EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2022
EMA/627695/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

COVID-19 Vaccine (inactivated, adjuvanted) Valneva

Common name: COVID-19 vaccine (inactivated, adjuvanted, adsorbed)

Procedure No. EMEA/H/C/006019/0000

Note

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

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List of abbreviations

Ab	Antibody
ADE	Atibody disease enhancement
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
Alum	aluminium hydroxide
AR	Adverse Reaction
AU	Arbitrary Unit
AZD1222	Vaxzevria (ChAdOx1-S [Recombinant]), AstraZeneca
BMI	Body Mass Index
BSA	Bovine Serum Albumin
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMA	Conditional Marketing Authorisation
COVID-19	Coronavirus disease 2019
CpG 1018	22-mer with unmethylated CG motifs (TGACTGTGAACGTTCGAGATGA)
CpG	Cytosine phosphate Guanine
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CSR	Clinical Study Report
DMEM	Dulbecco's Modified Eagle Medium
DPBS	Dulbecco's Phosphate Buffered Saline
DPI	day post infection
DSMB	Data and Safety Monitoring Board
e-diary	Electronic Diary
ELISA	Enzyme-Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immuno Spot
EMA	European Medicines Agency
FBS	Fetal Bovine Serum
FIH	First in Human
GCP	Good Clinical Practise
GLP	Good Laboratory Practices
GMC	Geometric Mean Concentration
GMFI	Geometric Mean Fold Increase
GMFR	Geometric Mean Fold Rise
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titre
IgG	Immunoglobulin G
IM	intramuscular
IMM	Immunogenicity Population
IQR	Inter Quartile Range
kDa	Kilo Dalton
LLOQ	Lower limit of Quantification
LoQ	List of Questions
MAA	Marketing Authorisation Application
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MNA	Microneutralisation Assay
MNA_{PHE}	Microneutralisation Assay performed at Public Health England
MNA_{VLA}	Microneutralisation Assay performed at Valneva
MO	Major Objection
moA	mode of action
mPPAS	modified Per Protocol Analysis Set
nAb	Neutralising Antibody
NHPs	Non-Human Primates
NT50	Neutralising Titre 50%
OC	Other Concern
PBMC	Peripheral Blood Mononuclear Cell
PBS	Phosphate Buffered Saline
PCR	Polymerase Chain Reaction
PHE	Public Health England

PIP	Paediatric Investigation Plan
PNA	Pseudotyped (Virus) Neutralisation Assay
PP	Per Protocol
PPAS	Per Protocol Analysis Set
PPND	pre-and-postnatal development
PPP	Per Protocol Population
PVD	Preclinical Vaccine Development
RBD	Receptor Binding Domain
RDTS	repeated dose toxicity study
rHA	recombinant Human Albumin
rHSA	recombinant Human Serum Albumin
RMP	Risk Management Plan
RR	Rolling review
RT	Room Temperature
RT-qPCR	quantitative Reverse Transcription Polymerase Chain Reaction
SA	Scientific Advice
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SC	subcutaneous
SD	Standard Deviation
SDS	Sodium Dodecyl Sulfate
SFU	Spot Forming Units
SmPC	Summary of Product Characteristics
SOC	System Organ Class
Th1	T-helper cell type 1
Th2	T-helper cell type 2
UK	United Kingdom
ULOQ	Upper Limit of Quantification
VAED	vaccine mediated enhanced respiratory disease
VLA2001	COVID-19 Vaccine (inactivated, adjuvanted) Valneva
VoC	Variant of Concern
WHO	World Health Organization
WT	Wild Type
yoa	years of age

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Valneva Austria GmbH submitted on 17 May 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for COVID-19 Vaccine (inactivated, adjuvanted) Valneva, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 October 2021.

The applicant applied for the following indication:

"COVID-19 Vaccine (inactivated, adjuvanted) Valneva is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 to 55 years of age

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

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 P/0184/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0184/2022 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 virus (inactivated) Wuhan strain hCoV-19/Italy/INMI1-isl/2020 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 relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 July 2021	EMA/SA/0000064690	*Manuela Mura*
5 November 2021	EMA/SA/0000072313	*Stephan Lehr, Karin Janssen van Doorn*

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

- *Manufacturing process, viral inactivation strategy, process validation (PV) strategy, control and testing strategy for VLA2001 for a MAA, stability programs, use of recombinant human albumin (rHA) in the manufacturing process, risk assessments for extractables and leachables, N-nitrosamine and elemental impurities, agreement with the comparability strategy for including new manufacturing sites*
- *Preclinical program to support approval*
- *Feasibility and probability of a successful conduct for a placebo-controlled field efficacy trial, immuno-bridging approach based on neutralising antibodies to support a MA, use of AZD1222 as a comparator, agreement with the phase 3 safety and immunogenicity trial in terms of sample size and endpoints, enrolment of elderly in clinical studies*

Scientific advice compliance

Quality

The Applicant received scientific advice on quality aspects (EMA/SA/0000064690, EMA/SA/0000072313). As regards EMA/SA/0000064690, the Applicant´s initial proposal to consider the manufacturing as a platform process is not sufficiently justified (instead product-specific information was presented which is endorsed). Considering the advice, a two-tiered cell bank system has been established; an (adapted) two-tiered system was implemented for the virus bank (MVSB, Production Inoculum (WVS)). As recommended, characterization of cell banks and master virus seed lot was conducted largely in line with current guidance (some results pending, **REC**). The use of alternative methods (NGS, mycoplasma PCR) was appropriately justified during assessment of this MAA (results for qualification of the NGS method are pending, **REC**).

The absence of Viral Inoculum Process Validation report, Process Impurity Clearance Study report and Bacterial Retention Study report by the time of MAA submission was considered acceptable, provided that outstanding information will be part of the response package to the CHMP LoOI (respective results were presented in the course of rolling review).

Recommendations related to specifications were only in part considered (e.g. test or aggregates and total protein not included for release testing). However, this is considered sufficiently justified based on the information provided in the MAA. For several method validations, the Applicant refers to validation studies performed with IXIARO. Respective other concerns were appropriately addressed during assessment of this MAA. Concerning Final Bulk Drug and Final Lot, the company has largely followed the advice given. Following issues have been appropriately addressed: extraction of 10 doses using

different syringes; adding CpG 1019 content assay; adding potency test on Final Bulk Vaccine and Final Lot level; provided information for recombinant Human Albumin as a novel excipient; leachable Study and nitrosamine risk assessment available.

Bacterial retention studies for sterile filters were appropriately performed during assessment of this MAA. The shelf life of 2 years in the SmPC is currently not acceptable and was appropriately reduced to 1 year.

As regards the second advice (PACMPs related to the implementation of an additional DS/FBP and additional DP manufacturing site), the recommendations were only in part considered, but appropriately addressed during assessment of this MAA.

Non-Clinical

The non-clinical development of VLA2001 was discussed with CHMP in the scientific advice procedure EMADOC-1700519818-705813 (Case No.: EMA/SA/0000064690). Specifically, the following three questions were asked:

- Whether the adjuvant CpG is considered a novel excipient and, if so, whether extensive safety studies for novel excipients need not be submitted as part of the VLA2001 MAA;
- Whether CHMP has any comments on the pre-clinical development programme from a Marketing authorisation perspective;
- Whether CHMP agrees that the proposed PPND study is adequately designed and will be sufficient from a MAA perspective.

In regard to the first question, CHMP answered that CpG may not be considered as novel excipient as it is already contained (at higher levels per dose) in the marketed product HEPLISAV-B. Even though CHMP recognized that the conducted non-clinical studies do not allow discriminating the toxicological profiles of the adjuvants and the antigen API (as no separate study groups were incorporated in the conducted studies), CHMP concluded that a separate testing of the adjuvants is not needed if no major safety concerns are identified with the final full formulation. In regards to the second question, CHMP concluded that the non-clinical pharmacology programme is adequate in principle to support a marketing authorisation. Additionally, CHMP remarked that absence of certain studies (e.g. safety pharmacology, secondary PD, biodistribution of antigen and adjuvants, effects of adjuvants in the absence of antigen) should be sufficiently justified. Finally, in regards to the last question, CHMP remarked that in addition to the conducted DART study, the Applicant is recommended to incorporate female fertility (stage 1 FEED) in the study.

The advice that was provided by CHMP in this procedure was largely adhered to. Concerns identified on the submitted non-clinical programme can be found in the non-clinical section of this report.

Clinical

The current MAA for VLA2001 under rolling review is based on two clinical trials:

1. **Study VLA2001-201**: first-in-human (FIH) Phase 1/2 dose finding trial on safety and immunogenicity to select the VLA2001 dose for further clinical trials *(Day 36 and Day 106 interim analysis)*
2. **Pivotal Study VLA2001-301**: Phase 3 superiority trial on the immunogenicity and safety of VLA2001 compared to the already licensed vaccine AZD1222 (*Day 43 interim analysis*)

The clinical development program of VLA2001 has been discussed with CHMP during a scientific advice (Case No. EMA/SA/0000064690). The Applicant sought advice concerning quality development, pre-

clinical development and clinical development. In terms of the clinical development, the Applicant's approach to infer VLA2001 efficacy by immunobridging to an authorised COVID-19 vaccine was considered generally acceptable. Main points of concern by the CHMP pertained to the lack of a control group in subjects 18-29 years of age and the planned assessment of seroconversion rates only as a secondary endpoint (recommended as co-primary endpoint instead). Notably, this scientific advice had been sought at a time where the study had already been initiated and the enrolment of the immunogenicity subset had been concluded.

The scientific advice was partially followed, seroresponse rates (non-inferiority VAL2001 vs AZD1222) have been implemented as co-primary objective for the pivotal study, whereas the issue of the lack of a control group in subjects 18-29 years of age remained (see especially the discussion on efficacy/immunogenicity).

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: Andrea Laslop Co-Rapporteur: Alar Irs

The CHMP confirmed eligibility to the centralised procedure on	14 October 2021
ETF recommendation on a request for appointment of Rapporteurs for a potential rolling review procedure on	30 November 2021
Applicant submitted documentation as part of a rolling review to support the marketing authorisation application on	1 December 2021
The procedure (Rolling Review 1) started on	2 December 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 February 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 February 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP members on	10 February 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	11 February 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	16 February 2022

ETF discussion on Rolling Review 1 took place on	17 February 2022
CHMP discussion on Rolling Review 1 took place on	24 February 2022
Applicant submitted documentation as part of a rolling review to support the marketing authorisation application on	14 March 2022
The procedure (Rolling Review 2) started on	14 March 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 March 2022
PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	1 April 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP members on	5 April 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	6 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 April 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	14 April 2022
ETF discussion on Rolling Review 2 took place on	12 April 2022
CHMP discussion on Rolling Review 2 took place on	22 April 2022
Applicant submitted documentation as part of a rolling review to support the marketing authorisation application on	2 May 2022
The procedure (Rolling Review 3) started on	3 May 2022
The CHMP assessment report was circulated to all CHMP and PRAC members on	11 May 2022
ETF discussion on Rolling Review 3 took place on	13 May 2022
The application was received by the EMA on	17 May 2022
The procedure started on	18 May 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 June 2022
The CHMP Rapporteurs' first Assessment Report was circulated to all CHMP and PRAC members on	8 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 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	15 June 2022

The ETF discussion on the application took place on	17 June 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 COVID-19 Vaccine (inactivated, adjuvanted) Valneva on	23 June 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)	23 June 2022

COVID-19 vaccine (inactivated, adjuvanted) Valneva 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 20 June 2022, there have been over 536 million confirmed cases of SARS-CoV-2 infection globally with approximately 6.31 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.

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.

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).

2.1.4. Clinical presentation, diagnosis

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.

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 (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, three monoclonal antibodies Ronapreve (casirivimab/imdevimab, EMEA/H/C/005814), Regkirona (regdanvimab, EMEA/H/C/005854) and Xevudy (sotrovimab, EMEA/H/C/005676) and 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. A fourth monoclonal antibody, Evusheld (tixagevimab / cilgavimab, EMEA/H/C/005788), is approved for the 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 5 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) and Nuvaxovid (EMEA/H/C/005808).

2.2. About the product

COVID-19 Vaccine (inactivated, adjuvanted) Valneva (VLA2001) is a purified, inactivated, and adjuvanted whole virus SARS-CoV-2 (Wuhan strain hCoV-19/Italy/INMI1-isl/2020) vaccine grown on Vero cells.

The vaccine manufacturing process makes the virus unable to replicate and delivers intact spike proteins on the virus surface. Adjuvants are added to increase the magnitude of vaccine-mediated immune responses.

Following administration, VLA2001 induces SARS-CoV-2 neutralising antibodies, as well as cellular immune responses (Th1) directed against the spike protein, which may contribute to protection against COVID-19. As the vaccine is made of whole virus particles, these present a wide range of native viral antigens. It is expected for VLA2001 that the immune response elicited is not limited to the S protein but also directed against other SARS-CoV-2 antigens.

COVID-19 Vaccine (inactivated, adjuvanted) Valneva is intended to be administered intramuscularly as a course of 2 doses administered 28 days apart.

The intended indication is: "*COVID-19 Vaccine (inactivated, adjuvanted) Valneva is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 to 55 years of age*

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

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as suspension for injection in a multi-dose vial. Each multi-dose vial contains 10 doses of 0.5 mL. One dose (0.5 mL) contains 33 Antigen Units (AU) of SARS-CoV-2 virus (inactivated) Wuhan strain hCoV-19/Italy/INMI1-isl/2020 as active substance.

Other ingredients are sodium chloride, sodium phosphate dibasic anhydrous (E339), potassium phosphate monobasic anhydrous (E340), potassium chloride (E508), water for injection, recombinant human albumin and the adjuvants aluminium hydroxide and CpG (cytosine phospho-guanine) 1018.

The product is available in multidose vials (type I glass) with a stopper (flurotec-coated bromobutyl) and a flip-off plastic cap with aluminium seal.

Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

2.3.2. Active Substance

General Information

The active substance of COVID-19 Vaccine (inactivated, adjuvanted) Valneva is a purified, inactivated SARS-CoV-2 virus strain, adapted to grow on Vero cells, purified as a whole virus and inactivated using β-propiolactone in order to preserve the native surface structure of the spike (S) glycoprotein (Perrin and Morgeaux 1995, Biologicals 23:207-11). The S protein is the main antigen target among all structural proteins of SARS-CoV-2 and monoclonal antibodies (mAbs), targeting the S protein can induce protective immunity against viral infection.

SARS-CoV-2 is a virus categorized as a betacoronavirus, belonging to the Coronaviridae family. SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. The virus is enveloped, has a round or elliptical and often pleomorphic shape, with a diameter varying between approximately 60 to 140 nm. Distinctive spikes, about 9 to 12 nm long, protrude from the virus particle's surface, resembling a solar corona.

Coronaviruses carry the largest genomes (26-32 kb) among all RNA virus families. The SARS-CoV-2 single-stranded RNA genome contains approximately 30 kb, encoding approximately 9860 amino acids. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) proteins.

The SARS-CoV-2 vaccine strain is based on the SARS-CoV-2 Italian strain (LAZ-INMI1-isl/2020, GISAID Accession number: EPI_ISL_410545). The full nucleotide sequence of the SARS-CoV-2 vaccine strain has been provided. Genome and virus structure have been appropriately described.

The applicant uses an inactivated whole-virus approach where live wild-type virus is grown in Vero cell culture and then inactivated via chemical treatment with β-propiolactone in order to preserve the native surface structure of the S-glycoprotein.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The active substance is manufactured at Valneva Scotland Limited (Oakbank Park Road, Livingston EH53 OTG, Scotland, UK). The manufacturing site is appropriately authorised and holds a valid GMP certificate.

The active substance manufacturing process has been adequately described. It consists of well understood unit operations typical for inactivated whole virus vaccines: working cell bank expansion, infection, crude viral harvest, nucleic acid and protein reduction with protamine sulphate, harvest concentration by ultrafiltration, inactivation with beta-propiolactone, virus purification, ultrafiltration/diafiltration, dilution with Dulbecco Phosphate Buffer Saline (DPBS) and rHA and sterile filtration into the final active substance.

The manufacturing process of the active substance starts with cell expansion of serum-free Vero working cell bank (WCB) in tissue culture flasks, in culture chambers and finally in single-use fixed-bed bioreactor. After expansion, cells are infected with the production inoculum (representing the Working Virus Seed Bank (WVSB)). The crude harvest is collected, clarified by precipitation of host cell nucleic acid with protamine sulphate and filtration, and concentrated by ultrafiltration. The resulting intermediate (filtered protamine sulphate treated concentrated harvest) is treated with beta-propiolactone (BPL) for viral inactivation. After hydrolysis of the remaining BPL, the inactivated viral solution is stored at 5 °C until required for further processing (up to 8 days). The viral solution is then purified by multimodal chromatography, and concentrated by Ultrafiltration/Diafiltration in formulation buffer, into Flexboy bags. The resulting Purified Inactivated Virus solution (PIV) is stored at 5 °C ± 3 °C until required for further processing. Following is the dilution of PIV using the active substance buffer and sterile filtration to finally yield the active substance. The active substance is immediately formulated into Final Bulk Product (FBP), which is part of finished product manufacturing: there is no hold time for the active substance. Hold times for the Inactivated Viral solution and for the PIV have been validated. Duration of all intermediate steps has been reported and hold times (defined for storage > 24 hours) have been validated.

The production inoculum required for the infection of Vero cells in the manufacturing process of the active substance is obtained by Vero cells expanded in minimal essential medium supplemented with foetal bovine serum (FBS), infected with aliquots of Master Virus Seed Bank (MVSB). A single harvest is taken after 2 days post infection, supplemented with a Tris/sucrose solution, filtered, aliquoted and stored until required. Data demonstrating stability of production inoculum have been provided.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step where applicable. The active substance manufacturing process is considered acceptable.

A batch is defined by the volume of active substance obtained from the thawing of Vero Working Cell Bank (WCB), expansion in cell culture and infection with the appropriate amount of Production Inoculum (representing the Working Virus Seed).

There is no reprocessing of the active substance or active substance intermediates. In-process controls (IPCs) have been appropriately described and adequately set to control the process.

During the active substance manufacturing process, the purified inactivated virus following the ultrafiltration/diafiltration step is filled into Flexboy bags which comply with Ph. Eur. The container used to collect the sterile filtered active substance is a single-use component. The material of construction of the contact layer complies with Ph. Eur. No other active substance container closure system is described, since the active substance is formulated immediately following sterile filtration and no hold time is applied to the active substance.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications for non-compendial raw materials are presented. Acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

The parent (Wuhan) viral strain Clade O virus strain hCoV-19/Italy/INMI1-isl/2020 was isolated in January 2020 at Istituto Nazionale Malattie Infettive (INMI) Lazzaro Spallanzani (Italy) on a patient infected in China (Hubei province). The research Virus Seed Bank was developed and manufactured at Valneva Nantes.

Prior to manufacture of commercial batches, for initial Vero cells Master Cell Bank (MCB) and Working Cell Banks (WCB), foetal bovine serum (FBS) was used. For commercial manufacture of the active substance, serum-free cell banks were generated. History and generation of cell substrates is appropriately described, with characterization and testing of cell lines principally performed in line with Ph. Eur. 5.2.3, ICH Q5A and ICH Q5D requirements. The serum-free MCB was not tested to confirm absence of Hepatitis C virus, Hepatitis E virus, CMV, EBV, HHV-1, HHV-2, varicella virus, HHV-6, HHV-7, HHV-8, human papilloma virus, human polyoma virus and parvovirus B19. However, several virus specific tests are performed at the level of the master virus seed (which has been generated using the serum-free MCB). Additional screening is performed at the level of the harvest for an additional panel of 14 human viruses. This approach in combination with the other (already performed) virus screening tests on the Vero Master cell bank is deemed sufficient to consider the cell bank system as properly qualified. Characterization results for End of Production Cell Bank (EoPCB) have in part been provided: EoPCB was shown to be negative for retroviruses, the result for tumorigenicity testing is still pending **(Quality recommendation 2)**. MCB and WCB stability (cell count and viability) is monitored concurrent with manufacture, the MCB is tested on a biennial basis at minimum. A protocol for the implementation of new WCBs has been provided and it is acceptable.

