) that was evaluated for SAE/MAAE and AESIs there were 6472 participants in the vaccine group and 6450 in placebo. The data analysis cut-off date was 15 March 2022, and at that timepoint safety follow up past dose two for the SafAS was at least 1 month for 4327 participants (66.9%) and at least 2 months for 2731 participants (42.2%). Participants enrolled were mostly between the age of 18 and 59 years (93.9%).

Additionally, interim data from another ongoing cohort, VAT00002 Supplemental Phase III Cohort 1 (n= 803) and interim data from VAT00008 stage 1 (5061 vaccinated, and 5078 in placebo group) investigating boosting and primary vaccination with the VidPrevtyn (D614) was also assessed. Except for differing antigens, this vaccine has the same composition, including adjuvant (AS03). In a data cut from May 2022, there were imbalances seen between vaccinated and placebo (primary vaccination) on PT and SOC level for adverse events reported for instance dizziness and paresthesia. The applicant initially identified dizziness and swelling face would have been listed as ADRs in the SmPC for the D614 however these AR are not listed for VidPrevtyn Beta, intended to be used as a booster only. The applicant should in the monthly reports for Vidprevtyn Beta perform close monitoring on dizziness, paraesthesia, swelling face/angioedema.

As per Scientific advice on 13 July 2022 (EMA/SA/0000096498), it was understood that the dataset from VAT00002 and VAT00013 included 1406 participants, having received at least one dose of a beta-containing booster formulation, including 270 individuals aged 60 years and above, with a mean safety follow-up over 4 months. In addition, around 13000 participants would have received either 2 doses of a beta containing formulation (5 µg B.1.351 + 5 µg D614 + AS03) or placebo in study VAT00008 stage 2, which is ongoing and still blinded. This study investigates primary vaccination but was nevertheless considered relevant to support conclusions on the safety of VidPrevtyn Beta. It was also considered that the dataset generated with the parental vaccine (D614) is supportive and should be included in the dossier for the booster vaccine, especially considering the presence of an adjuvant in the formulation. Overall, the safety database was considered sufficient for the purpose of the booster vaccine authorisation provided no concerns was identified during data assessment.

However, it should be mentioned that from the dataset received from VAT0008 only 2731 vaccinated have been followed up in line with EMA´s recommendations for COVID-19 vaccines (a follow up time >6 weeks post-dose two). VAT0008 stage 2 is still blinded.

Main study (basis for the safety profile in the SmPC)

The main study, VAT00002 Supplemental Cohort 2 included 705 participants boosted with VidPrevtyn Beta and 621 boosted with the 5 µg BV (B.1.351+D614) vaccines. Both booster groups (MV, BV) were primed with either two doses of the Comirnaty (378, 375), Spikevax (111, 108), Vaxzevria (100, 100), Jcovden (38, 38) or CoV2preSdTM-AS03 (D614) vaccines (78, 0) for MV and BV booster groups, respectively. Participants were boosted with MV or BV vaccine 4 to 10 months after receiving primary vaccination. Primary vaccination with the CoV2preSdTM-AS03 (D614) vaccine is not approved. Accordingly, participants receiving heterologous prime/boosting, are the most relevant population (627 and 621 participants in the MV and BV group, respectively).

The mean age (SD) of participants was 46.0 (± 15.8) and 43.7 (± 14.3) years for participants boosted with MV and BV vaccine, respectively. Correspondingly, 88 and 52 participants boosted with MV and BV vaccine respectively, were ≥65 years old. 38 out of the 88 participants ≥65 years old receiving MV booster, were in the protein primed group. Accordingly, only 50 participants ≥65 years in the MV group received heterologous prime/boosting. Overall, there were 14 and 4 participants aged > 75 years in the MV and BV booster groups, respectively.

About 60% of the participants had at least one high-risk medical condition (58.9% and 58.6% in the MV and BV booster groups, respectively).

Solicited local and systemic reactions were recorded for 7 days, and unsolicited adverse events were reported up to 21 days after booster immunization. AESI, MAAE and SAE were collected throughout the study. The mean participant duration in days (SD) was 144 (30.9) for participants receiving MV (B.1.351) or BV (B.1.351 + D614) booster dose.

Within 7 days after a booster injection of MV (B.1.351) or BV (D614 + B.1.351) vaccines, 83.0% and 85.1% of participants, respectively, experienced at least one solicited reaction, of which 8.7% and 7.0%, respectively, were of Grade 3 intensity. 77.1% and 78.4% of participants, respectively, experienced at least one solicited injection site reaction. Injection site pain was the most frequently reported injection site reaction for both vaccine groups. 60.0% and 64.8.% of participants, respectively, experienced at least one solicited systemic reaction, of which 6.9% and 6.3% were of Grade 3 intensity. The most frequently reported solicited systemic reactions in the MV and BV vaccines group were headache (41.4% and 43.0%), myalgia (37.8% and 41.9%), and malaise (33.0% and 33.1%).

Within 21 days after the booster injection of MV (B.1.351) or BV (D614 + B.1.351) vaccines, the overall proportion of participants who experienced at least one unsolicited adverse event was 23.1% and 24.8 %, respectively, with grade 3 unsolicited adverse events being 2.4% and 3.1%, respectively. The most frequently reported unsolicited adverse events for the MV and BV booster groups were cough (4.4% and 5.3), fatigue (4.1% and 3.7%), rhinorrhoea (3.7% and 3.5%), and headache (3.4% for both groups). The most frequently reported unsolicited adverse reaction for the MV and BV vaccine groups was fatigue (2.0% and 1.4%). Thereafter followed for the MV vaccine nausea (1.3%), injection site pruritus (0.7%) and lymphadenopathy (0.6%) and for the BV vaccine injection site pruritus (1.0%), nausea (0.8%) and lymphadenopathy (0.8%).

There were no serious adverse events in the MV group considered related to the study vaccine by the investigator. In the BV group there was an event of serum sickness-like reaction that was considered related to study treatment by the study investigator. No participants in the MV or BV booster groups, reported an AE leading to study discontinuation.

The list of AESI used in the clinical study diverged significantly from the list of AESIs that will be used post-marketing. When using the AESI list from the RMP version 0.2 for VAT0002; 27 participants

reported AESIs for the MV booster (1 atrial fibrillation, 19 covid-19 disease-related, 1 cataract, 1 eye irritation, 1 eye pruritus, 1 lacrimation increased, and 1 cerebrovascular accident). 29 AESIs were reported from participants for the BV booster (1 anaphylactic reaction, 1 seasonal allergy, 22 AE covid 19 infection related, 2 chilblains, 1 diabetes mellitus, 1 visual impairment and 1 cerebrovascular accident). One AE of chilblains was evaluated as related.

Based on this, it can be concluded that the safety profile of the MV and BV vaccine seems to be largely consistent.

Supportive data following booster vaccination with VidPrevtyn Beta

In VAT00013 a small population (n=80) were vaccinated with VidPrevtyn Beta, MV D614 (n=74) or Comirnaty (N=80) as a first booster; with a follow-up of 28 days. The AE frequencies seen for VidPrevtyn Beta are comparable to what is seen in VAT0002. For Solicited AE Injection site pain was most frequently reported (77.5%) which is similar for MV (B.1.351) booster in VAT0002 (76.2%). "Asthenia or malaise" was the most frequently reported solicited systemic adverse reactions (40%) followed by "headache" (33.8%), myalgia (23.8%) and chills (12.5%) after booster vaccination with MV (B.1.351). For local solicited AEs the frequencies seen overall was similar between VidPrevtyn Beta (88.8%), MV D614 (90.6%) and Comirnaty (92.7%) while for systemic AEs VidPrevtyn Beta (62.5%) and Comirnaty (64.6%) had a higher reactogenicity than MV D614 (49.4%). The majority of the solicited adverse events was of mild intensity. In the VidPrevtyn Beta group 36.3% of the participants reported at least 1 unsolicited AE compared to 30.6% of the participants in the MV D614 booster cohort.

In VAT000013 there was one SAEs reported for VidPrevtyn Beta; one "flare-up of polyarthritis" (AESI) with a relevant time to onset of 5 days evaluated by investigator to be related. The patient had had the same reaction after first and second dose of Comirnaty which makes this a positive rechallenge case with respect to COVID-19 vaccines. The applicant has confirmed that flare up of autoimmune disease (included polyarthritis) will be followed in PSURs post-marketing. When using the AESI list that will be used post marketing there was one additional AESI; 1 report of "mild eye pain", assessed as not related by the investigator.

No fatal cases were reported.

It is not possible to evaluate the use in special populations as this information has not been presented in the provided documentation and the sample size is small (n=80).

Supportive data following primary vaccination with 10 µg BV (B.1.351 + D614)

Study VAT0008 stage 2 primary vaccination with 10 µg BV (B.1.351 + D614) includes in the reactogenicity subset 2433 vaccinated and 2418 placebo participants. For solicited adverse events pain was the most frequently reported injection site reaction 7 days after either injection in the vaccine group (46.2%) and placebo group (26.6%). Headache was the most frequently reported solicited systemic reaction after any injection in the vaccine group (32.9%) and placebo group (26.4%) followed by malaise (27.5 % in the vaccine group and 21.0% in the placebo group), myalgia (25% in the vaccine group and 17.7% in the placebo group) and arthralgia (23 % in the vaccine group and 16.4% in the placebo group). For solicited adverse events the data from VAT0008 stage 2 is similar to the data from VAT0013 and VAT0002 for (B.1.351) booster formulations.