The Master Virus Seed Lot was tested for RNA sequence integrity (Next Generation Sequencing (NGS)), titre (including homogeneity testing) and absence of potential contaminants (mycobacteria, mycoplasma, sterility, relevant adventitious viruses). Sequence variants were observed when genetic stability was analysed at the level of MVSB, the Production Inoculum and the active substance intermediate (before inactivation). Non-silent mutations in the E protein have been detected at positions V5G, N15K and L19R, while in the S protein, non-silent mutations have been detected at positions G72R, N74K, T76I and S686G. The potential impact of the observed sequence heterogeneities on Spike protein structure and immunogenicity of the vaccine is unlikely. Furthermore, the occurrence of potential new sequence variants is monitored by NGS sequencing of each new PI lot as part of the supportive control testing strategy **(Quality recommendation 4).**

The strategy for extraneous agents testing of viral seeds has been justified based on a general risk assessment. The MVSB is screened for 14 relevant human viruses by qPCR, tested in vitro for adventitious agents using indicator cells (MRC-5, HeLa) and tested in vitro for bovine viruses. Absence of Hepatitis E contamination was confirmed by polymerase chain reaction (PCR). The testing strategy is complemented by NGS (as a justification for omission of *in vivo* testing). However, qualification of the NGS method using spiking experiments with a set of relevant human viruses is pending **(Quality recommendation 3)**. MVSB stability is monitored via yearly re-testing of virus titre as the main stability-indicating parameter, the currently available data (1 year) indicate stability.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

An assessment for critical parameters was performed according to ICH Q9, based on Failure Modes and Effects Analysis (FMEA) tool. The outcome of the risk assessment is provided. FMEA was written prior to initiation of the Process Validation Consistency batches and as such was based on the current knowledge at the time of the FMEA discussions. Critical Process Parameters (CPPs) were identified during the FMEA with recommended actions to include in the subsequent Process Performance Qualification (Process Validation) Plan and were afterwards verified during process validation.

Process validation

The active substance manufacturing process has been adequately validated. The Process Performance Qualification (Process Validation) for the active substance manufacturing was performed at Valneva Scotland Ltd. for the commercial process, demonstrating consistency in production. Data from three full scale production runs is provided with supportive data from an additional full scale production run.

The single process steps and the respective critical process parameters are described. Process validation data presented met the respective acceptance criteria. Process validation of manufacture of production inoculum has been completed and was found to be acceptable. Process impurity clearance studies to formally calculate the process impurity clearance factors and bacterial retention testing were appropriately performed.

A FMEA approach was taken to support the identification of the critical process parameters (CPPs) which are presented and found acceptable. Respective specifications and rationales are provided. Critical quality Attributes (CQAs) are presented. The acceptance criterion for "Crude Harvest – Time from Infection" has been justified. The filtered and concentrated viral harvest is inactivated using BPL. One of the Critical Process Parameters for the inactivation process is "Absence of pfu" by a validated plaque assay after completion of 24 hours (± 2 hrs) inactivation and hydrolysis. Inactivation kinetic samples from full scale batches were taken at T=0, 1, 2, 6, 24 hours in addition to an Inactivated Viral Solution sample and tested by plaque assay. Data demonstrates complete inactivation of SARS-CoV-2 using the defined inactivation process. The inactivation kinetics show a rapid inactivation after 1 hour below the detection limit of the plaque assay for the kinetic sample due to dilution factor required to inhibit the BPL contained in the sample at this point).

Bioburden was tested at the crude harvest and pre-filtration active substance stages. The acceptance limit for bioburden has been set to ≤ 1 cfu/mL after sterile filtration in the process. This limit has been set based on available Phase 3 clinical batches and commercial scale batches, where it has been demonstrated that the sterilising filtration performed during aseptic formulation of the active substance into final bulk vaccine is adequate to remove potential bioburden. Overall, the process is considered of low bioburden for these early process steps.

Essential process validation results (e.g. CPP and IPC results for the PPQ lots, inactivation validation results, impurity removal results) have been provided and are found acceptable.

The production scale for the active substance manufacturing process was adequately validated, and validation data presented in the dossier.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development program. The manufacturing process development for the early development phase (clinical phase 1/2), the clinical phase 3 material and the commercial process development phase is appropriately described. Critical process changes in development are outlined in tabulated form and a justification has been provided. The commercial manufacturing process for the active substance remains essentially the same as the process used for manufacture of Phase 3 clinical trial material. It is noteworthy to mention that Clinical Phase 3 material was produced at commercial scale up to the

Purified Inactivated Viral (PIV) stage, i.e. the final intermediate step prior to dilution and sterile filtration into active substance. The main differences are basically of volumetric nature in the final step of active substance dilution and required to ensure large batch sizes to cover the required demand. No substantial changes in the production principles or methods, used materials or consumables or testing strategy are implemented, and therefore the process adaptions are deemed as very low risk.

A detailed development report covering the upstream process development using serum free medium in fixed bed bioreactor has been provided. For downstream processing a separate development report has been provided covering the phase 1/2 material as well as the phase 3 and commercial process. Further, an extensive report regarding the development of the viral inactivation step has been provided. Additionally, a report demonstrating the comparability between phase 1/2 and phase 3 process and phase 3 and commercial process is provided. The reports were found acceptable.

Characterisation

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods. Characterisation studies were performed on selected active substance or active substance intermediate (PIV) samples of phase 1/2, phase 3 and commercial batches using the following methods: SE-HPLC (UV214 nm detection), SE-HPLC-MALS, SDS-PAGE, DLS, Nanotracking particle Analysis and Electron Microscopy. Respective results indicate that the majority of virus particles is present in the monomeric state. Furthermore, the impact of BPL modification on antigenic sites has been investigated. Considering the location of the most frequent BPL modifications on the spike protein, the results provide assurance of low impact on induction of neutralising antibodies. Sequence analyses of spike protein indicates heterogeneities to the reference sequence at certain amino acid positions; an impact of respective amino acid exchanges as regards immunogenicity and antigenic integrity is unlikely). Western blot data with S1- and S2-specific antibodies revealed no degradation products and indicate comparability of analysed batches with respect to uncleaved vs cleaved spike protein.

In summary, the characterization is considered appropriate for this type of active substance.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The active substance specifications contain tests for identity (ELISA), antigen content (ELISA), residual β-propiolactone (GC-MS), residual protamine sulfate (HPLC), Vero hcDNA (RT-qPCR), Vero HCP (ELISA), residual recombinant human albumin (HPLC), endotoxin (Ph. Eur), bioburden (Ph. Eur), appearance (visual examination, Ph. Eur.), virus titre (plaque assay), and pH (Ph. Eur.).

The proposed specifications cover relevant quality attributes and are overall in line with ICH Q6B.

The antigen content/identity of the active substance is determined by competitive liquid phase ELISA using an antibody that is directed against the SARS-CoV-2 Spike (S) glycoprotein. No meaningful protein content method has been identified for SARS-CoV-2, due to the excess of recombinant human albumin and trace amounts of residual protamine sulfate (PS). The inactivated virus proteins are present in very small amounts in comparison to the DPBS buffer containing rHA and residual PS from early purification steps. Therefore, to fulfil ICH Q6B requirements the antigen content by competitive liquid ELISA is used. It should however be noted that, in the manufacture of the SARS-CoV-2 vaccine, each single active substance batch generates one final bulk vaccine. Additionally, after dilution and sterile filtration, the active substance is immediately processed to aseptic formulation of the final bulk vaccine. Based on this, the antigen content measurement of the active substance serves only the purpose to confirm that the dilution of purified inactivated solution has been performed correctly, to

ensure that enough antigen has been formulated into the finished product to fulfil the respective specification.

The assay is considered an adequate substitute for an *in vivo* method because it is able to discriminate between potent and sub-potent material as demonstrated by conducted studies in hamsters using potent and sub-potent material (accelerated storage conditions at 25°C which show a drop in potency as measured by the competitive liquid phase ELISA from clinical phase III batch CL00003). The results show that stressed material with lower AU/dose also induces fewer neutralising antibodies.

The list of specifications has been expanded during the assessment to include tests for "pH" and "absence of pfu after inactivation". The applicant is requested to provide pH results and set an active substance specification when sufficient data (from approximately 30 batches) is available **(Quality recommendation 5)**. Although not tested at active substance level, viral inactivation (virus titre) is tested on the Inactivated Viral solution and has been included in the active substance specifications, since it is considered a critical specification, in order to demonstrate that there is no detectable live virus present.

The release specification of host cell protein (HCP) is deemed clinically justified.

Process-related impurities include host cell DNA and host cell protein (HCP), FBS, residual protamine sulphate, and residual β-Propiolactone. These impurities are controlled as part of the active substance specifications or reduced to negligible amounts (i.e. FBS). Residual levels of sucrose (added to inoculum) in the active substance are negligible considering the several dilution and purification steps.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Method validations were performed in line with ICH Q2 and are summarized in tabulated form; the respective verification and validation reports are presented and deemed acceptable. For Residual Protamine Sulphate and Host cell DNA the Applicant presents method validation reports for IXIARO, and this reliance on Prior Knowledge approach has been accepted. Information related to Prior Knowledge aspects have been included in the dossier. Additional testing on clinical phase 3 and PV batches confirmed the suitability of the methods. 30% coverage of the 2D gel spots and 70% recovery of the sum of the fluorescence signal are obtained with the anti-Vero cell HCP antibody of the 2nd generation kit. The Applicant states that lower detection rates were identified especially in the low molecular weight region of the Western Blot. Two HCP assays were used: HCP assay of 1st generation (Vero HCP ELISA kit (F500, Cygnus Technologies) for active substance release of clinical Phase 3 and process validation batches, and HCP assay of 2nd generation (Vero Cell 2G HCP ELISA Kit (F975, Cygnus Technologies) was used for active substance release of commercial batches. Results shows that the 2nd generation kit, which will be used on future commercial batches, quantifies 25% less HCP. Considering all these facts with route of administration (intramuscular (IM)), low volume of dose (0.5 mL) and limited frequency of injection, an acceptance limit of ≤80ng/dose is supported. This limit has been based on available Phase 3 clinical batches and commercial scale batches, where the adequacy of the purification steps have been demonstrated.

Batch analysis

Batch data from two clinical batches and three commercial scale batches are presented. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

For the reference standard used for determination of Antigen Content and Identity by Competitive liquid Phase ELISA, the Applicant is referring to section 3.2.P.6. The respective information is considered sufficient.

Stability

The active substance is immediately formulated following sterile filtration (no hold time is applied). Therefore, no stability data are presented in this section.

2.3.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is a sterile suspension intended for intramuscular injection, presented in a multidose glass vial of 10 doses.

The vaccine is adjuvanted with hydrated aluminium hydroxide and CpG 1018. The adjuvant aluminium hydroxide is commonly used for vaccine manufacture. The presented specification complies with the requirements of Ph. Eur. Monograph 1664 on Aluminium hydroxide, hydrated, for adsorption. The applicant established an additional specification for testing of bacterial endotoxin and confirmation of sterility according to Ph. Eur. after dispensing the aluminium hydroxide, which was found acceptable.

The synthetic oligomer cytosine phospho-guanine (CpG) 1018 is a known excipient, provided by Dynavax Technologies Corporation, is added as another adjuvant and contains an immunostimulatory sequence. Specifications and sufficient information on the formulation of CpG 1018 are provided. The specification for CpG 1018 covers appearance, identity (molecular weight and sequencing), purity (LC-MS), product related impurities, metals (ICP-MS), residual solvents (GC), concentration (UV), sodium content (ICP-OES), endotoxin and bioburden (both USP methods). Suitable parameters were validated for non-compendial methods. The applicant confirmed that compendial methods for endotoxin and bioburden testing were verified for their intended use. A Quality Agreement between Valneva Austria GmbH and Dynavax Technologies Corporation has been established, which includes obligations and responsibilities for Quality Assurance and Quality Control requirements. Dynavax will communicate any major changes in the CpG 1018 process and will also ensure that the quality profile of the adjuvant remains the same. Overall, the excipient CpG 1018 is well controlled.

Recombinant human albumin (rHA) is considered a novel excipient: At the active substance level, rHA is added in order to minimize antigen loss by unspecific adsorption on surfaces and during filtration. Of note, the rHA is derived from yeast. Although rHA from rice was previously used as process aid for a medicinal product registered in the EU, the rHA derived from yeast is regarded a novel excipient. The Applicant provided appropriate information on manufacturing and control of rHA in the chapter A.3 Novel Excipients of the dossier. The rHA release specification is based on requirements of the USP monograph on rAlbumin Human NF, which is considered appropriate due to the lack of a respective Ph. Eur monograph. The specification is mostly aligned with the specification of the rHA manufacturer i.e. selected process related impurities are tested as well (yeast antigens, column leachates (DBA/PBA), metal ions nickel and potassium). Overall, the specification is appropriately justified. The applicant integrated information derived from the rHA manufacturer on validation of analytical procedures, which confirms that analytical methods were validated according to USP and ICH guidelines. Stability data have been included confirming that the rHA remains physically and chemically stable for a period not exceeding 60 months at 5 ± 3 °C and 36 months at 25 ± 2 °C respectively. Additional information on manufacture and control is presented in section 3.2.A.3. of the dossier and it was considered sufficient.

Overall, sufficient and appropriate information on the manufacture, characterisation and controls of the novel excipient, according to the active substance format was provided.

The specification of Dulbecco´s Phosphate Buffered Saline (DPBS) is based on Ph. Eur. compendial tests for Endotoxin, pH, Osmolality and Sterility. Currently, the specifications for the DPBS excipient are not deemed sufficient and the Applicant has committed to introduce testing for all components of DPBS excipient (identity and content) and to submit the specifications post-approval, which was considered acceptable. The revised specifications should be provided when available. **(Quality recommendation 6)**

Remaining excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards.

Formulation studies established the final concentration of aluminium hydroxide and the adsorption time. It was appropriately shown that a concentration of 1 mg/ml aluminium hydroxide is able to immediately adsorb all virus and rHA from the active substance i.e. no virus and rHA was detected in the supernatant immediately after addition of aluminium hydroxide. It was established that after aluminium hydroxide adsorption the CpC 1018 adjuvant can be added. Binding of CpC 1018 to aluminium hydroxide was shown to be instantaneous but can be desorbed using phosphate. The degree of adsorption of CpG 1019 remains constant, with about one quarter of CpG 1019 bound and three quarters free in solution. Information presented on formulation development is considered acceptable.

Formulation changes during process development and manufacturing of clinical phase 1/2 and clinical phase 3 material are sufficiently described and justified. Besides the difference in scale (5 L vs. 40 L), the formulation of clinical phase 1/2 material was performed just prior to administration (bedside mixing) by adding CpG 1018 to the Aluminium Hydroxide adsorbed active substance. A further difference between clinical phase 1/2 and clinical phase 3 material is a slightly different composition of the buffer. A report demonstrating the comparability between phase 1/2 and phase 3 process and phase 3 and commercial process is provided in the dossier and it was found acceptable.

Process development for clinical phase 3 involved scaling up and including CpG 1018 into the formulation process (no bedside mixing) as well as enhancing analytical testing and specifications. There was no change in the process for dilution of the active substance or the final concentration of adjuvants.

For commercial manufacturing, the clinical phase 3 final bulk vaccine process was scaled-up without significant changes to the process. A comparability exercise was performed. Two clinical phase 3 batches were compared to three commercial scale lots (consistency batches). Final bulk vaccine quality attributes were in principle comparable.

Aseptic filling of the final bulk vaccine to final lot was developed with a focus on prevention of aluminium hydroxide sedimentation and adequate homogenization of the suspension. Differences in the filling process between clinical phase 3 and commercial process concern the scale up. Fill volume and equipment parameters were appropriately established by mixing studies and studies on the effect of unplanned stops during filling (homogeneity study).

There is no overage during the manufacturing. A set point volume of 5.5 mL (5.4-5.6 mL range) was defined and this fill volume is deemed suitable to allow the retrieval of ten doses using an injection device where the dead volume (syringe and needle) does not exceed 30 µL.

The Final Bulk Vaccine container closure system (CCS) consists of 50 L Stedim Flexboy bags that are also used to hold the Purified Inactivated Virus on Active Substance level. Information on extractables

and leachables were provided and found appropriate. Biocompatibility was presented and assessed. Overall, the CCS for Final Bulk Vaccine is adequate.

The Final Lot CCS consist of a Type I 6R clear glass injection vial closed with 20 mm injection Flurotec stoppers and secured by aluminium flip-off caps. Appropriate extractables and leachables assessment was performed on the rubber stopper. Testing of the CCS was performed to establish the fill volume depending on which injection device is used and to identify the amount of overfill to ensure retrieval of the last dose. Furthermore, functional testing established penetrability, fragmentation and self-sealing of the CCS according to Ph. Eur 3.2.9. Overall, the container closure system appears appropriate and is sufficiently described. The packaging material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

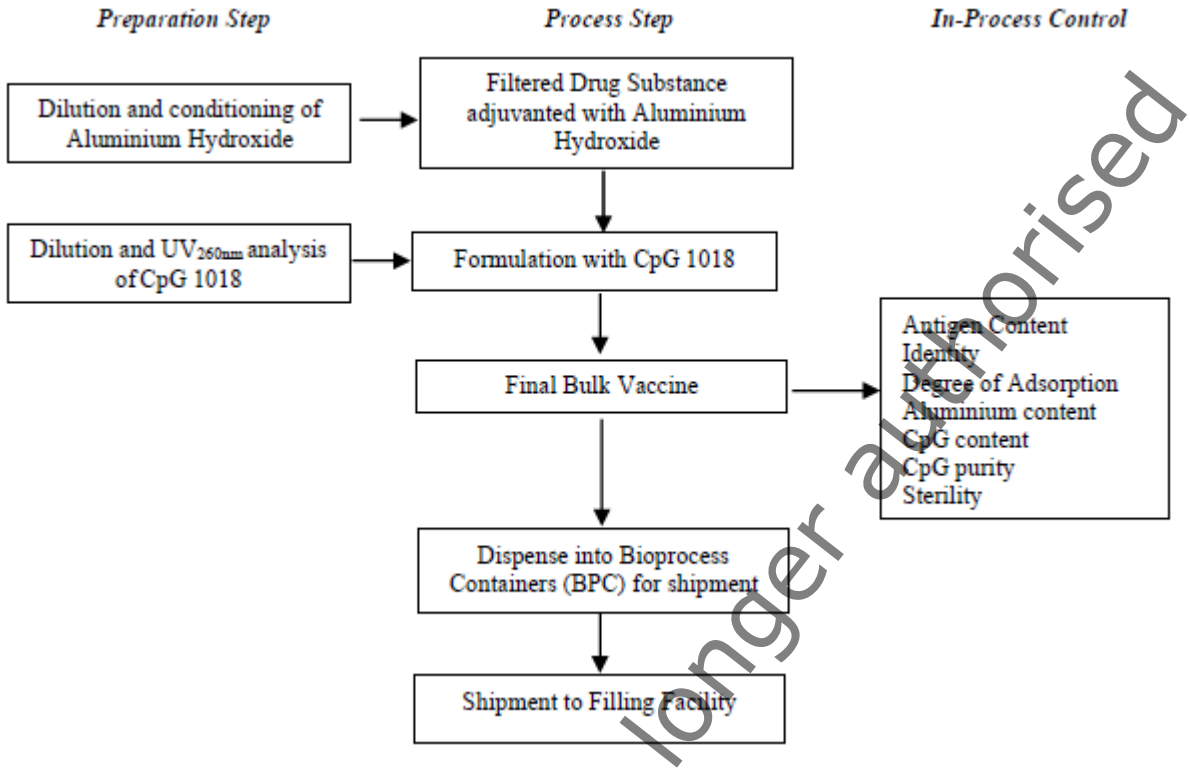
Manufacture of the product and process controls

The final bulk vaccine is manufactured at Valneva Scotland Limited (Oakbank Park Road, Livingston EH53 OTG, Scotland, UK). Aseptic filling of the finished product, visual inspection, labelling, packaging and storage takes place at Valneva Sweden AB (Asplund), Gunnar Asplunds Allé 16, Solna, Stockholms Lan, 171 69 Sweden. Batch release of the finished product by the Qualified Person is performed at Valneva Sweden AB or optionally at Valneva Austria GmbH, Campus Vienna Biocenter 3, Landstrasse, Vienna, 1030, Austria, if required. The sites are appropriately authorised and hold valid GMP certification.

The finished product manufacturing consists of aseptic formulation of final bulk vaccine and aseptic filling of the final lot. For final bulk vaccine manufacturing, aluminium hydroxide and CpG 1018 dilutions are prepared. Filtered active substance is adjuvanted at first with aluminium hydroxide and then formulated with CpG 1018. After in-process controls, the final bulk vaccine is dispensed into bioprocess containers and shipped to the filling facility. All the containers meet Ph. Eur. Requirements. For final lot manufacturing the final bulk vaccine is resuspended, transferred into the filling vessel and homogenized and then filled into vials, stoppered and capped.

A flow chart of the manufacturing process steps, including in-process controls as well as a narrative description of each step was provided.

Figure 1: finished product manufacturing process flow chart



Tables presenting Critical Process Parameters (CPPs) and in-process controls and their specifications are presented. The specifications for CPPs are unchanged compared to process validation. The specifications for in-process controls are mostly unchanged compared to process validation. Additional controls have been specified for Antigen Content/Identity. Furthermore, CpG 1018 Purity (by RP-HPLC) limit was tightened during the procedure.

The Applicant identified critical steps as those steps associated with sterile filtration, homogeneity of adjuvants and aseptic filling. At the level of final bulk vaccine the antigen content/identity, degree of adsorption, aluminium and CpG content, CpG purity and sterility are tested as in-process controls and specifications are presented. As requested during the procedure, the Degree of Adsorption by ELISA was appropriately tightened.

In order to address a major objection, the in-process control acceptance criteria for antigen content by ELISA of the Final Bulk Vaccine was tightened. Furthermore, the IPC result will be a mean value of three independent measurements in order to increase precision of the result. In addition a further limit was introduced: If the Final Bulk Vaccine measures in a certain range, the corresponding Final Lot must measure a specific amount to be released. This appropriately addressed the previously not clinically justified release limits (see also assessment of final lot specification below in this report).

For final lot manufacturing a maximum time for resuspension and transfer of final bulk vaccine to the filling vessel is defined as well as a maximum time for the filling process itself and the final visual inspection. These times were defined due to the critical influence of the temperature on the final bulk vaccine. Risks associated to the homogeneity of the product were addressed by a separate evaluation during manufacture process development. Fill volume of the vials is controlled as an in-process control. Overall, the proposed in-process control tests and their acceptance criteria are in line with expectations for this kind of manufacturing process.

The Applicant validated a final bulk vaccine batch size range. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate. The Process Performance Qualification (PPQ) was performed on three full scale batches of Final Bulk Vaccine and Final Lot based on a Failure Mode and Effects Analysis (FMEA) that identified Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs), which is appropriate. One supportive batch is also included in the PPQ evaluation which can be accepted. A batch size range for the Final Bulk Vaccine is proposed Ten process stops of more than 10 minutes (seven more than 15 min.) have been integrated during filling in order to challenge the robustness of the Aluminium Hydroxide homogeneity. The specified maximum Final Lot filling time was not reached by the filling process itself, but by filling of the certain batch and then storing QC release and stability samples for additional 1h 18 min at room temperature before returning to cold storage. This can be accepted as a surrogate in order to challenge the maximum filling time. In addition, media fill studies for Final Bulk Vaccine and Final Lot were performed as well as hold time studies for equipment. Gamma irradiation of Aluminium Hydroxide was appropriately qualified. No critical deviations were identified.

Overall, the process validation indicates that the final bulk vaccine and final lot manufacturing process is capable of manufacturing material of consistent quality. While the applicant confirms that the manufacturing target of 33 AU/0.5mL was applied to clinical and process validation batches, the release result for AU/dose for Final Lot process validation batches is consistently below the manufacturing target of 33 AU/0.5mL (all 29 AU/dose). The applicant explained that this is accounted for due to assay variability (which is about ±7%) and process variability. This can be accepted.

The applicant qualified shipping in a single temperature controlled vehicle by monitoring the temperature on final bulk vaccine. Shipping at 2-8 °C from Valneva Scotland to Valneva Sweden was performed one time. A transport validation with all aspects as recommended in EU GMP Guide Annex 15 was not presented by the Applicant, however a qualification of one commercial scale shipment using temperature loggers was performed, which is acceptable.

Bacterial retention studies of sterilising filters used for sterile filtration of the aseptically manufactured active substance and for diluted CpG 1018 confirm the suitability of the sterile filters.

Product specification, analytical procedures, batch analysis

The finished product specifications contain tests for: appearance (visual examination, Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), extractable volume (Ph. Eur.), identity (ELISA), antigen content (ELISA), degree of adsorption (ELISA), aluminium content (ICP-OES), CpG content (RP-HPLC), CpG purity (RP-HPLC), CpG degree of adsorption (RP-HPLC), endotoxin (Ph. Eur), and sterility (Ph. Eur.).

The proposed release specifications mainly comply with requirements of Ph. Eur. general monograph 0153 "Vaccines for Human use" and 0520 "Parenteral Preparations", where applicable. Aluminium is not tested per Ph. Eur 2.5.13 but using a suitable validated assay (ICP-OES), which is acceptable.

The finished product release specification is aligned with the finished product stability specification. Appearance, pH, osmolality, antigen content, degree of adsorption, aluminium content, CpG content, CpG purity, CpG degree of adsorption, endotoxin, and sterility are controlled at stability. Antigen content at the end of shelf life is controlled with acceptable acceptance criteria.

In response to a major objection, the applicant tightened the finished product antigen content (potency) specification and included an upper limit as well. However, the lower limit initially was not considered clinically justified. In order to address this issue, the applicant further tightened the lower limit for the Final Bulk Vaccine. Additionally, the reported value is an average from three independent

measurement in order to increase precision. Moreover, as an added level of control, a further limit was proposed: If the final bulk vaccine measures on the lower end of specification limits, the corresponding final lot must measure a certain specified amount to be released. The applicant's proposal in essence means that either the final bulk product or the final lot has to be witin an acceptable limit measured with the more precise assay. It is agreed that the Applicant's proposal meets the goal to ensure that the released final lot has a potency that is sufficiently representative of the lot used in the relevant clinical trial i.e. that the potency of the final lot is near the label claim of 33 AU/0.5mL. The Applicant appropriately implemented the newly proposed limits into the respective dossier chapters (3.2.P.3.3 and 3.2.P.3.4). A recommendation is given, to evaluate specification limits and process capability when data from 30 commercial batches have been obtained **(Quality recommendation 1)**.

The currently proposed acceptance criteria for aluminium content and CpG 1018 content can be used for the finished product specifications. The applicant is requested to review the finished product specifications for aluminium content and CpG 1018 content when sufficient data (from approximately 30 batches) are available **(Quality recommendation 7)**.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Based on a risk assessment, the applicant concluded that during manufacturing of Final Bulk Vaccine and Final Lot, there is no introduction of new process- or product related impurities, which is endorsed.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods (ICP-OES, RP-HPLC, competitive liquid phase ELISA) appropriately validated in accordance with ICH guidelines.

Methods for endotoxin and sterility are compendial methods which have been implemented according to the respective monographs of Ph. Eur. and/or USP and were verified for their intended purpose according to respective pharmacopeial requirements.

The Container Closure Integrity Test (CCIT) is a liquid immersion microbial challenge test and appropriate validation activities of the CCIT were presented.

Batch analysis

Batch analyses data for six final lot batches that were manufactured at full commercial scale up to the purified inactivated viral (PIV) stage are presented. These comprise of two clinical phase 3 batches, three process performance qualification (PPQ) batches and one PPQ supporting batch. When comparing the presented data, most quality attributes are comparable. The antigen content seems slightly higher for the clinical phase 3 batches compared to the PPQ batches, which is due to assay variance (±7%) and process variability. Batch results confirm the consistency of the manufacturing process.

Reference materials

The applicant presented detailed information and data on the identity, source, history, characterisation and stability of the reference material for the competitive liquid phase ELISA. The mean of a total of 34 data points for competitive liquid phase ELISA from different operators and different days was used to assign the primary reference standard value relative to the clinical phase 3 reference standard, which is appropriate. A clear link between the primary reference standard material and the clinical phase 3 material was established. The reference standard is formulated in a significantly different matrix than the samples, and the applicant confirmed representativeness of the reference standard by confirming parallel dose-response curves. The procedure and acceptance criteria for shift determination when introducing a new reference material was described. Appropriate information on establishment, control, stability and changeover of all critical reagents especially the antibodies used in this assay was provided.

Stability of the product

The Applicant proposes a shelf life of 6 months for the final bulk vaccine and 12 months for the final lot (finished product), which can be accepted based on presented data. The storage conditions as stated in the SmPC (stored in a refrigerator (2°C to 8°C)) are acceptable.

Clinical phase 1/2 stability batch data at long-term storage conditions of 5°C ± 3°C and accelerated conditions of 25°C ± 2°C were established. However, the dataset is limited.

For clinical phase 3 final bulk vaccine batches a stability study was not performed due to an error in sampling. Clinical phase 3 final lot stability batches were stored in upright and inverted position. All quality attributes are stable up to 11 months at 5°C ± 3°C. A downward trend in antigen content but no other quality attributes has been detected at accelerated conditions of 25°C ± 2°C over 6 months. A fast decline of antigen content below limit of quantification was confirmed after one month at 37 ± 2°C. Data for vials in upright and inverted positions were comparable. The stability data from the phase 3 clinical lots are deemed representative of the commercial product.

Final bulk vaccine process validation batches were tested in line with ICH conditions at 5°C ± 3°C, 25°C ± 2°C and 37 ± 2°C. Available results at long-term and accelerated conditions do not show obvious changes up to six months' time point. Forced degradation studies show a decrease of antigen content after 1-2 weeks below the limit of quantification with all other quality attributes remaining stable.

Final Lot process validation batches were tested in line with ICH conditions at 5°C ± 3°C, 25°C ± 2°C and 40 ± 2°C. Results at long term conditions do not show obvious changes for up to 12 months for two clinical finished product lots and up to nine months for the three PPQ finished product lots. Results at accelerated conditions do not show obvious changes up to six months' time point. The antigen content of samples stored at forced degradation conditions already declines below the limit of quantification after one week. All other quality attributes remain stable.

As requested, the Applicant appropriately included the quality attribute "CpG degree of adsorption" into the stability study specification in order to align with the finished product specification.

Taken together, based on the currently available data, a shelf life of 12 months is deemed acceptable for the final product at 5°C ± 3°C.

An in-use stability study was performed at 5°C ± 3°C and room temperature (25°C) with testing time points at 0, 3 and 6 hours. Only the antigen content was tested in this study, which is deemed acceptable because this assay has been shown to be stability indicating assay. Results were stable

over 6 hours and confirm in-use stability over 6 hours. Because the applicant has shown the comparability of phase 3 and commercial process batches, the in-use stability can be applied to commercial batches. As requested by ICH guidelines Q1A and Q1B, the Applicant should also perform a photostability study on at least 1 representative final product batch. The Applicant confirmed to perform this study post-approval and estimated to report the outcome of the study in Q1 2023, which is acceptable. Results should be provided when they are available **(Quality recommendation 8)**.

Post approval change management protocol(s)

Two post approval change management protocols (PACMPs) are included in the dossier. The first is related to the implementation of IDT Biologika GmbH as additional active substance and finished bulk product manufacturing site. This change furthermore includes upscaling of finished bulk product manufacture.

The second PACMP concerns the introduction of an additional facility, Valneva Sweden AB (Tomteboda) for filling, visual inspection, labelling and secondary packing of SARS-CoV-2 vaccine finished product.

Both PACMPs are acceptable.

Adventitious agents

The control as regards mycoplasma, bacteria and fungi are deemed appropriate.

Animal-derived materials used in the manufacture include FBS (covered by TSE Certificates of Suitability), bovine lactose (from milk obtained from healthy animals fit for human consumption), protamine sulphate of salmon origin, and bovine source tallow derivatives within filter components and tubings (manufactured under harsh conditions). The risk arising from TSE agents can be considered as negligible.

Potential sources of adventitious viruses are starting materials (i.e. FBS-containing MCB, FBS-containing WCB, and MVSB, all used prior to commercial manufacture and serum-free MCB, serum-free WCB, and serum-free MVSB used for commercial manufacture), raw materials and viruses inadvertently introduced during production. Appropriateness of control of cell and virus banks is discussed in section 'control of materials' above. Control of raw materials with respect to potential viral contaminants (e.g. FBS is tested for specific viruses, sterile filtered, heat inactivated and gamma-irradiated; other materials are unlikely to pose a risk as regards viral contamination) is considered appropriate.

Testing for adventitious viruses is performed during relevant steps of production (cell banks, master virus bank, production inoculum, protamine-sulphate treated harvest). Negative control cells used for upstream manufacturing are tested for haemadsorption, CPE and by *in vitro* assay in compliance with Ph. Eur. 2.6.16.

Viral clearance studies were performed to assess the effectiveness of β-propiolactone (BPL) treatment for inactivation of potential viral contaminants. The study has been performed in line with relevant guidance (ICH Q5A, CPMP/BWP/268/95) using three model viruses (i.e. BVDV, PPV, SV40). The down-scaled model of the virus inactivation step can be considered as representative for the commercial manufacturing process. Respective results indicate that BPL treatment at concentrations of ≥ 0.05 % effectively inactivates BVDV and PPV, while showing reduced capacity to inactivate SV-40 (nevertheless inactivation ≥1.0 log10 was observed). Fast inactivation (with inactivation below the limit of detection for the last 3 kinetic time points) was observed for BVDB. For PPV residual infectivity was observed but with a high inactivation of more than 7 log10 indicating that the BPL treatment is

effective for this virus type. Overall, it can be concluded that BPL treatment is also efficient for inactivation of a broad panel of potential viral contaminants.

GMO

Not applicable.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance of this vaccine is a purified inactivated SARS-CoV-2 virus strain, adapted to grow on Vero cells, purified as a whole virus and inactivated using β-propiolactone. The applicant's statement that the active substance can be considered as a new active substance (NAS) is supported.

The active substance process is appropriately described. Information with regard to hold times and their respective validation has been provided.

Batch release and process validation data presented indicate that the process is capable of delivering finished product of consistent quality.

The manufacturing process development for the early development phase (clinical phase 1/2) the clinical phase 3 material and the commercial process development phase is well described. Critical process changes in development are outlined in tabulated form and a justification has been provided.

Raw and starting materials including the cell banks and master virus seed used in the manufacture of VLA2001 are appropriately listed in the dossier. Information on the quality and control of these materials has been provided. Pending characterization data for cell banks and missing NGS qualification data may be provided post-approval (RECs). The data as currently provided is acceptable and the minor pending information has no impact on the Benefit/Risk ratio of the product.

An assessment for critical parameters was performed based on ICH Q9.

Characterisation studies indicate that the majority of virus particles is present in the monomeric state and revealed no degradation products of the S protein. Furthermore, the impact of BPL modification on antigenic sites has been investigated (impact of BPL modifications as regards immunogenicity is considered unlikely). Sequence analyses of spike protein was performed at the level of MVSB, Production Inoculum and active substance intermediate before inactivation. Non-silent mutations were identified at certain amino acid positions; their potential impact on immunogenicity and antigen integrity is unlikely. NGS RNA sequence analysis of each new PI lot should be continued as part of the supportive control testing strategy and setting of specifications should be evaluated upon availability of enough data (REC).

Process-related impurities including host cell DNA and HCP, FBS, residual Protamine Sulphate, and residual β-Propiolactone are appropriately controlled at the level of active substance or reduced to sufficiently low levels (FBS).

The proposed specifications cover relevant quality attributes and are overall in line with ICH Q6B. Acceptance criteria for residual HCP was revised. The Applicant is requested to provide pH results and set active substance specification limits when sufficient data (from approximately 30 batches) is available (REC).

Method validations are summarized in tabulated form and respective verification and validation reports are presented.

The active substance is formulated immediately following sterile filtration and no hold time/storage is applied to the active substance. Therefore no stability data are presented. Description and specifications of the 400 L tote bags used to collect the sterile filtered active substance is presented and they are acceptable.

The proposed release limits and the control strategy to ensure that the released finished product has a potency that is sufficiently representative of the lot used in the relevant clinical trial i.e. that the potency of the finished product is near the label claim of 33 AU / 0.5 mL is now deemed acceptable. However, the Applicant is requested to evaluate process capability when data from 30 commercial batches have been obtained (analysed with the improved application of the method), with an analysis of the batch population distribution around the Antigen Target of 33 AU/0.5 mL. It is also requested to review the finished product potency specification based on these additional batch data. Importantly, results from ongoing clinical trials comprising additional DP batches can also be included in the re-evaluation of potency specification limits (REC).

The currently proposed acceptance criteria for aluminium content and CpG 1018 can be used for the finished product specifications. However, the Applicant should revise these finished product specifications when data from more batches are available. It is requested to provide an estimation when sufficient data (from about 30 batches) will be available. (REC)

Sufficient and appropriate information was provided for the novel excipient recombinant human albumin.

Analytical methods for release testing were described and properly validated.

The finished product manufacturing processes was shown to yield product of consistent quality that was compliant with the specifications.

Detailed and appropriate information and data on the identity, source, history, characterisation, value assignment, shift assessment, critical reagents and stability of the reference material for the competitive liquid phase ELISA was provided.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the rolling review phase, a major objection on the lower limit for the potency specification and on insufficient information on the reference standard were raised. The major objections were addressed by strengthening the control strategy and providing missing information, which was considered satisfactory.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These points are put forward and agreed as eight recommendations for future quality development.

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 has been presented to give good assurance 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:

Description of post-authorisation measures
Quality recommendations
1. The Applicant is requested to evaluate process capability when data from 30 commercial batches have been obtained (analysed with the improved application of the method), with an analysis of the batch population distribution around the Antigen Target of 33 AU/0.5 mL. It is also requested to review the Finished Product potency specification based on these additional batch data. Importantly, results from ongoing clinical trials comprising additional FP batches can also be included in the re-evaluation of potency specification limits.
2. Section 3.2.S.2.3 and the relevant appendix should be updated with the result of the Tumorigenicity assay performed on the Serum Free EoPCB WCB when it is received from the CRO (expected July 2022).
3. The Applicant is requested to provide the results of the qualification of the NGS method that is used to replace the *in vivo* virus testing on the Master virus seed bank, when the results are available.
4. NGS RNA sequence analysis of each new PI lot should be continued as part of the supportive control testing strategy and setting of specifications should be evaluated upon availability of enough data.
5. The Applicant is requested to provide pH results and set Active Substance specification limits when sufficient data (from approximately 30 batches) is available.
6. The Applicant is requested to provide the identity and content specifications for the Dulbecco Phosphate Buffer Saline (DPBS) excipient when available.
7. The Applicant is requested to review the DP specifications for aluminium content and CpG 1018 content when sufficient data (from approximately 30 batches) are available.
8. The Applicant is requested to perform a photostability study on one representative final product batch (in accordance with ICH guidelines Q1A and Q1B) and to communicate the results when they become available.