Within 21 days after any injection, the proportion of participants in VAT0008 stage 2 who reported at least 1 unsolicited AE was 6.3% for the vaccine group and 8.1% for the placebo group. This is significantly fewer than in VAT0002 were the overall proportion of participants who experienced at

least one unsolicited AE was 23.1% (MV CoV2 preS dTM-AS03 (B.1.351) and 24.8% (BV CoV2 preS dTM-AS03 (D614 + B.1.351).

The overall frequency of participants with any AE in the reactogenicity subset in VAT0008 stage 2 for the primary BV (D614 + B.1.351) vaccine is 59.5%, compared to 26.0% in the Safety Analysis Set population. Reporting frequency overall of 59.5% is much lower than what was reported from the participants from VAT0002 in the pooled safety series (84.9%) for the MV (B.1.351) booster.

When comparing the unsolicited AE frequencies from VAT0008 stage 2 BV (D614 + B.1.135) primary vaccination and frequencies from the MV booster (B.1.135) in VAT0002 supplemental phase III cohort 2, it is observed that the frequencies where much lower in the primary vaccination scheme in VAT00008. This is in line with what was also seen for MV D164 vaccine that was evaluated in VAT0008 stage one.

The reporting frequencies of AE varied for different races in VAT0008 for vaccinated and placebo recipients respectively; Asian participants (0.8% and 2%), Black or African American participants (8.8% and 10.7%), American Indian or Alaska Native participants (5.9% and 16.7%) and White participants (50% and 35.7%).

The same tendency is seen for VAT0008 stage 2 that the AE frequency in the white population is much higher than for the other races as seen for VAT00008 stage 1. However, only a small number of white participants was included in VAT0008 stage 1 and 2.

There were 11 participants (0.2%) in the Vaccine Group and 7 (0.1%) in the Placebo Group that reported a related MAAE.

When using the AESI list that will be used post marketing for VAT00008 stage 2, 103 participants report an AESI. The AESIs reported are: (1 acute respiratory distress, 80 covid-19 cases, 13 conjunctivitis, 4 arthritis, 2 conjunctivitis allergic, 2 seizure, 1 eye pain, 1 Lacrimation increased, 1 vision blurred) while for placebo 99 participants reported an AESI (1 Hepatic failure, 1 anaphylactic reaction, 93 covid-19 cases, 2 arthritis, 5 conjunctivitis, 3 conjunctivitis allergic, 1 eye pain, 2 Lacrimation increased, 1 eye pruritus, 1 hordeolum, 1 diabetes mellitus, 1 Azotaemia). One case of vision blurred, and 19 cases of suspected COVID-19 was listed as related. Four participants in the vaccine group died during the study. All were evaluated to be unrelated.

In total there were 85 SAEs, 44 were in the vaccine group and 41 in placebo. None was related to study intervention. The data is still blinded. Since the study is still blinded it precludes the assessment leading to uncertainty in the data, as information regarding description of SAE after vaccination is currently unknown for participants in VAT0008 stage 2. The question is not closed but as the study is supportive this was further pursued.

Pericarditis/myocarditis and cardiac adverse events in the clinical studies

There are no reported events of pericarditis or myocarditis in the studies evaluated. However, some adverse events in the SOC Cardiac Disorders were reported in all studies that should be noted:

In the pooled MV (B.1.351) and BV (D614+B.1.351) booster group from VAT00002. There were in the SOC cardiac disorders registered 10 AE (4 angina pectoris, 1 atrial fibrillation, 2 palpitations and 3 tachycardia). One case of palpitation was evaluated as related to the study-vaccine. There were in addition 2 cases of chest discomfort, 2 cases of chest pain where one was related (MV B.1.351) and 4 cases of "non-cardiac chest pain" where one was related (MV B.1.351).

For the BV (D614+B.1.351) primary vaccination group from VAT0008 stage 2, there were in the SOC cardiac disorders reported one case of Rheumatic heart disease registered in the vaccine group and 1 angina pectoris in the placebo group. There were also one related case of hypertension in the vaccine-

and 1 related case of hypertension in the Placebo-group. There were in addition 4 cases of "non-cardiac chest pain" in the vaccine group versus 2 in the placebo-group where none was evaluated to be related.