2.4. Non-clinical aspects

2.4.1. Introduction

Valneva's COVID-19 Vaccine (VLA2001) is a highly purified, inactivated, whole virus adjuvanted SARS-CoV-2 vaccine grown on Vero cells developed for active immunisation of individuals to prevent COVID-19 disease. The vaccine production platform, developed by Valneva as part of its Japanese encephalitis vaccine (Ixiaro, EMEA/H/C/000963), uses an inactivated whole-virus approach where live wild-type virus is grown in Vero cell culture and then inactivated via chemical treatment with β-propiolactone in order to preserve the native surface structure of the S-glycoprotein. The vaccine is based on the "Wuhan strain" and contains aluminium hydroxide and CpG 1018 as adjuvants.

COVID-19 Vaccine Valneva is intended for authorisation as a multi-dose vial. The volume for intramuscular injection is 0.5 mL (one dose) which contains 33 Antigen Units (AU) of inactivated SARS-CoV-2. The vaccine is to be injected intramuscularly (i.m.) in the deltoid region in 2 doses, 28 days apart.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

Immunogenicity of VLA2001 in mice

Non-clinical pharmacodynamics studies of VLA2001 have been performed in female BALB/c mice in two separate experiments. Mice (> 6 weeks old) were immunised twice subcutaneously, three weeks apart (Day 0 and Day 21), with three different doses (ranging from 0.3 AU to 35 AU per dose) with and without CpG 1018 (in addition to antigen & aluminium). Immune responses were characterised by measuring binding IgG by ELISA, neutralising antibodies by a plaque reduction neutralisation test (PRNT), Th1/Th2 and IgG subclasses.

VLA2001 was immunogenic in mice and an increase in immunogenicity was observed when CpG 1018 was used together with aluminium as adjuvants, when measured by ELISA. The VLA2001 vaccine also induced a neutralising antibody response as measured by a pseudovirus-based neutralisation assay. The presence of CpG 1018 skewed the immune response in mice towards a distinct Th1 response. However, this conclusion is solely based on humoral responses as no data from cellular responses in mice have been presented to support this.

One known potential cause for vaccine mediated enhanced respiratory disease (VAERD) or antibody disease enhancement (ADE) may be a strong Th2 response. The detected Th1 response in VLA2001 could therefore be seen as an indicator for the reduction of potential risks for VAERD or ADE upon infection. However, suboptimal doses of vaccine have not been tested for potential VAERD.

Immunogenicity of VLA2001 in rats

Immunogenicity of VLA2001 vaccine was tested as a part of the repeated dose and local tolerance toxicity study (RDTS) in female and male rats. Sixty rats were dosed in the study, 50 receiving VLA2001.

Rats were given i.m. injections (2 sites × 0.2 mL, 28 AU) on three occasions with 2 weeks interval over a period of 29 days (days 1, 15, 29). Serum samples from the animals assigned to the recovery phase of the study were analysed to assess the immunogenicity of the VLA2001 vaccine and monitor the immune response over time.

Very low although detectable antibody titres were observed in rats after receiving a single dose of the VLA2001 vaccine. The second immunisation increased antibody titres significantly. However, after the second immunisation antibody titres reached a plateau and a third immunisation did not further increase antibody titres. A slightly higher immune response was observed in female compared to male rats.

Immunogenicity of VLA2001 in hamsters

The immunogenicity study in Syrian Golden Hamster (6-8 weeks of age) was performed using clinical phase 3 batch which was part of the stability degradation studies and stored at different conditions of temperature and relative humidity. Hamsters were injected subcutaneously twice (day 0 and Day 28) with 100 µl/animal, and serum was collected at Day 42. The induced neutralising antibody response was determined using a microneutralisation assay (MNA), which was designed to test immunogenicity of the SARS-CoV-2 vaccine candidate.

The neutralisation response against two strain of the virus tested (Wuhan and Alpha) was seen in all animals using the clinical batch stored at long term (+5°C ± 3°C) storage condition. A decline in the immune response, was seen when using material stored under accelerated (+25°C ± 2°C, 60% rH ± 5% rH) storage condition. No neutralising antibodies were detected upon injection of material stored under forced degradation conditions (+37°C ± 2°C, 60% rH ± 5% rH) and placebo.

A passive transfer study was performed in Syrian hamster. The study aimed to assess the ability of pooled human serum from vaccinated individuals to protect hamsters against severe lung pathology, reduce clinical signs and reduce viral levels in the respiratory tract. To achieve this, hamsters were administered pooled serum via the intraperitoneal route, prior to challenge the following day with SARS-CoV-2. The study designed included 8 groups where different concentrations of serum or placebo was administered.

Increase in SARS-CoV-2 neutralising antibodies in treatment groups following passive transfer indicated that the procedure was successful in these animals. Following SARS-CoV-2 challenge, hamsters in treatment groups receiving higher amounts of neutralising antibodies had less clinical observations compared to those animals receiving less nAb and the control group. A trend for reduction in pathology was detected in the lungs of hamsters from groups receiving higher amounts of neutralising antibodies when compared to negative control groups, with a significant reduction of pathology in the lung of hamsters that received clinical trial serum comprising the highest SARS-CoV-2 neutralising titre of serum samples.

Overall, no signs of disease enhancement were observed.

Immunogenicity and efficacy of VLA2001 in non-human primates

Safety, immunogenicity and efficacy of VLA2001 against SARS-CoV-2 challenge was evaluated in a study with 24 male cynomolgus macaques. Clinical and laboratory endpoints were investigated in the NHPs following two different dosages of the vaccine VLA2001 (adjuvanted with aluminium + CpG 1018). VLA2001 was administered intramuscularly and with an immunisation scheduled of 2 doses 3 weeks apart (days 0 and 21). The antigen doses were planned to be 11 and 53 AU in the medium and high dose groups, respectively. However, after reassessing the antigen level using 2nd generation antigen ELISA, the AU value of the high dose was adjusted from 53 to 35 AU and the medium dose vaccine from 11 to 7 AU. The high dose antigen level is on par with the dose used clinically and therefore considered acceptable. A third group was injected with Dulbecco's Phosphate Buffered Saline (DPBS) and served as negative control. Unadjuvanted vaccine formulation was not tested in the study. However, this is considered acceptable as the need for adjuvant was documented in the pharmacology study in mice. Following immunisation all animals were challenged and exposed to SARS-CoV-2 by intranasal and intratracheal routes.

Animals were monitored during the immunisation as well as during the challenge phase of the whole study (e.g. body weight, temperature, Draize score, complete blood count and haematological assessment, behavioural and clinical scoring). In addition, examination of lung pathology, histopathology of selected tissues (lymph nodes, injection site, liver, spleen and kidneys) and characterisation of immune response types (Th1/Th2) were also performed in the challenge studies.

The immune response was determined by ELISA and by a serum neutralisation assay. Genomic and subgenomic viral RNA (virus colonization) was quantified in nasopharyngeal fluids, tracheal fluids, rectal fluids, and bronchoalveolar lavage (BAL) fluids of the control and the vaccinated NHP using RT-qPCR (quantitative reverse transcription polymerase chain reaction).

No clinically significant observations were made upon injection, in terms of fever or modification of haematological parameters. Some treatment related non-adverse histopathological changes were observed, including increased splenial cellularity and granulomatous inflammation at the injected site. Animals immunised with VLA2001 adjuvanted with alum and CpG 1018 induced SARS-CoV-2-binding IgGs, a SARS-CoV-2-neutralising serological response, and a Th1-biased CD4+ T cell response against spike glycoprotein (S1, S2 and RBD) and nucleocapside.

Placebo-treated control animals exhibited clinical signs of SARS-CoV-2 infection after SARS-CoV-2 challenge. When comparing the histopathological results of lungs with results from other SARS-CoV-2 challenge studies in NHPs, it seems that the pathological reactions observed were relatively mild, characterized by a low increase in the number of lymphocytes, neutrophils and macrophages. Type II pneumocytes hyperplasia was rarely observed. The main observed lesions were macrophagic infiltration of the alveoli and inflammatory infiltration of the alveolar interstitium. Diffuse alveolar damage was extremely rare. Contrastingly, control animals showed moderate to severe levels of inflammation and presence of eosinophils at day 7 after challenge. The CT scans in this study also showed low to no signs of lung lesions with no differences between the groups.

Viral loads were assessed using RT-qPCR for both genomic and sub-genomic viral RNA. The quantities of both viral RNAs peaked 2-4 days post challenge in nasopharyngeal and tracheal fluids in the control group. Rectal genomic and sub-genomic viral RNA peaked on day 7 for 4 and 3 animals in the control group, respectively. At day 3 post exposure positive detection of BAL genomic and sub-genomic viral RNA was seen in 6 and 3 animals in the control group, respectively. No genomic or sub-genomic viral RNA was detected in any of the vaccinated animals at day 3. Experience from similar studies in published literature and other COVID-19 vaccines indicate that peak viral loads in BAL occur on Day 2-3 after challenge. It is thus acceptable to do the single BAL measurement on Day 3. However, it would have been preferred if BAL fluids were collected and analysed for the same timepoints as the other fluids. Overall, animals in the control group acquired only mild COVID-19 disease, like detectable viral RNA in the upper and lower respiratory tract and lung lesions. Vaccination reduced the incidence and magnitude of viral replication (detection of viral genomic RNA) in the respiratory tract and reduced the lung histopathology score.

Overall, no signs of disease enhancement were observed.

It can be concluded from the study in NHP, that immunisation with the VLA2001 vaccine adjuvanted with alum and CpG 1018 to cynomolgus monkeys led to a robust immune response, and demonstrated to be effective against the disease symptoms of SARS-CoV-2 infection in those animals. Furthermore, it reduced also the viral replication in this animal model.

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 dedicated studies have been performed, which is in accordance with applicable guidelines.

2.4.2.4. Pharmacodynamic drug interactions

No studies on 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 is based on two GLP-compliant toxicology studies: a repeated dose toxicity study in rats and a developmental and reproductive toxicity study.

The repeated dose toxicity study was conducted with the phase I clinical trial material, whereas the DART study uses the phase III clinical batch. Overall, the vaccine batches used in the non-clinical toxicology studies are considered acceptable.

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

In the repeated dose toxicity study in rats, the animals received three intramuscular injections containing 28 AU per dose, within 2 a week's timeframe (days 1, 15 and 29), i.m. administration of 0.2 mL VLA2001 on each of the hind limbs. The aim of the study was to determine the potential toxicity of VLA2001, to evaluate the potential of reversibility for any of the findings (study was terminated at study day 51).

The following endpoints were evaluated in this study: mortality, clinical observations, body weight, food consumption, body temperature, ophthalmology, clinical pathology parameters (haematology, coagulation, clinical chemistry, and urinalysis), AGP and A2M analysis (acute-phase inflammatory proteins), immunogenicity analysis, organ weights and macroscopic and microscopic examinations.

The repeated dose toxicity of the two adjuvants applied in VLA2001 (CpG 1018 and alum) was not investigated in separate adjuvant study groups. Indeed, both adjuvants were only applied together with the vaccine in the test-article (VLA2001) groups, whereas none of the adjuvants was administered to control group rats (in fact, only a 0.9% [w/v] sodium chloride solution was applied in the control group).

The administered dose was a bit lower compared to the dose administered to patients in the phase 3 clinical trial (33 AU/0.5 mL).

The Applicant observed test article related transient swelling of the hind limbs in some of the VLA2001-treated rats. Additionally, there was a test article related decrease in body weight (below 3%) after VLA2001 administration, with correlated decreases in food consumption within 4 days after VLA2001 administration. Furthermore, test article related haematological alterations (alterations in white blood

cell counts, particularly decreases in lymphocyte counts, lower platelet counts, increases in neutrophils and monocytes, alterations in red blood endpoints) and coagulation alterations (increased APTT and fibrinogen) were observed. In addition, VLA2001-related increased spleen and liver weights (and microscopically increased cellularity of lymphoid and plasma cells in the spleen) was also noted. After the recovery period, there was no full recovery of the liver and spleen organ weight increases.

At or close to the site of administration (hind limbs), necrosis/inflammation of myofibers, femorotibial joint inflammations and sciatic nerve inflammation was observed. It has been hypothesised that these inflammatory responses to the i.m. administration of VLA2001 were caused by a propagation of inflammation from the nearby injection site.

All test-article related microscopic findings were not fully resolved after the administration-free recovery phase of the study.

In clinical chemistry investigations, test article related decreases in serum triglycerides, total protein concentrations and calcium levels were observed. Additionally, decreased albumin but increased globulin levels were also reported. These clinical chemistry alterations are typical for administered vaccine products and suggest a (systemic) inflammatory response towards VLA2001 (the mode of action of this vaccine product). Also, test article related increases of serum inflammatory proteins, increases in body temperature, increases in neutrophil and monocyte counts, and macroscopic enlargement of the popliteal, iliac and inguinal lymph nodes were observed. All these effects are expectable consequences of the administration of a vaccine product and support the mode of action of VLA2001 (immunisation against COVID-19).

It is agreed that most of the observed alterations in study 514449 are not specific to VLA2001 but are specific to the administration of a COVID-19 vaccines – and in general to the administration of vaccine products – to rats.

2.4.4.3. Genotoxicity

The adjuvant CpG 1018 is already an approved adjuvant in the EU (Heplisav-B, EMEA/H/C/005063). Based on the data provided, CpG 1018 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

No consistent adversities were observed in the male and female reproductive tracts of Han Wistar rats during macroscopic and microscopic investigation in the frame of the submitted repeated dose toxicity studies.

A GLP-compliant (except for the antibody assessment) combined embryofoetal development (EFD) and littering phase study was performed in Han Wistar Rats. The clinical trial lot used in the phase III study was administered via the clinical route of administration (IM) at 80% (i.e., 26.4 AU/0.4 mL/dose) of the full human dose, still providing an acceptable safety factor on a mg/kg basis. Rats receiving VLA2001 were dosed on Day 1 (22 days prior to pairing), Day 14 (14 days after the second dose/9 days prior to pairing), and Gestation Day. The study included a control group.

The following endpoints were evaluated in this study: mortality, clinical observations, body weights, gravid uterus and corrected body weights, food consumption, oestrus cycle, organ weights and macroscopic examinations, maternal performance, ovarian and uterine examinations and litter observations, foetal data and mean foetal ossification. Additionally, vaccine induced antibodies in the blood of dams, foetuses and pups were analysed (this study portion was not conducted under GLP-compliance). Overall, the results showed no adverse changes to measured parameters attributed to VLA2001. No adverse effects on mating behaviour, maternal performance or other parameters evaluating pregnancy outcome were observed. A reduced pregnancy rate compared to expectable rates in rats was observed during the study. Live birth, viability index and lactation indices were 100%, and no toxicologically relevant effects on gestation length, sex ratio or any other toxicity in mother and pup were reported. Of note, the only difference between the control and the test-article group was a lower incidence of foetuses with the variant increased ossification of the calcaneus (in the EFD phase) in the test-article group.

VLA2001 was shown to be highly immunogenic at this dose in rats, with a maximum immune response after the second dose. The third immunisation did not further increase the antibody titres. Thus, in the gestation period only one dose was administered.

Antibodies were detected in foetuses (10-fold lower than the levels in female rats), suggesting that SARS-CoV-2 specific antibodies can be passed on to the foetuses through placental transfer. Slightly increased titres were observed in the pups than in the female rats in the littering phase, indicating possible uptake via milk.

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.

2.4.4.7. Other toxicity studies

The Applicant conducted eight studies on the non-clinical qualification of the excipient recombinant human albumin (rHA) that is used in VLA2001, and that can be categorised as novel excipient in the EEA. Specifically, pharmacology and toxicology in vivo studies have been performed with this excipient primarily to compare it's safety with that of human serum albumin (HSA). In these studies, acute toxicity in rats up to 4 g/kg (i.v.), repeated dose toxicity in rats (5 x 1000 and 2000 mg/kg i.v.; 5 x 100 mg/kg i.m. and s.c., respectively), pharmacokinetics in rabbits (1 x 500 mg/kg i.v. and 5 x 80 mg/kg s.c.), the potential of inducing anaphylaxis in a guinea pig study, and the potential of rHA to induce neoantigenicity in rabbits were examined.

These studies demonstrate that the toxicological profile of rHA was identical to the one of HSA. Acute and repeated administration of rHA and HSA in CD rats demonstrated no significant differences in the toxicological profile of both albumin products. In the pharmacokinetic rabbit studies, the pharmacokinetic profiles (biodistribution, half-lives, bioavailability) of rHA and HSA appeared very similar. Finally, in the two conducted immunogenicity studies, yeast impurities have been removed in the rHA product in comparison to earlier lots, therefore no neoantigenicity was demonstrated. In regards to the latter, no epitopes different from non-pasteurised HSA were detected in the new rHA product.

Lastly, following an assessment on the safety margins of process contaminants potentially contained in the rHA excipient in VLA2001, these impurities do not trigger any toxicological concern.

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 nonclinical pharmacodynamics studies were conducted in mice, rats, hamsters and NHP, which are species determined to be relevant for the assessment of the immunogenicity, efficacy, and safety of vaccines. A general assessment on the suitability of the chosen animal species for the primary pharmacology studies (e.g. susceptibility for SARS-CoV-2 infection) was provided.

VLA2001 was immunogenic in mice and an increase in immunogenicity was observed when CpG 1018 was used together with aluminium as adjuvants. The addition of CpG 1018 induced a skewed Th1 response.

It should be noted that the subcutaneous route of administration used in the mice study differed from the other non-clinical studies, the clinical trials and the intended use of the vaccine, where intramuscular injection has been used. Also, only female mice were included in the study. It would have been preferred that both genders were included in the mouse study. However, including only females is considered acceptable since the immunological responses were clearly demonstrated. It should also be considered that the age of the mice is only stated as older than 6 weeks and no information about the initial body weight was specified in the study report. Age may have a significant effect on the immune response, and if the age of the mice in the different groups varied significantly this may have affected the outcome of the study.

VLA2001 was also found immunogenic in rats in the repeated dose toxicity study. Very low detectable antibody titres were observed in rats after receiving a single dose of the VLA2001 vaccine, although after the second dose significantly increased antibody titres were observed. After the second immunisation antibody titres reached a plateau and a third immunisation did not further increase antibody titres.

The passive transfer study in hamster with different doses of VLA2001-immune human sera (containing different antibody levels) transferred to hamsters prior to SARS-CoV-2 challenge demonstrated a non-significant trend between the degree of protection and neutralising antibody titres. Similar but inverse correlation was seen between clinical signs of disease and neutralising antibody titres. It should be noted that the study consisted of groups with few animals and that semi-quantitative subjective scoring methods were used to evaluate the severity of lesions observed in the lung and nasal cavity; thus the data should be interpreted with caution. Overall, no signs of disease enhancement were observed at dilute serum concentrations, i.e. antibody levels mimicking suboptimal immunisation. The results from the Syrian hamster study showed a tendency for protection of animals from SARS-CoV-2 disease following passive transfer with the human clinical trial serum, with the degree of protection appearing to correlate with the neutralising titre of the serum transferred.

The overall results from the non-human primates (NHP) study showed that VLA2001 led to a robust immune response and demonstrated to be effective against the disease symptoms of SARS-CoV-2 infection in those animals, and reduction of the viral replication in this animal model. Comparing the histopathological results of lungs with results from other SARS-CoV-2 challenge studies in NHPs, it seems that the pathological reactions observed were relatively mild. However, considering that the

overall results from the NHP study indicated that the vaccine is indeed efficacious in monkeys, and the necessary proof for vaccine efficacy relies on human clinical data this was not further pursued.

In relation to the potential risk of Vaccine-associated enhanced respiratory disease (VAERD), the scientific advice provided by CHMP in July 2021 (EMA/SA/0000064690) stated that investigations of suboptimal doses of the vaccine are important as the vaccine platform is more at risk of VAERD. As such, the risk for VAERD was discussed with particular attention on suboptimal dosing, considering no significant difference in humoral and cellular responses was observed between the medium and high dose groups in the NHP immunogenicity study. Several cytokines were measured repeatedly after challenge with no major differences between control and vaccinated NHPs. Further, the immune response was specified as Th1-biased at both dose levels. The risk of VAERD was also discussed in the context of the passive transfer study performed in Syrian hamster, where overall, no signs of disease enhancement were observed at dilute serum concentrations, i.e. antibody levels mimicking suboptimal immunisation.

In summary, administration of the vaccine adjuvanted with alum and CpG 1018 to different animal models (mouse, rat, and NHP) can be regarded as safe and immunogenic. VLA2001 vaccine was able to prevent or reduce the development of mild COVID-19 clinical signs in the challenged non-human primate animal model.

Overall, the toxicology programme is acceptable. The use of Han Wistar rat model is an accepted rodent species for non-clinical toxicity testing and has shown to develop an immune response to the SARS-CoV-2 antigen with other approved COVID-19 vaccines. In addition, the intramuscular route of exposure was selected as this is the intended route of human exposure. Taken into consideration animal welfare and appropriate dosing volumes, the total volume administrated to rats was split into two injection sites which is in accordance with vaccine guidelines. Although acceptable, the relatively large administration volume applied in both studies was considered as the maximal dose volume for this species.

In relation to the repeat-dose toxicity study in rats the absence of stand-alone adjuvant study groups is highlighted. Stand-alone adjuvant groups are often incorporated in non-clinical toxicology studies to discriminate effects caused by the adjuvant(s) and the vaccine active substance. This discrimination is not feasible with the data provided. Consequently, no non-clinical information is available that would allow an appropriate assessment of the safety profile of the CpG 1018 and alum adjuvant combination. While this uncertainty remains, the absence of this information is acceptable due to the acceptable safety profile of both adjuvants in the clinical setting.

In contrast to most of the observed alterations that constitute typical inflammatory responses towards administration of vaccine products in rats, the observed femorotibial joint inflammations near the injection site are considered unusual. Nevertheless, as no obviously vaccine-related cases of arthritis were observed in the pivotal clinical study, femorotibial joint inflammations after VLA2001 administration appear to be confined to rat repeated dose toxicity studies.

Intramuscular administration of VLA2001 on three occasions at 2 weekly intervals to Han Wistar rats was associated with transient body weight loss, lower food consumption, a transient increase in body temperature and inflammatory proteins, clinical pathology differences, higher spleen and liver weights, and microscopic findings at, and around, the administration sites, the spleen and draining lymph nodes. After a 3-week treatment free period microscopic findings were still evident, but with relative lower incidences in the administration sites and spleen, indicating partial recovery. The observations can be considered physiological and immunological responses to the vaccine.

In relation to the developmental and reproductive toxicology studies, no fertility and early embryonic development studies have been performed with VLA2001, which is acceptable for this type of vaccine.

Overall, no test item-related adverse effects were obtained in the conducted combined EFD and PPND study, neither in dams nor the developing foetuses/pups, at the tested dose of 26.4 AU/0.4 mL/dose, administered three times (d1 and d14 before mating and on gestation d6). No adverse effects on mating behaviour, maternal performance or other parameters evaluating pregnancy outcome were observed. A reduced pregnancy rate compared to expectable rates in rats was observed during the study. However, this was observed in both, the control and the test item group, and thus not regarded adverse.

Live birth, viability index and lactation indices were 100%, and no toxicologically relevant effects on gestation length, sex ratio or any other toxicity in mother and pup were reported.

A lower incidence in ossification (variant "increased ossification, calcaneus") was observed in the EFD phase. However, as this was the only difference observed between control and test item groups without any other area that would indicate a reduction in ossification, this finding was regarded to present a transient ossification delay in development producing the apparent finding of abnormal skeletal structure, thus was considered non-adverse and of minimal concern from a risk assessment perspective.

The process contaminants contained in the rHA excipient in VLA2001 did not trigger any toxicological concern.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, SARS-CoV-2 virus (inactivated) Wuhan strain hCoV-19/Italy/INMI1-isl/2020 is not expected to pose a risk to the environment.

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 virus (inactivated) Wuhan strain hCoV-19/Italy/INMI1-isl/2020 is not expected to pose a risk to the environment.

2.5. Clinical aspects

2.5.1. Introduction

The applicant has submitted two clinical trials:

1. Study VLA2001-201: first-in-human (FIH) Phase 1/2 dose finding trial on safety and immunogenicity to select the VLA2001 dose for further clinical trials (Day 36 and Day 106 interim analysis)
2. Pivotal Study VLA2001-301: Phase 3 superiority trial on the immunogenicity and safety of VLA2001 compared to the already licensed vaccine AZD1222 (Day 43 interim analysis)

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 ID	Study type (Phase)	Main characteristics (participants, treatment, objective, visits)	Endpoints	Start	Status Results (av./exp.)
VLA2001-201	Dose finding / safety (Phase 1/2)	⇒ based on CSP v3.0 3 different dose levels: 3, 7, 35 AU/dose § 50 participants per dose group*, 18-55 years • Day 36/ V 4: Dose finding: at two weeks after 2nd vaccination with VLA2001 (SAP, v 2.0) • Day 106/ V5: follow-up after 2nd vaccination with VLA2001 (SAP, v 3.0)	Safety and Immuno-genicity	Dec 2020	Ongoing • Day 36: February 2021 • Day 106: Aug 2021 (CSR1.0, 10 Sept 2021)
Pivotal Study VLA2001-301	Superiority Efficacy / safety (Phase 3) Adults	⇒ based on CSP v2.0, SAP v1.0 Dose 33 AU/dose§ 4000 participants: • ≥30 years: 3000 participants randomised 2:1 to VLA2001 and AZD1222 (randomised, observer-blind) • 18 – 29 years: 1000 participants treated with VLA2001 (open-label, not randomised) Active control with licensed vaccine AZD1222 in adults (≥30 years) - superiority/non-inferiority in co-primary immunogenicity endpoints.	≥30 years: Immuno-genicity and Safety 18-29 years: safety only	April 2021	Ongoing • Day 43: First interim analysis (CSR, 1.0, 17 Nov 2021) LPLV: mid 2022

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

No pharmacokinetics studies have been conducted for VLA2001. 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).

Mechanism of action

VLA2001 is a purified, inactivated, and adjuvanted whole virus SARS-CoV-2 (Wuhan strain hCoV-19/Italy/INMI1-isl/2020) vaccine grown on Vero cells. As the virus is inactivated, it cannot replicate in cells once administered. However, the whole virus particles present a wide range of native viral antigens. It is expected for VLA2001 that the immune response elicited is not limited to the S protein but also directed against other SARS-CoV-2 antigens. The inactivation of SARS-CoV-2 by β-propiolactone for VLA2001 allows for preservation of surface structure proteins.

Inactivated virus vaccines are usually combined with one or more adjuvants to improve their ability to induce an immune response (immunogenicity). In general, adjuvants have been shown to increase the

magnitude of vaccine-mediated immune responses.

After i.m. injection, some of the inactivated SARS-CoV-2 viruses are phagocytosed by antigen-presenting immune cells that present some of the viral antigens on their surface finally evoking an adaptive immune response. The adaptive immune response is mediated by activated B cells that produce antibodies (humoral immunity) and by activated T-cells (cellular immunity).

To date, there is no established correlate of protection for COVID-19. Nevertheless, neutralising antibodies against the S-protein are considered a valid endpoint to infer efficacy from an already authorised COVID-19 vaccine for which efficacy has been demonstrated even in the absence of an established correlate.

Assays

In the clinical programme, vaccine-induced immune responses in the form of neutralising antibodies were measured using neutralisation assays (live virus and pseudovirus neutralisation). Evaluation of neutralising antibody responses was the primary objective of the pivotal Phase 3 study supporting licensure. Additional measures of immunity (in Phase 1/2 and Phase 3) include evaluation of binding antibody responses (ELISA), as well as T cell responses (T-Spot; intracellular cytokine staining).

The MNA assay run at Public Health England has been validated accordingly and is considered adequate for the intended purpose. The T-spot assay and the intracellular cytokine staining have been qualified and are considered adequate for the intended purpose.

The data from a Micro Neutralisation Assay (MNA), validated at Public Health England, using the SARS-CoV-2 Victoria strain, is considered valid for the intended use to support the immunobridging approach. Calibration against the WHO standard was not performed, but alternatively a conversion factor was established for the assays performed according the initial protocol at Public Health England. Deficiencies were identified regarding the use of additional and not validated neutralisation assays, applying modified protocols, other virus strains and evaluation procedures (e.g. by imputing BQL values of certain virus strains only).

A Human SARS-CoV-2 Pre-Spike lgG ELISA was developed for detection of SARS-CoV-2 Pre-Spike specific lgG antibodies in human serum samples. The conversion of the obtained binding antibody results to WHO standard was not performed but alternatively an internal standard has been prepared and this was subsequently calibrated with WHO international standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code 20/136).

The Applicant applied a CE-marked T-SPOT COVID commercial test kit based on the ELISPOT standard immunological assay principle to assess SARS-CoV-2 specific T-cell responses. Previous publications on this subject matter reported up to 80% false positive results for uninfected individuals due to alleged T cell cross-reactivity. The Applicant justified its selection of truly negative patient sera and correct peptides for test negative controls and explained that pre-formed T-cell reactivity was reflected in the evaluation protocol. The performance of the assay was verified and seems suitable for evaluation of T-cell response to SARS-CoV-2 with a positive agreement with PCR of 95.8% at ≤60 days after first PCR and negative agreement of 98.0%, both if only determinate responses (≤4, ≥8 spots) were analysed. Thus, test conditions permit to identify SARS-CoV-2- specific T-cell memory engaged in individuals who underwent a mild infection vs. humans who have not been infected with this virus.

An Intracellular Cytokine Staining (ICS) assay was developed to measure cytokine production following stimulation with peptide pools in cryopreserved peripheral blood mononuclear cells (PBMC) from infected and/or vaccinated individuals. The assay met the defined acceptance criteria during assay qualification. This is acceptable.

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 VLA2001 is based on bridging clinical immunogenicity results to AZD1222 which has been shown to be protective against COVID-19. No efficacy studies with VLA2001 have been performed. This approach was considered acceptable by the CHMP in a scientific advice procedure (EMA/SA/0000064690).

The data from a Micro Neutralisation Assay (MNA), validated at Public Health England, using the SARS-CoV-2 Victoria strain, is considered valid for the intended use to support the immunobridging approach. Calibration against the WHO standard was not performed, but alternatively a conversion factor was established for the assays performed according the initial protocol at Public Health England. Deficiencies were identified regarding the use of additional and not validated neutralisation assays, applying modified protocols, other virus strains and evaluation procedures (e.g. by imputing BQL values of certain virus strains only). Thus, all neutralisation data besides the Micro Neutralisation Assay according to the PHE protocol need to be considered preliminary.

A Human SARS-CoV-2 Pre-Spike lgG ELISA was developed for detection of SARS-CoV-2 Pre-Spike specific lgG antibodies in human serum samples. The conversion of the obtained binding antibody results to WHO standard was not performed but alternatively an internal standard has been prepared and this was subsequently calibrated with WHO international standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code 20/136). This approach was deemed acceptable. The evaluation of binding antigens is an additional measure of immunity and not the primary objective of the pivotal Phase 3 study supporting the licensure therefore submitting the missing data regarding the validation post-approval, is acceptable (**Clinical pharmacology recommendation 1**):

- The supplemental validation for assessment of specificity at LLOQ with use of negative samples in Q3/2022 and to provide the corresponding results, should be provided;
- The cross-reactivity to human adenoviruses in ELISA binding assay during the additional validation of the method, and company's assessment, in the corresponding report should be provided in Q3/2022;
- The results of the non-specific positive serum (healthy donor serum) testing with several concentrations of inhibitors and assessment outcome during the additional validation of the method, should be provided with the corresponding report in Q3/2022;
- Method description and the validation data needs to be updated with the details of anti-spike antibody (Manufacturer, cat. No and lot N) used in immunoblot analysis of all lots of anti-spike proteins in both validation and clinical studies.

Cell-based assays to detect T cell responses (T-Spot; intracellular cytokine staining) are considered adequate for the intended purpose.

2.5.4. Conclusions on clinical pharmacology

The pivotal evidence for this MAA is based on induction of neutralising antibodies by VLA2001 vaccination compared to vaccination with the authorised vaccine AZD1222 with known efficacy. This is acceptable. The immunogenicity results used to infer efficacy are presented in the clinical efficacy

section.

The microneutralisation assay at Public Health England (MNAPHE) employed to measure neutralising antibodies against SARS-CoV-2 to support the primary immunogenicity evaluation, is considered validated. Cell-based assays to detect T cell responses (T-Spot; intracellular cytokine staining) are considered adequate for the intended purpose.

The CHMP considers the following measures necessary to address the clinical pharmacology issues:

Description of post-authorisation measures
Clinical pharmacology recommendations
1. The applicant committed to improve the ELISA analytical method for binding antibodies by: • providing additional supplemental validation for assessment of specificity at LLOQ with use of negative samples in Q3/2022 and to provide the corresponding results; • assessing the cross-reactivity to human adenoviruses in ELISA binding assay during the additional validation of the method and to provide a corresponding report in Q3/2022; • testing the non-specific positive serum (healthy donor serum) with several concentrations of inhibitors and assess the outcome during the additional validation of the method and to provide the corresponding report in Q3/2022; • updating the method description and the validation data with the details of anti-spike antibody (Manufacturer, cat. No and lot N) used in immunoblot analysis of all lots of anti-spike proteins in both validation and clinical studies.

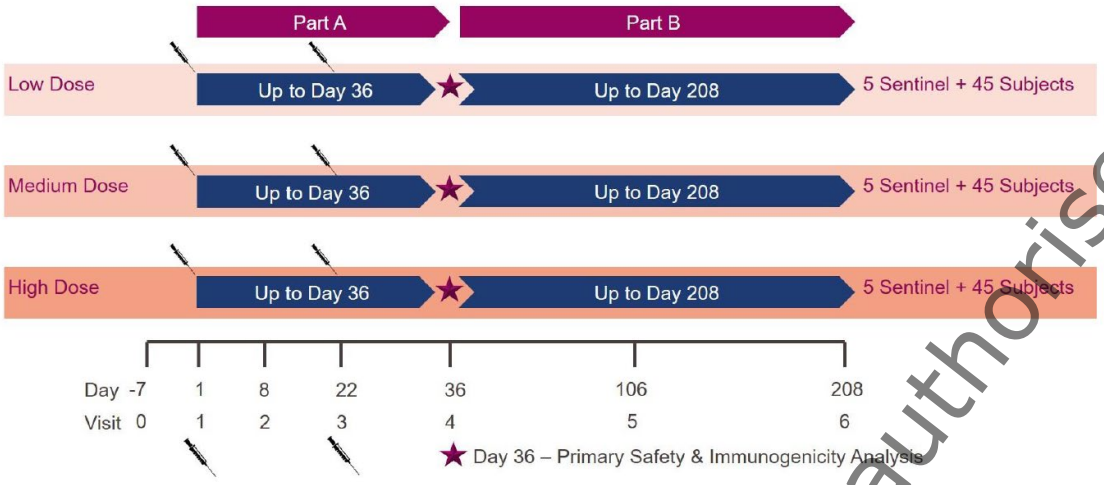
2.5.5. Clinical efficacy

2.5.5.1. Dose response study

Study VLA2001-201 is a first-in-human (FIH), Phase I/II, multicentre (n=4, all UK), two part (Day 1 to Day 36 and Day 37 to Day 208), dose-escalation study (low [3 AU/dose], medium [7 AU/dose], high dose [35 AU/dose]) to evaluate safety, tolerability and immunogenicity of two doses (21 days apart) of VLA2001 (inactivated, CpG 1018 [1 mg/dose] & alum [0.5 mg/dose] -adjuvanted SARS-CoV-2 vaccine candidate) in healthy subjects (n=153 in total, 18-55 yoa) to select the VLA2001 dose for further clinical trials. The study is currently on-going and commenced with the first visit of the first subject on 16 December 2020.

For safety reasons, the first 15 participants were included into the study in an open-label, not randomised manner following a staggered dose escalation of VLA2001 (i.e. sentinel approach). The remaining 138 participants were enrolled, screened, and randomised in a 1:1:1 fashion to the 3 dose groups in the blinded part of the study. The study design is included below.

Figure 3: **study design for FIH study VLA2001-201**



Serum samples to measure SARS-CoV-2 neutralising antibody levels were collected from participants on Day 1 (prior to vaccination), Day 8, Day 22 (prior to vaccination), Day 36, Day 106, and Day 208. An authorized laboratory measured neutralising antibodies to SARS-CoV-2 using wild-type virus microneutralising assay (WT-MNA).

In addition to the functional assays, samples were analysed for IgG against SARS-CoV-2 by S-ELISA.

The cell-mediated immune response (T-cell response) was assessed on Day 1 and Day 36 by characterizing peripheral blood mononuclear cells (PBMCs); methods included T-cell ELISpot assays to SARS-CoV-2 antigens and intracellular cytokine staining (ICS) for Day 1 and Day 36.

Overall, 285 participants were screened in this study and 153 participants were randomised: 51/153 participants each (33.3%) in the low dose, medium dose, and high dose groups. No participants terminated the study early as of the Day 106 visit.

The mean (SD) age at the time of informed consent was 33.5 (9.10) years with a range of 18 to 55 years. Mean age was similar across all dose groups.

The majority of study participants were white (143/153, 93.5%). Overall, 83/153 participants (54.2%) were male, and 70/153 participants (45.8%) were female. The percentage of males was higher than females in the low dose and medium dose groups with 52.9% and 66.7% males respectively, whereas in the high dose group, there was a higher percentage of females (56.9%). Overall, 67/70 female participants (95.7%) were of childbearing potential; only 1 female participant in each dose group was not of childbearing potential.

None of the study participants in any dose group had a positive test result for COVID-19, HBsAg, HCV, or HIV at the time of screening.

A first interim analysis was performed when the last participant had completed Day 36 (14 days after the second vaccination; March 10th 2021). A second interim analysis was performed after all participants have completed Day 106 visit (June 30th 2021). The data cut-off date for the current (first) CSR was June 30th 2021.

150/153 participants (98.0%) have been included in the Per-Protocol Analysis Set (PPAS) and 148/153 participants (96.7%) have been included in the Modified Per-Protocol Analysis Set (mPPAS) in the first interim analysis which supported the dose selection for the phase 3 clinical development. Modified PPAS included all participants from PPAS except those participants who were tested positive for COVID-19 anytime during study after first vaccination.

The analysis population sets are included in the below table.