Pericarditis and myocarditis are included in the list of AESI that will be monitored post-marketing (PASS VAT0007) and should also be included in the RMP as an important potential risk. The Applicant agrees to add "Myocarditis/ Pericarditis" as an important potential risk in the safety specification in the RMP.

Safety in special patient populations

Based on data from the main study (VAT00002 Supplemental Cohort 2) the frequency of participants in VidPrevtyn Beta group reporting at least one solicited adverse event was higher for participants not reporting a high-risk medical condition than for participants reporting such conditions (89.8% and 78.2%, respectively). This was also observed for non-serious unsolicited adverse events (28.3% and 19.5%, respectively). However, the frequency of participants reporting at least one serious AE and/or MAAE was similar for participants reporting at least one high-risk medical condition and for participants without such conditions (serious AE: 1.2% and 1.0%, MAAEs: 13.7% and 11.0%, respectively). Similar figures were seen for the BV booster group.

Pregnant and lactating women

Pregnant and lactating women were excluded from the study participations. However, there were 49 pregnancies following primary vaccination reported in the supportive study VAT00008 stage 2. The applicant provided updated information on outcomes so far during the assessment. Three of the 49 cases reported normal delivery, there was 1 ectopic pregnancy and 13 has reported spontaneous abortion. As the data is still blinded it is not clear how many of the 13 abnormal pregnancy terminations are after vaccination. Four of the 13 abnormal pregnancy terminations included cases where the participant had taken herbal concoction (2 cases), cannabis abuse/HIV (1 participant) and a traffic accident (1 case). For the remaining 9 cases limited information is available and as long as the study is blinded it hampers the assessment. Three of the cases had an TTO for the event within 28 days after last vaccination. At the data cut of 15 March 2022 there was 4 SAE registered under the SOC Pregnancy, puerperium and perinatal conditions in the vaccinated group and 4 SAE in the Placebo group. Pregnancy will be followed in summary safety reports.

The applicant has proposed three studies that will further evaluate safety in pregnant women and infants post marketing that is listed in the RMP (VAT0006, VAT0007 and VAT00012).

Uncertainties in the safety evaluation

The safety database for the MV booster is limited to 705 participants. Since the safety database is less than 3000 individuals, uncommon adverse reactions (≥1/1,000 to < 1/100) may not be detected and the frequencies may not be precise, which is of concern. This is reflected in the SmPC. The supportive data presented is mainly based on primary vaccination and not booster vaccination which is the current indication to be evaluated. To increase the knowledge on less common adverse events of VidPrevtyn Beta, the safety database needs to be expanded.

The applicant will expand the safety database with a category 3 PASS study (VAT0008 crossover and booster phase). The Applicant's assumption is that the safety database of VidPrevtyn Beta could reach 3000 individuals by April 2023.

The Applicant will submit monthly reports to EMA with information on the number of participants having received the booster dose and AE/ARs reported. The monthly reports should also include "heavy menstrual bleeding" for increased monitoring as the PT has newly been identified as an adverse reaction after Spikevax and Comirnaty vaccination.

Further data will be obtained from the booster phase of the VAT00008 study (Category 3 study in the RMP). In this Phase III study having enrolled 23727 participants, all participants are offered a VidPrevtyn Beta booster dose and followed for 12 months after receipt of booster. Monthly updates from VAT00008 extension study will be sent. Whenever the safety database of VidPrevtyn Beta will reach 2000 and 3000 participants, the safety section of the SmPC will be reviewed to consider if an update is needed.

When the safety database reaches 2000 and 3000 participants with at least 6 weeks safety follow up time, the Applicant commits to review the SmPC and assess whether any updates are required.

There are few elderly, pregnant, lactating, individuals with autoimmune diseases and immunocompromised included in the studies. Follow-up time is short, and long term safety is not known.

There is no safety data on use of the vaccine as a second, third and fourth booster, and it is reflected in 4.8 in the SmPC that the data is from use as a first booster.

No interaction studies have been performed with other vaccines.

2.5.10. Conclusions on the clinical safety

After review of the interim safety data from VAT0002, the main study to support safety of the booster vaccine, the reactogenicity profile of the MV (B.1.351) booster vaccine is considered acceptable. The most frequent ADRs are injection site pain (76.2%), headache (41.4%), myalgia (37.8%), malaise (33.0%), arthralgia (28.7%), and chills (19.9%). Due to the size of the safety database for VidPrevtyn Beta (n=705), uncommon adverse reactions may not be detected. Data with the use of bivalent booster from VAT0002 (D614+B.1.351) and bivalent primary vaccination from VAT0008 (D614+B.1.351) expand the safety database and give support to the safety profile. However, there are limitations in these data related to differences in antigens (BV versus MV) for both studies and the use as primary series in VAT0008.