Table 4: analysis population sets (study VLA2001-201)

Statistics	Dose group of VLA2001			
	Low Dose [3 AU/dose] n (%)	Medium Dose [7 AU/dose] n (%)	High Dose [35 AU/dose] n (%)	Overall n (%)
First and second interim analysis (Day 36 and Day 106)				
Randomised	51	51	51	153
Safety analysis set (SAS)	51 (100)	51 (100)	51 (100)	153 (100)
Full analysis set (FAS)	51 (100)	51 (100)	51 (100)	153 (100)
First interim analysis: Day 36 analysis[A]				
PP analysis set[1] (PPAS)	51 (100)	49 (96)	50 (98)	150 (98)
Modified PP set (mPPAS)	49 (96)[2]	49 (96)	50 (98)	148 (97)
Second interim analysis: Day 106 analysis[B]				
Day 36 (re-analysis)[C]				
PP analysis set[1] (PPAS)	51 (100)	49 (96)	50 (98)[4]	150 (98)
Modified PP set[2] (mPPAS)	50 (98)	49 (96)	50 (98)[4]	149 (97)
Day 106				
PP analysis set[3] (PPAS)	50 (98)	49 (96)	45 (88)[4]	144 (94)
Modified PP set[2] (mPPAS)	48 (94)	49 (96)	45 (88)[4]	142 (92)

PP: Per Protocol. PPAS: per-protocol analysis set, mPPAS: modified per-protocol analysis set.
A: first interim analysis cut-off date: 10 March 2021. Period Day 1 to Day 36.
B: second interim analysis cut-off date: 30 June 2021. Period Day 1 to Day 106.
C: a re-analysis of the Day 36 analysis was performed considering the changes in the PPAS at Day 106 and the change in LLOQ.
1: 3 participants did not receive the second vaccination (2 participants in the medium dose group and 1 participant in the high dose group)
2: For sensitivity analysis, the modified PP excluded participants with a confirmed SARS-CoV-2 infection during the study up to day 36. A participant was erroneously excluded in first interim analysis from the mPPAS Day 36 (COVID 19 infection started 26 days after second dose and thereby after Day 36). This participant is included in second interim analysis mPPAS Day 36 but excluded from mPPAS Day 106.
3: At Day 106, 9 participants were found to have received a licensed vaccine which represents a protocol violation. Therefore, those 9 participants had to be excluded from the PPAS Day 106.
4: A participant (ICS technical error) in the high dose group is not reflected in this cumulative overview for PPAS and mPPAS, since they are only excluded from PPAS and mPPAS for ICS. ICS data for Day 1 and Day 36 in the high dose group are only available at the time of the second interim analysis and displayed in both Day 36 and Day 106.

Overall, at the Day 106 data cut date, 131/153 participants (85.6%) reported an AE. The incidences of AEs were similar in the low dose and high dose group (88.2% and 90.2%, respectively) compared with the medium dose group (78.4%). The incidences of vaccine-related AEs were the same in the low and high dose groups (84.3%) and slightly lower in the medium dose group (78.4%). Solicited AEs were reported in 125/153 participants overall (81.7%). The incidences of solicited AEs were the same in the low and high dose groups (84.3%) and slightly lower in the medium dose group (76.5%). The incidences of medically attended AEs were the same in the low and high dose groups (5.9%), but higher in the medium dose group (11.8%). For detailed information pertaining to safety, refer to Clinical Safety section.

Table 5: Second interim analysis – SARS-CoV-2 Neutralising Antibody Titres (ND50) over timepoints – D1, D36 and D106 (PPAS D36)

Visit Statistic	Low Dose N=51	Medium Dose N=49	High Dose N=50	Overall N=150
		Overall		
Day 1				
n	51	49	50	150
GMT (95% CI)	31.0 (31.00, 31.00)	32.8 (30.48, 35.24)	32.0 (30.83, 33.19)	31.9 (31.07, 32.75)
Median	31.0	31.0	31.0	31.0
Min, Max	31.0, 31.0	31.0, 232.0	31.0, 72.0	31.0, 232.0
p-value (overall dose groups comparison) [A]	–	–	–	0.349
Day 36				
n	51	49	50	150
GMT (95% CI)	163.2 (121.10, 219.88)	218.9 (169.41, 282.92)	536.1 (425.53, 675.34)	267.0 (226.52, 314.77)
Median	119.0	233.0	560.5	264.5
Min, Max	31.0, 3618.0	31.0, 1307.0	31.0, 2033.0	31.0, 3618.0
p-value: overall dose groups comparison [A]	–	–	–	<0.001
p-value: low dose vs medium dose [B]	–	–	–	0.182
p-value: medium dose vs high dose [B]	–	–	–	<0.001
p-value: low dose vs high dose [B]	–	–	–	<0.001
Day 106				
n	50	49	50	149
GMT (95% CI)	66.8 (52.52, 84.97)	82.4 64.26, 105.63)	238.0 (173.15, 327.19)	109.6 (92.35, 130.13)
Median	31.0	77.0	214.5	97.0
Min, Max	31.0, 1088.0	31.0, 1589.0	31.0, 5902.0	31.0, 5902.0
p-value: overall dose groups comparison A	–	–	–	<0.001
p-value: low dose vs medium dose B	–	–	–	0.476
p-value: medium dose vs	–	–	–	<0.001
Visit Statistic	Low Dose N=51	Medium Dose N=49	High Dose N=50	Overall N=150
high dose B				
p-value: low dose vs high dose B	–	–	–	<0.001

CI=confidence interval; DSCF= Dwass, Steel, Critchlow-Fligner; GMT=geometric mean titre; Max=maximum; Min=minimum; ND50=50% neutralizing dilution

A p-value was calculated using Kruskal Wallis Test for comparison of dose groups.

B p-value for pairwise dose group comparison was calculated using DSCF multiple comparisons post-hoc procedure. This was calculated only if the Kruskal Wallis test was significant (i.e., p-value for overall dose groups comparison was ≤0.05.).

Source: Table 14.3.1.1

Immune response was measured by neutralising antibody titres against SARS-CoV-2 on Day 8, Day 22, Day 106, and Day 208. Neutralising antibodies GMTs showed a clear dose-dependent response

with the highest values in the high dose group. Across all dose groups the GMTs were highest at Day 36, second highest at Day 106, followed by Day 22; at Day 8, titres were barely above baseline values.

Seroconversion in terms of neutralising antibodies (defined as 4-fold increase from baseline) was clearly dose-dependent with the highest proportion of seroconverted participants in the high dose group. Across all dose groups the proportions of participants with seroconversion were highest at Day 36 (25 subjects (49.0%) in the low dose group, 35 subjects (71.4%) in the medium dose group, and 45 subjects (90.0%) in the high dose group), second highest at Day 106, followed by Day 22; at Day 8, no seroconversion at all was present.

The cellular immune response on Day 1 and Day 36 was also studied as an exploratory endpoint. Overall, statistically significant differences were seen in the spot forming units between Day 1 and Day 36 values for all of the panels tested in all dose groups (panel 1: spike protein N terminus; panel 2: spike protein C terminus; panel 3: nucleocapsid protein; panel 4: membrane protein; panel 13: cross-reactive panel; and panel 14: spike protein, full sequence). A statistically significant difference was seen among the dose groups at Day 36 ($p<0.001$) for the panel 14 spike protein (full sequence) in terms of IFN-gamma spot forming units.

Determination of optimal dose level of VLA2001 for pivotal Phase 3

An optimal dose level of VLA2001 was determined after reviewing all of the safety and immunogenicity data from the first Day 36 interim analysis. Incidences of solicited AEs at Day 36 were similar among the groups (ranging from 76.5% [medium dose group] to 84.3% [low and high dose groups]) as were the incidences of unsolicited AEs (ranging from 35.3 [medium dose group] to 47.1% (low dose group). Since there were significantly higher GMTs of SARS-CoV-2 neutralising antibody titres in the high dose group and the safety was comparable among the low, medium, and high dose groups, the high dose (35 AU/dose) was selected to be tested in further studies.

Additionally, at Day 36, the GMT of neutralising antibody titres in the high dose group were at or above levels for a panel of convalescent sera (GMT 522.5 [95% CI: 332.00, 822.2]).

2.5.5.2. Main study

A Randomized, Observer-blind, Controlled, Superiority Study to Compare the Immunogenicity Against COVID-19, of VLA2001 Vaccine to AZD1222 Vaccine, in Adults (VLA2001-301)

Methods

- **Study Participants**

Main inclusion criteria

- Participants of either gender aged 18 years and older at screening.
- Medically stable such that, according to the judgment of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.
- Women of childbearing potential (WOCBP) must be able and willing to use at least 1 highly effective method of contraception (i.e. include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy, hormonal oral [in combination with male condoms with spermicide], transdermal, implant, or injection, barrier [i.e. condom, diaphragm with spermicide]; intrauterine device; vasectomized partner [6 months minimum], clinically sterile partner; or abstinence) for a minimum of 3 months after the last dose of study vaccine.

A female participant is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 consecutive months (without an alternative medical cause) or otherwise permanently sterile.
Note: Participants not of childbearing potential are not required to use any other forms of contraception during the study. Non-childbearing potential is defined as participant confirmed:

- Surgical sterilization (e.g., bilateral oophorectomy, bilateral salpingectomy, bilateral occlusion by cautery, hysterectomy, or tubal ligation).
- Postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to screening).

- WOCBPs must have a negative pregnancy test prior to each vaccination.

Main exclusion criteria

- Participant is pregnant or planning to become pregnant within 3 months after study vaccine administration.
- History of allergy to any component of the vaccine.
- Significant infection (e.g. positive SARS-CoV-2 RT-PCR) or other acute illness, including fever > 100 °F (> 37.8 °C) 48 hours before vaccination.
- Participant has a known or suspected defect of the immune system, such as participants with congenital or acquired immunodeficiency, including infection with HIV, status post organ transplantation or immuno-suppressive therapy within 4 weeks prior to the expected day of randomization (Visit 1).
- History of cerebral venous sinus thrombosis, heparin-induced thrombocytopenia or
- antiphospholipid syndrome.
- Participant has a history of malignancy in the past 5 years other than squamous cell or basal cell skin cancer. If there has been surgical excision or treatment more than 5 years ago that is considered to have achieved a cure, the participant may be enrolled. A history of hematologic malignancy is a permanent exclusion. Participants with a history of skin cancer must not be vaccinated at the previous tumour site.
- Significant blood loss (> 450 mL) or has donated 1 or more units of blood or plasma within 6 weeks prior to the expected day of randomization (Visit 1).
- Receipt of immunoglobulin or another blood product within the 3 months before expected day of randomization (visit 1) in this study or those who expect to receive immunoglobulin or another blood product during this study.
- Receipt of medications and or vaccinations intended to prevent COVID-19.
- Receipt of any vaccine (licensed or investigational), other than licensed influenza vaccine, within 28 days prior to the expected day of randomization (Visit 1).

- **Treatments**

Both VLA2001 and AZD1222 were administered i.m. in a two-dose schedule with vaccinations given 28 days apart.

VLA2001 is a highly purified, inactivated, whole virus SARS-Cov-2 vaccine grown on Vero cells. The vaccine production platform, developed by Valneva, uses an inactivated whole-virus approach where live wild-type virus is grown in cell culture and then inactivated (i.e., making it unable to replicate and infect cells) via chemical treatment. Valneva uses β-propiolactone inactivation in order to preserve the native surface structure of the S-protein. VLA2001 has similar biological, physical, and chemical properties as the approved vaccine IXIARO, produced using the same platform. VLA2001 was administered by IM injection. The final administered volume of VLA2001 is 0.5 mL.

For this clinical study, the vaccine was provided in multi-dose glass vials as a liquid formulation containing aluminium hydroxide and CpG 1018.

AZD1222 is a recombinant, replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tPA leader sequence at the N terminus. AZD1222 was administered by IM injection. AZD1222 was available as multi-dose vials.

- **Objectives**

The purpose of this study is to compare the immunogenicity of VLA2001 vaccine to AZD1222 vaccine in adults.

Only immunogenicity objectives are listed here. The study also included (primary) objectives concerning the safety of VLA2001. Study objectives have been updated based on the most recent protocol version 7.0. Objectives include evaluation of immune responses after a third VLA2001 dose as well as immune responses in adolescents which are, however, not part of this application. Only objectives relevant to the adult population primary series (consisting of two VLA2001 doses) are shown below:

Primary Objectives

1) To demonstrate the superiority of VLA2001 (Wuhan strain) compared to AZD1222 administered in a 2-dose immunization schedule 4 weeks apart, in terms of Geometric Mean Titre (GMT) ratio as well as non-inferiority in terms of seroconversion rate of neutralising antibodies, at 2 weeks after the second vaccination (Day 43) in adults aged 30 years and older.

Secondary Objectives

2) To assess immunogenicity of a 2-dose primary immunization schedule with VLA2001 in adults aged 18 years and above.
3) To evaluate cellular immune responses following administration of VLA2001 in adults.

Exploratory Objectives

4) To assess the efficacy of VLA2001 in the prevention of COVID-19 in an adult population, aged 30 years and older.

SAP

The objective of the analysis described in this SAP is to investigate non-inferiority of participants aged 18-29 years of age compared to participants ≥30 years in VLA2001-301 as well as non-inferiority of participants in VLA2001-304 (≥56 years) to participants ≥30 years in VLA2001-301 in a 2-dose immunization schedule, in terms of geometric mean titre (GMT) of SARS-CoV-2-specific neutralising antibodies and SARS-CoV-2 S-protein IgG ELISA at 2 weeks after the second vaccination (i.e. Day 43).

- **Outcomes/endpoints**

Only immunogenicity variables are listed here. The studies included (primary) safety endpoints. Study objectives have been updated based on the most recent protocol version 7.0 that also include evaluation of immune responses in adolescents which are, however, not part of this application. Only endpoints relevant to the adult population primary series are shown below:

Primary Endpoints

1) Immune response measured after completion of a 2-dose immunization schedule with VLA2001, as determined by the GMT ratio in adults on Day 43
2) Seroconversion (defined as 4-fold increase from baseline) of SARS-CoV-2-specific neutralising antibodies on Day 43.

Secondary Endpoints

3) Proportion of adult participants with seroconversion after receipt of 2 doses of study vaccination on Day 8 (age 55+ only), Day 29, Day 71 and Day 208. Seroconversion is defined as ≥ 4-fold increase in SARS-CoV-2 neutralising antibody titre against the Wuhan strain and binding IgG antibodies directed against the S-protein of the Wuhan strain between Day 1 and the defined post-vaccination time points.
4) Immune response in adults on Day 8 (age 55+ only), Day 29, Day 71 and Day 208, as determined by the GMT of SARS-CoV-2-specific neutralising antibodies.
5) Immune response in adults on Day 8 (age 55+ only), Day 29, Day 43, Day 71 and Day 208, as determined by the GMT of IgG antibodies to SARS-CoV-2 S-protein.
6) Assessment of T-cell responses (Th1/Th2 polarization) from PBMCs on selected time points in a subset of participants after in vitro stimulation with SARS-CoV-2 antigens using e.g. ELISpot (IFNγ) or intracellular cytokine staining (IL-2, IL-4, IL-5, IL-13, TNF-α, IFN-γ).

SAP

The following data will be analysed descriptively.

- SARS-CoV-2-specific neutralising antibodies serostatus at Day 1 vs. SARS-CoV-2 S-protein IgG ELISA serostatus at Day 1 (frequency statistics, seropositive and seronegative), if both parameters available
- SARS-CoV-2-specific neutralising antibodies at Day 0 and Day 43 (GMT and GMT ratio)
- SARS-CoV-2 S-protein IgG ELISA at Day 0 and Day 43 (GMT and GMT ratio)
- Seroconversion rates (SCRs) and SCR difference of SARS-CoV-2-specific neutralising antibodies at Day 43
- Fold Increase of SARS-CoV-2 Neutralising Antibody Titres
- SCR and SCR difference of SARS-CoV-2 S-protein IgG ELISA at Day 43

Exploratory Endpoints:

- Number of COVID-19 cases per treatment group.

- **Sample size**

The sample size for this study is selected in order to establish a comprehensive safety database and to characterize the safety profile of VLA2001. 3000 participants vaccinated with VLA2001 will allow for the detection of at least 1 rare event (incidence rate 1/1000) with a probability of 94% in this study. The VLA2001 safety database will then provide safety data on more than 3000 vaccinated participants.

The planned number of 600 participants per group in the immunogenicity subset will allow for a statistical power of 90% to detect superiority in terms of the Day 43 GMT ratio VLA2001/AZD1222 with an expected ratio of 1.3, a standard deviation of 0.6 (on a LOG10 scale), expected drop-out rate of

10% and a two-sided significance level of 5%.

- **Randomisation and Blinding (masking)**

In the age group 30 years and above, 3000 participants were randomized in a 2:1 ratio, to receive either VLA2001 or AZD12222. In addition, for the immunogenicity analyses, 1200 participants were randomized 1:1 based on sero-negative status (rapid antibody test) at screening. Thus, the non-immunogenicity subset was randomized at a 7:2 ratio in order to reach the overall sample size of the study and an overall ratio of 2:1. Regarding the 200 participants selected for the PBMC sample collection, these participants have been included at 5 pre-selected sites (site 08, 14, 21, 22 and 23). Every participant included in the immunogenicity-subset at these specific sites was also part of the PBMC subset until the target number of participants had been reached. Subsequently no further PBMC blood draw was conducted.

Participants aged 18-29 years receiving VLA2001 were non-randomized.

The Phase III study was designated as an observer-blind study. While participants aged 30 years and above were blinded as they received either VLA2001 or AZD1222, participants aged 18-29 years were placed in a non-randomized treatment group and only received VLA2001 without a control. Furthermore, members of the DSMB, the pharmacist preparing the dose of the 2 vaccines and the CRA monitoring the vaccine inventory were unblinded.

- **Statistical methods**

The Safety Population includes all participants who entered into the study and received at least one vaccination. The Safety population was to be used for all baseline, safety and tolerability analyses including demographic data, local/systemic tolerability, laboratory data, Adverse Events (AEs), Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs). All analyses based on the safety population were carried out using the actual treatment received.

The Immunogenicity Population (IMM) includes all randomized and vaccinated participants who were SARS-CoV-2 seronegative and have at least one evaluable post-baseline antibody titre measurement after vaccination. Participants who met the case definition of confirmed COVID-19 during the study were not to be included in the IMM.

The Per-Protocol population (PP) consists of the IMM population subjects who have no major protocol violations that impact the immune response.

Immunogenicity analyses were to be presented for both IMM and PP population. Immunogenicity analysis will also be presented for participants with confirmed COVID19-infection during the study.

No imputation was to be done for missing data values. For the participants who are discontinued from the trial, all data until the point of discontinuation is used in the summary and analyses.

The evaluation of the primary objective of this study comprised the following co-primary comparisons of immune response on Day 43 after completion of a 2-dose immunization schedule:

- Geometric mean titres (GMT) of SARS-CoV-2-specific neutralising antibodies; test on superiority within the IMM population;
- Seroconversion rate (defined as 4-fold increase from baseline) with regards to SARS-CoV-2 specific neutralising antibodies; test on non-inferiority within the PP population.

The study was to be interpreted as successful for VLA2001 if both tests - superiority of GMT as well as non-inferiority of seroconversion rate - are statistically significant in favour of VLA2001.

Superiority was tested on the Day 43 GMT ratio VLA2001/AZD1222. The null hypothesis was that the ratio is equal to 1, and the alternative hypothesis was that the ratio is not equal to 1. Testing was done

at a two-sided significance level of 5%. This co-primary immunogenicity endpoint (Day 43 GMT) was compared between treatment groups using a two sided t-test applied to neutralisation titres after log10 transformation.

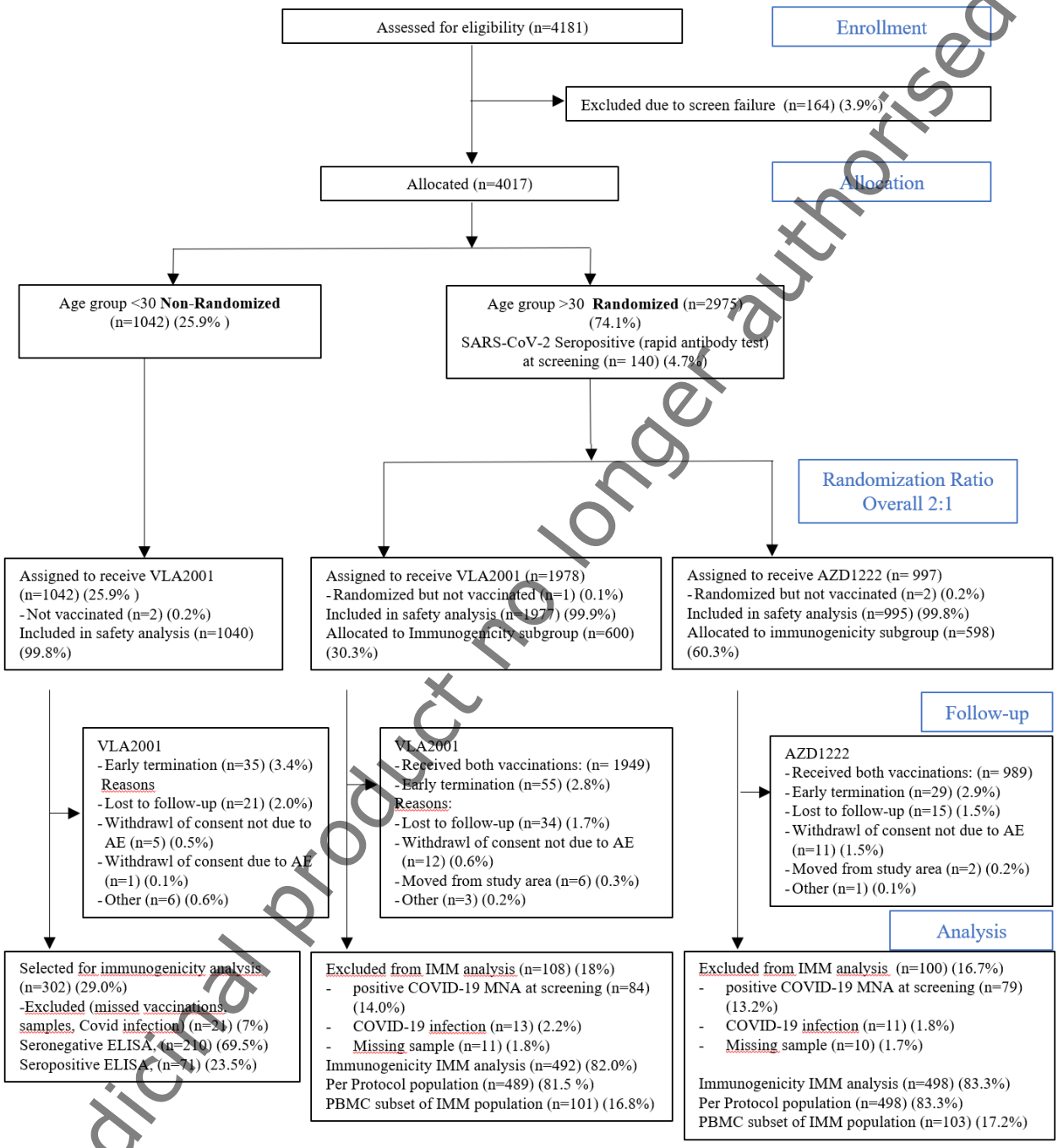
GMTs along with corresponding 95% CI were provided by using log10 transformed neutralising titre. For sensitivity analysis, GMTs along with corresponding 95% CI were to be estimated by applying analysis of variance (ANOVA) for log10 transformed neutralising antibody titre including the factors treatment group and study site.

Non-inferiority was tested on the difference in Day 43 seroconversion rates (VLA2001- AZD1222) using a non-inferiority margin of -10% in the PP population. A two-sided 95% confidence interval for the difference was calculated, non-inferiority of VLA2001 was to be postulated in case the lower limit was greater than -10%. Non-inferiority of seroconversion rates will also be assessed using a -5% margin.

A primary statistical analysis was to be performed after all participants have been vaccinated and have completed Day 43 visit. A second statistical analysis will be performed, when all participants have reached Day 208. Additional statistical analysis will be performed for day 71.

Results

Figure 4: **Participant flow**



- **Recruitment**

Date of first participant, first visit (screened): 28 April 2021

Date of last participant, last visit: Study is ongoing

Data cut date (primary analysis at day 43): 11 August 2021 (at least 4 weeks follow-up after second vaccination for each participant)

Date of Clinical Study Report: 17 November 2021 (Interim CSR final 1.0)

Study Centre(s): 26 study sites in the UK

- **Conduct of the study**

According to the Applicant, VLA2001-301 was conducted according to GCP Guidelines and current version of the Declaration of Helsinki.

The protocol was amended several times. Protocol version 3.0 was never implemented. The current CSR is based on protocol version 2.0 (dated 15 April 2021), while the newest protocol version sent during assessment is version 7.0. All protocol versions have been provided together with an overview of the major protocol changes.

The current interim CSR V 1.0 is based on protocol version 2.0.

There was an MHRA inspection in August 2021.

- **Baseline data**

A summary of demographic characteristics of the safety population is presented in the table below.

Table 6: Demographic and Baseline Characteristics (Safety population)

Characteristics	VLA2001 Age <30 years N=1040 n (%)	VLA2001 Age ≥30 years N=1977 n (%)	AZD1222 N=995 n (%)	All Participants N=4012 n (%)
Age at time of informed consent (years)				
n	1040	1977	995	4012
Mean (SD)	24.4 (3.23)	35.4 (5.02)	35.6 (4.81)	32.6 (6.66)
Median	25.0	34.0	35.0	33.0
Min, Max	18, 29	30, 68	30, 71	18, 71
Body Mass Index at screening (kg/m2)				
n	1037	1975	993	4005
Mean (SD)	25.44 (5.054)	27.25 (5.370)	27.43 (5.535)	26.83 (5.394)
Median	24.40	26.20	26.50	25.90
Min, Max	16, 49	16, 80	17, 58	16, 80
Age group (years), n (%)				
18-29	1040	0	0	1040
30-55	0	1958	990	2948
Above 55	0	19	5	24
Sex, n (%)				
Male	555 (53.4)	1135 (57.4)	567 (57.0)	2257 (56.3)
Female	483 (46.4)	839 (42.4)	427 (42.9)	1749 (43.6)
Diverse	2 (0.2)	3 (0.2)	1 (0.1)	6 (0.1)
Childbearing potential, n (%)				
Yes	482 (46.3)	812 (41.1)	410 (41.2)	1704 (42.5)
No	1 (0.1)	27 (1.4)	17 (1.7)	45 (1.1)
Ethnicity, n (%) [A]				
White	955 (91.8)	1844 (93.3)	927 (93.2)	3726 (92.9)
Mixed	39 (3.8)	38 (1.9)	23 (2.3)	100 (2.5)
Asian	23 (2.2)	54 (2.7)	22 (2.2)	99 (2.5)
COVID-19 test result at screening				
Seropositive	52 (5.0)	108 (5.5)	32 (3.2)	192 (4.8)
Seronegative	988 (95.0)	1869 (94.5)	963 (96.8)	3820 (95.2)
SARS-CoV-2 rapid antigen test				
Negative	1040 (100)	1977 (100)	995 (100)	4012 (100)

Max = maximum; Min = minimum; SD = standard deviation
A Most frequently reported (≥2% incidence) ethnicities are included.
Source: Table 14.1.2

Disposition of participants based on risk factors at baseline is as follows.

Table 7: Demographic and baseline characteristics in relation to risk factors (Safety population)

Regulatory Table 4.1
Demographic and Baseline Characteristics
Safety Population

Age Group: Overall

	VLA2001 Age Under 30 (N=1040) n (%)	VLA2001 Age 30 and Above (N=1977) n (%)	AZD1222 (N=995) n (%)	Overall (N=4012) n (%)
Subjects With a Risk Factor	175 (16.8)	512 (25.9)	272 (27.3)	959 (23.9)
COPD	0	1 (0.1)	0	1 (0.0)
Cardiac	14 (1.3)	21 (1.1)	8 (0.8)	43 (1.1)
Diabetes	0	3 (0.2)	2 (0.2)	5 (0.1)
Obesity	167 (16.1)	494 (25.0)	266 (26.7)	927 (23.1)

A summary of demographic characteristics of the IMM subset is presented in the table below.

Table 8: Demographic and baseline characteristics (immunogenicity population)

Regulatory Table 4
Demographic and Baseline Characteristics
Immunogenicity Population

Age Group: Overall

	VLA2001 Age Under 30 (N=0) n (%)	VLA2001 Age 30 and Above (N=492) n (%)	AZD1222 (N=498) n (%)	Overall (N=990) n (%)
Age at the time of informed consent (years)				
n	0	492	498	990
Mean (SD)	0	36.1 (4.77)	35.8 (4.18)	36.0 (4.48)
Median	0	36.0	35.0	35.0
Min, Max	0	30, 68	30, 50	30, 68
Age Group				
30-55	0	489	498	987
Above 55	0	3	0	3
Sex				
Male	0	272 (55.3)	293 (58.8)	565 (57.1)
Female	0	218 (44.3)	205 (41.2)	423 (42.7)
Diverse	0	2 (0.4)	0	2 (0.2)
Childbearing potential				
Yes	0	213 (43.3)	198 (39.8)	411 (41.5)
No	0	5 (1.0)	7 (1.4)	12 (1.2)
Reason for no childbearing potential				
Surgically Sterile	0	3 (0.6)	5 (1.0)	8 (0.8)
Postmenopausal	0	0	1 (0.2)	1 (0.1)
Other	0	2 (0.4)	1 (0.2)	3 (0.3)
Ethnicity				
WHITE	0	468 (95.1)	466 (93.6)	934 (94.3)
ASIAN	0	8 (1.6)	11 (2.2)	19 (1.9)
MIXED	0	5 (1.0)	10 (2.0)	15 (1.5)
CHINESE	0	4 (0.8)	3 (0.6)	7 (0.7)
HISPANIC	0	3 (0.6)	2 (0.4)	5 (0.5)
BLACK	0	1 (0.2)	1 (0.2)	2 (0.2)
LATIN AMERICAN	0	1 (0.2)	1 (0.2)	2 (0.2)
ARAB	0	0	1 (0.2)	1 (0.1)
INDIAN	0	1 (0.2)	0	1 (0.1)
JAPANESE	0	1 (0.2)	0	1 (0.1)
LATINA	0	0	1 (0.2)	1 (0.1)
MEDITERRANEAN	0	0	1 (0.2)	1 (0.1)
SPANISH	0	0	1 (0.2)	1 (0.1)
Height at screening (cm)				
n	0	491	497	988
Mean (SD)	0	173.60 (9.453)	174.20 (9.558)	173.90 (9.506)
Median	0	174.00	174.40	174.00
Min, Max	0	150, 199	149, 200	149, 200
Weight at screening (kg)				
n	0	491	497	988
Mean (SD)	0	81.78 (17.211)	82.82 (18.990)	82.30 (18.126)
Median	0	79.00	80.00	79.70
Min, Max	0	46, 143	47, 183	46, 183
Body Mass Index (BMI) at screening (kg/m2)				
n	0	491	497	988
Mean (SD)	0	27.08 (5.077)	27.23 (5.565)	27.15 (5.326)
Median	0	25.90	26.40	26.15
Min, Max	0	17, 49	17, 58	17, 58
COVID-19 Test Result at screening				
Seronegative	0	492 (100.0)	498 (100.0)	990 (100.0)
SARS-CoV-2 rapid antigen test				
Negative	0	492	498	990
Subjects With a Risk Factor	0	125 (25.4)	126 (25.3)	251 (25.4)
COPD	0	1 (0.2)	0	1 (0.1)
Cardiac	0	7 (1.4)	1 (0.2)	8 (0.8)
Diabetes	0	0	0	0
Obesity	0	119 (24.2)	126 (25.3)	245 (24.7)

The following table depicts demographic and baseline characteristics for the subset that was used to compare neutralising and binding antibody titres in individuals 18-29 yoa with individuals >30 yoa.

Table 9: Demographic and baseline characteristics (Per-Protocol Analysis Set excluding participants with COVID-19 infection)

Characteristics	VLA2001 Age <30 years N=210	VLA2001 Age ≥30 years N=498	VLA2001 All Participants N=708
Age at time of informed consent (years)			
n	210	498	708
Mean (SD)	24.8 (3.04)	36.1 (4.78)	32.8 (6.76)
Median	25.0	36.0	33.0
Q1, Q3	22, 27	33, 38	28, 37
Min, Max	18, 29	30, 68	18, 68
Age group (years), n (%)			
18-29	210 (100)	0 (0.0)	210 (29.7)
30-55	0 (0.0)	495 (99.4)	495 (69.9)
Above 55	0 (0.0)	3 (0.6)	3 (0.4)
Sex, n (%)			
Male	111 (52.9)	275 (55.2)	386 (54.5)
Female	99 (47.1)	221 (44.4)	320 (45.2)
Diverse	0 (0.0)	2 (0.4)	2 (0.3)
Childbearing potential, n (%)			
Yes	99 (100)	217 (98.2)	316 (98.8)
No	0 (0.0)	4 (1.8)	4 (1.3)
Ethnicity, n (%)[a]			
White	194 (92.4)	474 (95.2)	668 (94.4)
Mixed	9 (4.3)	5 (1.0)	14 (2.0)
Asian	4 (1.9)	8 (1.6)	12 (1.7)
Body Mass Index at screening (kg/m^2)			
n	209	497	706
Mean (SD)	25.9 (5.63)	27.1 (5.10)	26.8 (5.29)
Median	24.7	26.1	25.7
Q1, Q3	21.6, 28.9	23.4, 29.8	22.9, 29.5
Min, Max	17.1, 47.3	17.4, 48.6	17.1, 48.6

Max=maximum; Min=minimum; n=number of participants; Q=quartile; SD=standard deviation
[a] Most frequently reported (≥1% incidence overall) ethnicities are included.
Note: Percentages are based on non-missing observations (Total).
Source: Table 14.3

- **Numbers analysed**

The analysis populations are summarized in the table below.

Table 10: Analysis Populations (All Enrolled Participants)

	VLA2001 Age <30 years N=1042 n (%)	VLA2001 Age ≥30 years N=1978 n (%)	AZD1222 N=997 n (%)	All Participants N=4181 n (%)
Safety population	1040 (99.8)	1977 (99.9)	995 (99.8)	4012 (96.0)
Immunogenicity population	0	492 (24.9)	498 (49.9)	990 (23.7)
Per Protocol population	0	489 (24.7)	498 (49.9)	987 (23.6)
PBMC subset of IMM population	0	101 (5.1)	103 (10.3)	204 (4.9)

IMM=Immunogenicity population; PBMC = peripheral blood mononuclear cells
Note: Percentages are computed based on number of randomized participants except.
'N' for overall column presents the count of all participants that signed informed consent.
Source: Table 14.1.1

The following table depicts numbers analysed in the subset (Per Protocol Analysis Set excluding participants with COVID-19 infection) that was used to compare neutralising as well as binding antibody titres in individuals 18-29 yoa with individuals >30 yoa.

Table 11: Demographic and baseline characteristics (Per-Protocol Analysis Set excluding participants with COVID-19 infection)

	VLA2001 Age <30 years N=302	VLA2001 Age ≥30 years N=602	VLA2001 All N=904
Per-Protocol Analysis Set (excluding participants with COVID-19 infection)	**210 (69.5)**	**498 (82.7)**	**708 (78.3)**
Reason not in Per-Protocol Analysis Set (Excluding Participants with COVID-19 Infection)			
Not seronegative at Day 1	71 (77.2)	67 (64.4)	138 (70.4)
Covid-19 infection up to data cut	10 (10.9)	15 (14.4)	25 (12.8)
No sample available at Day 43	6 (6.5)	11 (10.6)	17 (8.7)
No sample available at Day 1	4 (4.3)	5 (4.8)	9 (4.6)
Received less than two study vaccinations	0 (0.0)	4 (3.8)	4 (2.0)
Not vaccinated	1 (1.1)	2 (1.9)	3 (1.5)
Total	**92**	**104**	**196**
COVID-19 infections up to Day 43 sample (Per-Protocol Analysis Set)	**0 (0.0)**	**2 (0.3)**	**2 (0.2)**
Day 43 immunogenicity sample excluded from Per-Protocol analysis	**2 (0.7)**	**10 (1.7)**	**12 (1.3)**
Reason not included in Per-Protocol Analysis			
Difference 2nd vaccination Day 43 sample <10 days	1 (50.0)	9 (90.0)	10 (83.3)
Non-study Covid-19 vaccination prior Day 43 sample	1 (50.0)	1 (10.0)	2 (16.7)
Total	**2**	**10**	**12**
Baseline Seropositive Analysis Set <30 years	**68 (22.5)**	**0 (0.0)**	**68 (7.5)**
Reason not in Baseline Seropositive Analysis Set <30 years)			
≥30 years	0 (0)	602 (100)	602 (72.0)
Not seropositive at Day 1	226 (96.6)	0 (0.0)	226 (27.0)
No sample available at Day 1	4 (1.7)	0 (0.0)	4 (0.5)
No sample available at Day 43	3 (1.3)	0 (0.0)	3 (0.4)
Not vaccinated	1 (0.4)	0 (0.0)	1 (0.1)
Total	**234**	**602**	**836**

COVID-19=Coronavirus-2019; n=number of participants.
[a] Subset of participants aged 18-29 years is a combination of all participants who had at baseline a seropositive SARS-CoV-2 rapid antibody result and a random selection of 250 participants who had a negative SARS-CoV-2 rapid antibody result. Subset of participants ≥30 years were randomised to be included based on baseline seronegative status for SARS-CoV-2 rapid antibody.
Note: In general, percentages are based on number of participants selected for immunogenicity testing (N). Percentages on exclusion reasons are based on excluded participants (Total). Participants without evaluable immunogenicity result on Day 1 are excluded from analysis sets since baseline serostatus cannot be determined.
Source: Table 14.1

- **Outcomes and estimation**

Participants 30 years and older were randomly assigned to receive VLA2001 or AZD1222. All participants 18 to 29 years of age were placed in a non-randomized treatment group and received VLA2001.

The data described below for the primary immunogenicity analysis (first interim CSR) are based on all visits up to the data cut point of 11 August 2021 (Day 43 analysis). Additional analyses conducted at later time points have been provided.

Primary endpoints

Co-primary endpoint analysis: Geometric Mean Titre Ratio of neutralising antibodies at Day 43

On Day 1, in participants 30 years and older, GMT was 31.0 for both groups. By Day 43, GMT (95% CI) was 803.5 (95% CI: 748.5, 862.6) in participants who received VLA2001 and 576.6 (95% CI: 543.6, 611.7) for participants who received AZD1222. The difference was statistically significant in favour of VLA2001 (p<0.0001). With a GMT ratio of 1.39 (95% CI: 1.25, 1.56) superiority was confirmed for this co-primary endpoint on GMT titre ratio at Day 43.