The safety database for the MV (B.1.351) booster is currently being expanded in the VAT00008 crossover and booster Phase. These data should be provided once available. When the safety database reaches 2000 and 3000 participants, the Applicant plans to review the SmPC. The Applicant will submit monthly reports to EMA.

Long-term safety data are not available but is proposed to be monitored in several post marketing studies described as additional pharmacovigilance activities in the RMP.

2.6. Risk Management Plan

2.6.1. 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 (e.g., 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.

2.6.2. Pharmacovigilance plan

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 (e.g., 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 protein vaccine in adults 18 years of age and older <u>Secondary safety objectives</u>: • 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.	• 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 (e.g., 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	30-Sep-2024

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. <u>Primary objective</u>: To determine whether there is an increased risk of AESIs and safety concerns following vaccination with VidPrevtyn Beta, as a booster dose. <u>Secondary objective</u>: 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 inflammatory disorder status, frailty (with unstable conditions or co-morbidities), if feasible. <u>Exploratory objective</u>: To describe the safety profile of VidPrevtyn Beta in pregnant or breast-feeding women, if feasible.	• Myocarditis and Pericarditis • Pre-defined AESI • Use in pregnancy and while breast-feeding • Use in immunocompromised subjects • Use in frail subjects with unstable health conditions and co-morbidities (e.g., 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
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. • <u>Exploratory objective</u>: 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 Study Planned	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.	• Use in pregnancy	Protocol submission Final study report	30-Jul-2022 Final study report planned for submission within 12 months after study completion 16-May-2028

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. <u>Master protocol coprimary objectives</u>: 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 31-Mar-2025

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.

2.6.3. Risk minimisation measures

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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	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
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

Safety concern	Risk minimization measures	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)	**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

Safety concern	Risk minimization measures	Pharmacovigilance activities
		• VAT00007 Post-Authorization Safety Study, Final study report: 31-Dec-2025
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.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63(3) of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the *Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/726359/2022 rev.4, from 13 September 2022)*[1] which aim at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

Labelling flexibilities

The temporary labelling flexibilities granted to VidPrevtyn Beta are as follows:

- Packaging (i.e. outer carton + intermediate pack + vial label) in English only
- Use of one Global Trade Item Number (GTIN) within the unique identifier
- Omission of blue box information*
- No package leaflet included in the outer carton* (but printed package leaflets provided separately by the MAH, who will be responsible for the distribution of the printed package leaflet locally)
- Temporary exemption from the obligation to provide the printed package leaflet in national language(s). Except for the countries listed below, package leaflets distributed alongside the supplies of the vaccine can be printed in English only.

  The following Member States still require the printed package leaflet in their national language(s): Austria, Belgium, Bulgaria, Croatia, Czech Republic, Germany and Portugal.
- The number of printed package leaflets does not correspond to the number of doses.
- Release of packs printed at risk with the EU marketing authorisation number EU/1/21/1580/00**3** instead of EU/1/21/1580/00**1** (**until the end of December 2022**).
- Supply of adjuvant vial labels and adjuvant intermediate cartons printed with "Vidprevtyn" (instead of "VidPrevtyn Beta") due to at-risk printing activities (**until May 2023**).
- Supply of packs displaying "VidPrevtyn Beta 5 micrograms" (outer carton and antigen intermediate pack) or "VidPrevtyn Beta 5 mcg" (antigen vial label), instead of "VidPrevtyn Beta" only due to at-risk printing activities (**until May 2023**).

  **Missing information will be provided via the QR code in all EU official languages.*

[1] Available at https://www.ema.europa.eu/en/documents/other/questions-answers-labelling-flexibilities-covid-19-vaccines_en.pdf

Unless otherwise specified above, these labelling flexibilities are granted **until the end of April 2023**.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.8.3. Quick Response (QR) code

A request to include a QR code in the labelling (i.e. outer carton and antigen intermediate carton) and package leaflet for the purpose of providing statutory and additional information to healthcare professionals and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- Statutory information: SmPC, package leaflet, vaccination card, blue box information, contact information for adverse event reporting, contact information for local representative.
- Additional information: video with instructions for mixing of the two components of the vaccine.

2.8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, VidPrevtyn Beta SARS-CoV-2 prefusion Spike delta TM protein, recombinant (B.1.351 strain) is included in the additional monitoring list as it contains a new active substance and it is a biological medicine.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is a disease caused by the novel coronavirus SARS-CoV-2. The clinical manifestation of COVID-19 is non-specific and variable. It can range from no symptoms (asymptomatic) to severe pneumonia and death. The disease burden is highest amongst subjects with increased age; however, all age groups are susceptible. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19.

3.1.2. Available therapies and unmet medical need

At the time of authorisation of this vaccine, several products have received marketing authorisation for the treatment of COVID-19. These encompass antiviral therapy (PF-07321332/ritonavir, remdesivir), anti-inflammatory therapy (dexamethasone), IL-6 inhibitor (tocilizumab), IL-1 inhibitor (anakinra) as well as monoclonal antibodies directed against the SARS-CoV-2 spike protein (casirivimab/imdevimab,

regdanvimab and sotrovimab). In addition, a combination of two monoclonal antibodies (tixagevimab / cilgavimab) was authorised based on its ability to reduce the risk of COVID-19 infection. These therapies may show variable efficacy depending on the severity and duration of illness as well as against different variants of concern.

There are 4 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease to be used for primary immunisation and booster: Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Jcovden (EMEA/H/C/005737) and Nuvaxovid (EMEA/H/C/005808). Other 2 vaccines are also approved for primary immunisation: Vaxzevria (EMEA/H/C/005675) and COVID-19 Vaccine (inactivated, adjuvanted) Valneva (EMEA/H/C/006019/0000). The mRNA vaccines include in their marketing authorisation adapted Omicron vaccines.

3.1.3. Main clinical studies

3.2. Favourable effects

The post-hoc analysis in VAT00013 met the primary endpoint. The neutralising Ab geometric mean titre ratio (GMTR) against Omicron BA.1 variant strain of VidPrevtyn Beta relative to Comirnaty was 2.53 (95% confidence interval [CI]: 1.80; 3.57) meeting the superiority criterion.

The descriptive analysis of GMTs and GMTRs in VAT00002 indicates that VidPrevtyn Beta strongly restores immunity in previously COVID-19 primed individuals.

For the first co-primary objective, the neutralising Ab geometric mean titre ratio (GMTR) of MV CoV2 preS dTM-AS03 (B.1.351) vaccine booster dose in Pfizer/BioNTech primed participants aged 18-55 years at D15 to the 2-dose primary series in the Comparator Group at D36 was 1.96 (98.3% confidence interval [CI]: 1.54; 2.50). For the second co-primary objective, the geometric mean of individual ratio of post-booster neutralising Ab GMTs at D15 relative to pre-booster neutralising Ab GMTs in Pfizer/BioNTech primed participants aged 18-55 years at D01 was 35.41 (98.3% CI: 26.71; 46.95), which meets the superiority criterion of lower limit of the 2-sided 98.3% CI of GMTR > 2.

A notable increase of nABs after a booster dose of the VidPrevtyn Beta against the D614 and the B.1.351 strain irrespective of priming vaccine/priming platform in both adult age cohorts (18-55 and ≥56 years of age) and in individuals with high-risk conditions is observed. Moreover, VidPrevtyn Beta induced a notable increase in neutralising antibody titres to all Omicron subvariants in younger and older adults primed with Comirnaty on D15, when compared to pre-boost levels.

3.3. Uncertainties and limitations about favourable effects

No correlate of protection against COVID-19 exists. Neutralising activity of SARS-CoV-2 by hyperimmune sera is used as a surrogate in vitro marker to infer a protective effect, as this is thought to most closely reflect the in vivo scenario of antibody-mediated protection. However, no threshold for a protective effect has been established. The comparative approach of VidPrevtyn Beta to Comirnaty with known efficacy is therefore essential for the interpretation of a potential protective effect of VidPrevtyn Beta.

The descriptive analysis of the nAB titres in VAT00002 indicates that VidPrevtyn Beta notably restores the immune response after priming with different COVID-19 vaccines. The sample size of participants over 65 years of age is limited to 140 who were boosted with VidPrevtyn Beta or the BV (D614+B.1.351) vaccine.

A direct comparison of the induced booster immune response of the MV (B.1.351) vaccine against the evaluated SARS-CoV-2 strains in the different groups and age cohorts is impeded by varying baseline antibody titres against the strains in each intervention group, each age cohort and the comparator group. The different baseline titres most probably reflect the SARS-CoV-2 naïve serostatus in the comparator group and to an unknown extent the immune response to primary vaccination as well as natural infection before booster in the intervention booster groups.

The assessment of nAB immune response after a booster dose of VidPrevtyn Beta against the Omicron subvariants BA.1, BA.2, and BA.4 was performed in different laboratories in a small subset of participants, i.e. 10 subjects ≥56 years of age and 20 subjects 18-55 years. No immunogenicity data estimating the nAB immune response against Omicron subvariants are available for priming COVID-19 vaccines from Comirnaty.

The main trials VAT00013 and VAT00002 Phase III showed several methodological limitations, most notably the lack of pre-specified hypotheses and the small sample size. Nevertheless, these aspects are not considered to have critically impacted the integrity of the results.

The immunogenicity/efficacy in the immunocompromised individuals might be different from those observed in the overall population therefore the Applicant should provide immunogenicity and safety data on this population from the two planned studies (VAT00027 and VAT00028) as soon as results are available.

The Beta variant to which VidPrevtyn Beta is directed against is no longer prevalent, but preliminary studies with a number of assays including non-validated assays show cross reactivity to Omicron variants. For data based on non-validated assays, the results are uncertain and should be interpreted with caution.

There is no efficacy data for VidPrevtyn Beta. The level of protection and duration of protection afforded following vaccination with MV (B.1.351) is therefore uncertain.

3.4. Unfavourable effects

The safety of VidPrevtyn Beta is mainly characterised by local and systemic reactions and the most common adverse reactions were injection site pain (76.2%), headache (41.4%), myalgia (37.8%), malaise (33.0%), arthralgia (28.7%), and chills (19.9%). Most adverse reactions occurred within 3 days following vaccination and were mild to moderate in severity. Overall, the median duration of local and systemic adverse reactions was 1 to 3 days. Higher frequencies of reactions were reported in participants aged 18-55 years compared to older participants.

There were no serious adverse events in the VidPrevtyn Beta considered related to the study vaccine.

The extended safety database set (n=3795) consists of the VAT00002 Cohort 2 booster groups (MV and BV) and the reactogenicity subset of VAT00008 (BV Primary vaccination). Most of the adverse events proposed to be listed in the SmPC, have the same frequency category in VidPrevtyn Beta safety database (n=705) and in the extended safety database.

No fatal cases were reported.

3.5. Uncertainties and limitations about unfavourable effects

Long term safety data is not available at this stage. It is important to analyse the full safety follow-up of the ongoing trials. 86,5% of the participants in VAT00002 had a safety follow up of ≥2 months, which is considered acceptable.

Pooling of data from booster and primary vaccination introduces uncertainty in the frequency estimates. Frequencies of adverse reactions in the SmPC is calculated based on the MV (B.1.351) safety set. The sample size of 705 participants is too small to detect most uncommon adverse events. The safety database needs to be expanded. Further data post-authorisation is awaited.

Not all details requested could be provided as the data are still blinded.

Available data (non-clinical, clinical) do not raise a concern regarding vaccine-associated enhanced disease. The possibility of enhanced disease cannot be excluded with certainty. The current version of the RMP lists vaccine-associated enhanced respiratory disease as an important potential risk in the summary of safety concerns.

There are no data on use in breast- feeding women. There are few elderly and participants with autoimmune disease included in the studies.

Narcolepsy has not been reported in the context of this application. Nevertheless, due to the vaccine's composition using AS03 as adjuvant, narcolepsy is recommended to be closely monitored post-authorisation.

Adverse events of myocarditis/pericarditis have been reported following vaccination with mRNA vaccines, with increased rates in younger and especially male vaccine recipients. No such events have been reported during the VidPrevtyn Beta studies. However, the trials are not large enough to detect such potential adverse events.

There is no safety data on use of the vaccine as a second, third and fourth booster.

Interaction with other vaccines. There are no data available of concomitant administration of VidPrevtyn Beta with other vaccines.

3.6. Effects Table

Table 69:Effects Table for VidPrevtyn Beta as a booster for active immunisation to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine

Effect	Short description	Unit	Intervention	Control	Uncertainties / Strength of evidence	References
Favourable effects						
VAT00013						
Immune response (primary endpoint)	Superiority SARS-CoV-2 Neutralisation against BA.1	nAb GMT (95% CI)	1327.5 (1005.0, 1753.4)	524.0 (423.3, 648.6)	2.53 (1.80, 3.57) -met	VAT00013
Immune response (secondary endpoint)	Non-inferiority seroconversion rate against BA.1	n/% (95% CI)	100 (92.9;100)	96.2 (87.0, 99.5)	3.8 (-3.9; 12.8) --met	
	Non-inferiority seroconversion rate against D614G	n/% (95% CI)	96.2 (87.0;99.5)	93.2 (83.5; 98.1)	3.0 (-6.9; 12.8) -met	
	Superiority SARS-CoV-2 Neutralisation against D614G	nAb GMT (95% CI)	6459 (5103; 8174)	4507 (3695; 5498)	1.43 (1.06; 1.94) – endpoint not met	
VAT00002						
Immune response (co-	Non-inferiority SARS-CoV-2	nAb GMT	7172 (6363; 8083)	3658 (3123; 4286)	1.96 (1.54; 2.50) – the comparator	

Effect	Short description	Unit	Intervention	Control	Uncertainties / Strength of evidence	References
primary endpoint)	Neutralisation against D614G	(95% CI)			is VidPrevtyn (D614) primary series (not approved)	
	Superiority GMTR post-/pre-booster	(98.3% CI)	-	-	35.41 (26.71; 46.95)	
Unfavourable effects						
Any solicited local ARs Any Grade 3 events	Incidence	%	77.1% 3.3%	78.4% 1.9%	The comparator is Bivalent booster (D614 + B.1.351) (not approved)	
Any solicited systematic ARs Any Grade 3 events	Incidence	%	60.0% 6.9%	64.8% 6.3%	The comparator is Bivalent booster (D614 + B.1.351) (not approved)	
Grade 3 unsolicited AEs	Incidence	%	2.4%	3.1%	The comparator is Bivalent booster (D614 + B.1.351) (not approved)	
injection site pain	Incidence	%	76.2			
Headache	Incidence	%	41.4			
Myalgia	Incidence	%	37.8			
Malaise	Incidence	%	33.0			
Arthralgia	Incidence	%	28.7			
Chills	Incidence	%	19.9			
	Incidence	%				

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The immunogenicity data submitted indicate that VidPrevtyn Beta restores the immune response in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine.

Regardless of the immunogenicity endpoint evaluated including neutralising Ab responses against a panel of variants (D614G, Delta, Beta, and Omicron BA.1), the immune response elicited by VidPrevtyn Beta was higher than that elicited by Comirnaty booster vaccine. Moreover, the descriptive analysis of nABs shows a notable increase of GMTs on day 15 after booster vaccination with VidPrevtyn Beta. This is irrespective of the priming vaccine/priming platform and the age cohort. An increase was also observed in individuals with high-risk medical conditions.

However, the pivotal trial VAT00013 was not designed as a pivotal study. Post-hoc analyses were determined retrospectively to allow comparison of the superiority of an approved mRNA vaccine against Omicron BA.1 for the scope of this application. The most important limitation was that the primary analysis of neutralising antibodies was performed with a non-validated assay. The retesting of VAT00013 samples with the validated monogram assay from study VAT00002 resolved this issue.

The observed safety profile of VidPrevtyn Beta did not reveal any major safety concerns. However, there are certain limitations in the dataset due to the small size of the safety database (N=705). Data with the use of bivalent booster from VAT0002 (D614+B.1.351) and bivalent primary vaccination from VAT0008 (D614+B.1.351) expand the safety database and give some support to the safety profile. Furthermore, there are limitations in these data related to differences in antigens for both studies and the use as primary series in VAT0008.

The observed adverse reactions (solicited and unsolicited, short term) are acceptable based on severity, duration and reversibility and considered typical for a non-live, adjuvanted vaccine. No safety issues were detected in participants with high risk medical conditions. The database is limited for pregnant and breast-feeding women, for elderly, in the immunocompromised individuals and individuals with autoimmune diseases. There is no safety data on use of the vaccine as a second, third and fourth booster. No interaction studies have been performed with other vaccines.

3.7.2. Balance of benefits and risks

The vaccine has been developed using an immunobridging approach using neutralising antibodies against the S-protein to infer efficacy from an already authorised COVID-19 vaccine with proven efficacy. The benefit/risk balance of VidPrevtyn Beta for the sought indication "*VidPrevtyn Beta as a booster for active immunisation to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine (see sections 4.2 and 5.1). The use of this vaccine should be in accordance with official recommendations*" is positive.

No safety concerns have been identified based on available information, although due to the limited size of the safety database (n=705) only common adverse events is likely to be identified. The experience is limited for the elderly population as well as in pregnant, breast-feeding women and for immunocompromised. Long-term safety data is not available.

Furthermore, in view of the development programme, the nature of the product and the data package provided, the dossier is considered comprehensive vis-à-vis the dossier requirements for a vaccine authorisation using an immuno-bridging approach.

3.8. Conclusions

The overall benefit/risk balance of Vidprevtyn Beta is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vidprevtyn Beta is favourable in the following indication(s):

"*VidPrevtyn Beta is indicated as a booster for active immunisation to prevent COVID-19 in adults who have previously received an mRNA or adenoviral vector COVID-19 vaccine (see sections 4.2 and 5.1).*

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that SARS-CoV-2 prefusion Spike delta TM protein, recombinant (B.1.351 strain) is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).