Table 12: SARS-CoV-2 Neutralising antibody titres (ND50) on Day 1 and Day 43 (Immunogenicity population)

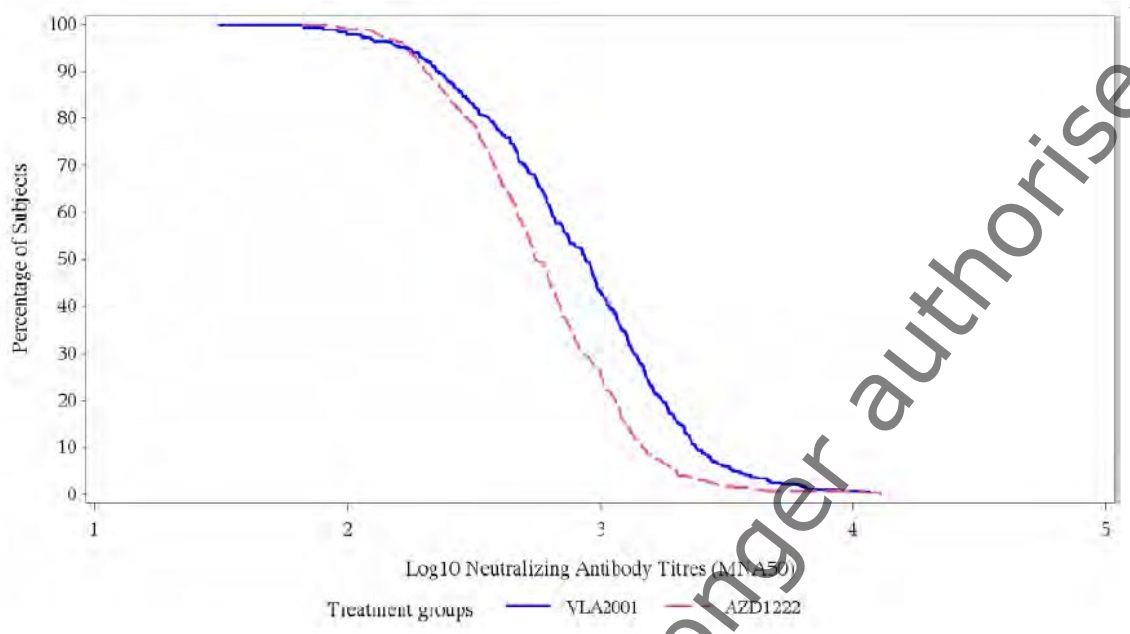
Visit Statistic	VLA2001 Age ≥30 years N=492	AZD1222 Age ≥30 years N=498	Difference N=990
Overall			
Day 1			
n	492	498	990
GMT (95% CI)	31.0 (31.00, 31.00)	31.0 (31.00, 31.00)	31.0 (31.00, 31.00)
GMT ratio (95% CI)	–	–	1.00 (1.00, 1.00)
Median	31.0	31.0	31.0
Min, Max	31, 31	31, 31	31, 31
p-value (overall dose groups comparison) [A]	–	–	NE
Day 43			
n	492	493	985
GMT (95% CI)	803.5 (748.48, 862.59)	576.6 (543.59, 611.66)	680.6 (649.40, 713.22)
GMT ratio (95% CI)			1.39 (1.25, 1.56)
Median	867.0	553.0	659.0
Min, Max	31, 12800	66, 12800	31, 12800
p-value, overall dose groups comparison [A]	–	–	<0.0001

CI=confidence interval; GMT=geometric mean titre; Max=maximum; Min=minimum; ND50=50% neutralizing dilution

A. p-value and CI were calculated using a 2-sided t-test applied to log10 transformed data.

Source: Table 14.3.1.1.

Figure 5: Reverse Cumulative Distribution Function for SARS-CoV-2 Neutralising Antibody Titres (ND50) for Day 43 by treatment group (IMM population)



ND50=50% neutralizing dilution
Day 43: VLA2001 (n=492); AZD1222 (n=493)
Source: Figure 1.5.4

Results based on age (30 to 55 years) were similar to those seen overall. There were no participants aged ≥55 years in the AZD1222 group.

Results were also analysed based on BMI (obesity, yes or no). In participants who were considered obese, the GMT (95% CI) at Day 43 was similar between the VLA2001 (689.3 [590.97, 803.92]) and the AZD1222 group (640.1 [565.27, 724.75]). Results for those who were not considered obese were similar to those seen overall.

Results for the PP population were similar to those for the IMM population.

Co-primary endpoint analysis: Seroconversion in terms of neutralising antibodies at Day 43

Seroconversion was defined as a ≥4-fold increase in SARS-CoV-2-specific neutralising antibody titre levels between Day 1 and post-vaccination sample collection time points.

At Day 43, in the PP population, 97.4% (95% CI: 0.954,0.986) of participants in the VLA2001 group were seroconverted and 98.9% (95% CI: 0.974,0.996) in the AZD1222 group. No statistically significant difference between the treatment groups were noted (p=0.0911). Non-inferiority was confirmed with a lower bound of the 95% CI for the difference between the randomised groups of -3.3%.

Table 13: Proportion of Participants with Seroconversion in Terms of Neutralising Antibodies on Day 43 (PP population) (study VLA2001-301)

Visit	VLA2001 N=492	AZD1222 N=498	Overall N=985
Overall			
Day 43			
Participants with seroconversion (≥4-fold increase)			
n	456	449	905
n (%)	444 (97.4)	444 (98.9)	888 (98.1)
95% CI [A]	0.954, 0.986	0.974, 0.996	0.970, 0.989
p-value [B]	–	–	0.0911
95% CI for difference [B]	–	–	-0.033, 0.002
Participants with			
≥2-fold increase, n (%)	454 (99.6)	449 (100.0)	903 (99.8)
≥10-fold increase, n (%)	381 (83.6)	356 (79.3)	737 (81.4)
≥20-fold increase, n (%)	280 (61.4)	204 (45.4)	484 (53.5)

CI=confidence interval; ND50=50% neutralizing dilution

Note: Seroconversion was defined as ≥4-fold increase in SARS-CoV-2-specific neutralizing antibody titre levels between Day 1 and post-vaccination sample collection time points.

A Exact 95% Clopper-Person CI for proportion.

B P value or 2-sided CI is for the difference in proportions (VLA2001-AZD122) of participants with seroconversion at each particular visit.

Source: Table 14.3.2.1.

In general, results for the IMM population were similar to the PP population: 97.0% (CI: 0.950, 0.983) of participants who received VLA2001 and 98.8% (CI: 0.974, 0.996) of participants who received AZD1222 met the definition of having seroconversion. Importantly, non-inferiority was also confirmed in the IMM population with a lower bound of the 95% CI for the difference between the randomized groups of -3.6%.

Secondary endpoints

Immune response as measured by neutralising antibody titres against SARS-CoV-2 over time

Results measured by neutralising antibody titres for Day 8 and Day 29 have not been provided as part of the interim CSR.

Fold Increase of SARS-CoV-2 Neutralising antibody

Fold increase was defined as a participant's post baseline titre at a visit divided by the baseline (Day 1) titre. Results at day 43 for the PP population were similar to those seen in the IMM population as reflected in the below table.

Table 14: Fold increase of SARS-CoV-2 antibody titres (ND50) – Day 43 (Immunogenicity Population)

Visit Statistic	VLA2001 N=492	AZD1222 N=498	Overall N=990
Overall			
Day 43			
n	492	493	985
GMFI (95% CI) [A]	25.9 24.14, 27.83	18.6 17.54, 19.73	22.0 20.95, 23.01
Median	867.0	553.0	659.0
Min, Max	31.0, 12800.0	66.0, 12800.0	31.0, 12800.0
p-value (between VLA2001 and AZD1222) [B]	–	–	<0.0001

ANOVA=analysis of variance; CI=confidence interval; GMFI=geometric mean fold increase; Max=maximum; Min=minimum; ND50=50% neutralizing dilution

A The fold increase was defined as a participant's post baseline titre at a visit divided by the baseline (Day 1) titre.

B p-value was calculated using the ANOVA model.

Source: Table 14.3.2.9

Immune Responses as Measured by IgG binding antibodies to SARS-CoV-2 S-protein

A summary of SARS-Cov-2 S-protein IgG antibody titres determined by ELISA at Day 1 and Day 43 for the IMM population is presented in the table below.

Table 15: IgG Antibody Titres against SARS-CoV-2 S-protein (ELISA) Over Time Points - (Immunogenicity Population)

Visit Statistic	VLA2001 N=492	AZD1222 N=498	Overall N=990
Overall			
Day 1			
n	489	496	985
GMT (95% CI) [A]	25.2 25.03, 25.41	25.6 25.16, 25.96	25.4 25.17, 25.61
Median	25.0	25.0	25.0
Day 29			
n	484	489	973
GMT (95% CI) [A]	44.3 (41.32, 47.46)	740.8 (680.90, 805.96)	182.4 (166.36, 200.06)
Median	25.0	716.2	178.0
Day 43			
n	492	493	985
GMT (95% CI) [A]	2361.7 (2171.08, 2569.11)	2126.4 (1992.42, 2269.45)	2240.9 (2124.81, 2363.27)
Median	2898.7	2112.4	2421.7

CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; GMT=geometric mean titre; Max=maximum; Min=minimum

A CI calculated using log10 transformed

Source: Table 14.3.2.7.

Results for the PP population were similar to those seen for the IMM population.

Proportion of participants with Seroconversion in terms of S-protein binding IgG antibodies

Seroconversion was defined as a ≥4-fold increase in SARS-CoV-2-specific IgG antibody titre levels between Day 1 and post-vaccination sample collection time points.

Table 16: Proportion of Participants with Seroconversion in Terms of S-protein Specific IgG Antibodies (ELISA) – (Immunogenicity Population)

Visit	VLA2001 N=492	AZD1222 N=498	Overall N=990
Day 29			
Participants with seroconversion (≥4-fold increase)			
n(%)	76 (15.5)	466 (93.6)	542 (54.9)
95% CI [A]	(0.126,0.193)	(0.930,0.970)	(0.525,0.589)
p-value [B]			<.0001
Participants with ≥ 2-fold increase	174 (35.6)	478 (96.0)	652 (66.1)
Participants with ≥ 10-fold increase	22 (4.5)	424 (85.1)	446 (45.2)
Participants with ≥ 20-fold increase	8 (1.6)	304 (61.0)	312 (31.6)
Day 43			
Participants with seroconversion (≥4-fold increase)			
n	492	494	986
n (%)	482 (98.0)	488 (98.8)	970 (98.4)
95% CI [A]	0.963, 0.990	0.974, 0.996	0.974, 0.991
p-value [B]	–	–	0.3094
95% CI for difference [B]	–	–	-0.024, 0.008
Participants with			
≥2-fold increase, n (%)	486 (98.8)	489 (99.0)	975 (98.9)
≥10-fold increase, n (%)	465 (94.5)	485 (98.2)	950 (96.3)
≥20-fold increase, n (%)	443 (90.0)	468 (94.7)	911 (92.4)

CI=confidence interval; ELISA=enzyme-linked immunosorbent assay

Note: Seroconversion was defined as ≥4-fold increase in SARS-CoV-2-specific neutralizing antibody titre levels between Day 1 and post-vaccination sample collection time points.

A Exact 95% Clopper-Person CI for proportion.

B P value or 2-sided CI is for the difference in proportions (VLA2001-AZD122) of participants with seroconversion at each particular visit.

Source: Table 14.3.2.5.

Results for the PP population were similar to those seen for the IMM population.

T-cell Responses by Interferon Gamma T-cell ELISpot (T-spot)

A summary of T-cell response by interferon gamma T-cell ELISpot for the spike protein (full sequence), nucleocapsid protein and membrane protein are presented in the Table below.

Table 17: T-Cell Response by Interferon Gamma T-cell ELISpot for the Nucleocapsid Protein and the Membrane Protein – Day 43 (Immunogenicity Population)

Panel	VLA2001 N=77 n (%)	AZD1222 N=79 n (%)	Overall N=156 n (%)
Nucleocapsid Protein			
n	71	70	141
Mean (SD)	9.2 (15.20)	0.6 (2.25)	4.9 (11.69)
Min, Max	0.0, 111.0	0.0, 18.0	0.0, 111.0
p-value (Day 1 vs Day 43) [A]	<0.0001	<0.3070	–
p-value (between study groups) [B]	–	–	<0.0001
Membrane Protein			
n	71	70	141
Mean (SD)	3.9 (4.99)	0.3 (0.78)	2.1 (4.01)
Min, Max	0.0, 26.0	0.0, 5.0	0.0, 26.0
p-value (Day 1 vs Day 43) [A]	<0.0001	0.1168	–
p-value (between study groups) [B]	–	–	<0.0001
Spike Protein, full sequence			
n	71	70	141
Mean (SD)	18.0 (23.54)	27.2 (27.10)	22.6 (25.70)
Median (IQR)	10.0 (14.00)	20.0 (22.00)	14.0 (23.00)
Min, Max	0.0, 152.0	2.0, 130.0	0.0, 152.0
p-value (Day 1 vs Day 43) [A]	<.0001	<.0001	
p-value (Between study groups) [B]			0.0323

SD=standard deviation

A P-value calculated using paired t-test comparison within treatment between study days.

B P-value calculates using T-test between study groups

Source: Table 14.3.2.13.

The results of the T-cell responses by IFN-gamma T-Cell ELISpot (T-spot) related to the full spike protein for days 1, 29, 43 and 71 were provided as included in the below table.

Table 18: Assessment of T-cell responses by IFN-gamma T-Cell ELISpot (T-spot) against Spike protein full sequence – Days 1, 29, 43 and 71 (Immunogenicity Population)

Table 14.3.2.13
Assessment of T-cell responses by interferon (IFN) gamma T-cell ELISpot (T-spot): Secondary Immunogenicity Analysis
Immunogenicity population

Overall

Parameter/ Visit	Statistic	VLA2001 (N=77)	AZD1222 (N=79)	Overall (N=156)
Panel 14 Spike Protein, full sequence				
Day 1	n	77	79	156
	Mean (SD)	2.8 (13.98)	1.4 (2.07)	2.1 (9.93)
	Median (IQR)	1.0 (2.00)	1.0 (2.00)	1.0 (2.00)
	Min, Max	0.0, 123.0	0.0, 11.0	0.0, 123.0
Day 29	n	73	75	148
	Mean (SD)	6.1 (18.73)	33.2 (32.78)	19.8 (29.95)
	Median (IQR)	2.0 (4.00)	24.0 (48.00)	7.0 (25.00)
	Min, Max	0.0, 148.0	0.0, 198.0	0.0, 198.0
Day 43	n	71	70	141
	Mean (SD)	18.0 (23.54)	27.2 (27.10)	22.6 (25.70)
	Median (IQR)	10.0 (14.00)	20.0 (22.00)	14.0 (23.00)
	Min, Max	0.0, 152.0	2.0, 130.0	0.0, 152.0
	p-value (Day 1 vs Day 43)	<.0001	<.0001	
	p-value (Between study groups)			0.0323
Day 71	n	75	72	147
	Mean (SD)	16.2 (34.87)	25.7 (29.70)	20.8 (32.67)
	Median (IQR)	8.0 (13.00)	15.0 (19.50)	11.0 (18.00)
	Min, Max	0.0, 292.0	0.0, 133.0	0.0, 292.0
	p-value (Day 1 vs Day 71)	<.0001	<.0001	
	p-value (Between study groups)			0.0803

IQR: Interquartile range
Note: [1] p-value calculated using paired t-test comparison within treatment between study days.
Note: [2] p-value calculated using T-Test between study groups.
Data Sources: ADSL, ADIS
Data Cut-Off Date: Up to 11AUG2021.
Program Location: E:\Projects\1232Valneva\Stats\Programs\T_14_3_2_13.sas Date: 12NOV2021:03:47

T-cell Responses by Intracellular Cytokine Staining (ICS)

Data on intracellular Cytokine Staining will be included in a later version of the CSR.

Cellular Immune Response (Reactogenicity Against Stimulation Panel)

A stratification based on the baseline T-spot reactivity (i.e., "reactive on Day 1" and "non- reactive on Day 1") was performed. Sample was considered reactive against individual stimulation panel if normalized SFU ≥6. At Day 43, 74.3% of a subset of study participants in the VLA2001 group were reactive against peptide pools spanning the full-length S-protein. In addition, in the VLA2001 group 45.9% were reactive against the N-protein and 20.3% against the M-protein.

Table 19: Cellular Immune Response (Reactogenicity Against Stimulation Panel) – Reactive Percentages on Day 1 and Day 43 (Immunogenicity Population)

Visit Panel	VLA2001 N=492	AZD1222 N=498	Overall N=990
Overall			
Panel 1: spike protein N terminus			
Day 1			
n	77	79	156
Reactive	0	0	0
Day 43			
n	74	74	148
Reactive	38 (51.4)	58 (78.4)	96 (64.9)
Panel 2: spike protein C terminus			
Day 1			
n	77	79	156
Reactive	1 (1.3)	1 (1.3)	2 (1.3)
Day 43			
n	74	74	148
Reactive	32 (43.2)	43 (58.1)	75 (50.7)
Panel 3: nucleocapsid protein			
Day 1			
n	77	79	156
Reactive	0	0	0
Day 43			
n	74	74	148
Reactive	34 (45.9)	1 (1.4)	35 (23.6)
Panel 4: membrane protein			
Day 1			
n	77	79	156
Reactive	1 (1.3)	0	1 (0.6)
Day 43			
n	74	74	148
Reactive	15 (20.3)	0	15 (10.1)
Panel 14: spike protein, full sequence			
Day 1			
n	77	79	156
Reactive	2 (2.6)	3 (3.8)	5 (3.2)
Day 43			
n	74	74	148
Reactive	55 (74.3)	64 (86.5)	119 (80.4)

n=the number of samples available for analysis; PBMC=peripheral blood mononuclear cells; SFU=spot forming units

Note: The sample was considered reactive against an individual stimulation panel if normalized SFU≥6. The denominators for the percentages are the number of available samples at each visit within each parameter. Data are based on spot forming units per 2.5×10^5 PBMC.

Source: Table 14.3.2.11

Results for the PP population were similar to those seen for the IMM population.

Exploratory endpoint

Number of COVID-19 Cases

The number of COVID-19 cases was an exploratory efficacy endpoint in study VLA2001-301. A similar percentage of participants in different treatment groups became COVID-19 positive. All COVID-19 cases were assessed as mild or moderate by the investigator.

139 (7%) COVID-19 cases (exploratory endpoint) occurred in participants ≥30 years and 87 (8.4%) in participants 18-29 years who received VLA2001. 60 (6%) cases occurred in participants who received COVID-19 Vaccine (ChAdOx1-S [recombinant]). All COVID-19 cases were assessed as mild or moderate by the investigator.

Table 20: Positive reported COVID-19 cases after vaccination (Safety Population)

Number of	VLA2001 Age <30 years N=1040 n (%)	VLA2001 Age ≥30 years N=1977 n (%)	AZD1222 N=995 n (%)	All Participants N=4012 n (%)
Participants who tested COVID-19 positive after 1st dose of vaccination	2 (0.2)	7 (0.4)	2 (0.2)	11 (0.3)
Days from 1st vaccination to COVID-19 positive after 1 dose of vaccination				
n	2	7	2	11
Mean (SD)	22.5 (6.364)	16.33 (10.58)	20.0 (2.83)	17.5 (9.04)
Median	22.5	16.0	20.0	18.0
Min, Max	18, 27	1, 28	18, 22	1, 28
Participants who tested COVID-19 positive after 2nd dose of vaccination	87 (8.4)	139 (7.0)	60 (6.0)	286 (7.1)
Days from 2nd vaccination to COVID-19 positive test				
n	87	139	60	286
Mean (SD)	57.9 (30.19)	63.0 (34.09)	70.1 (31.89)	63.0 (32.66)
Median	65.0	63.0	76.5	66.0
Min, Max	3, 130	7, 126	15, 124	3, 130
Participants who tested COVID-19 positive 14 or more days after 2nd dose of vaccination	82 (7.9)	131 (6.6)	60 (6.0)	286 (7.1)
Days from 2nd vaccination to COVID-19 positive test				
n	82	131	60	286
Mean (SD)	61.0 (28.35)	66.2 (32.47)	70.1 (31.89)	65.5 (31.22)
Median	66.0	69.0	76.5	67.0
Min, Max	15, 130	14, 126	15, 124	14, 130

Max=maximum; Min=minimum; CI=confidence interval; SD=standard deviation

Source: Table 14.3.2.16.

Additional immunogenicity data

Immunogenicity data in seronegative individuals 18-29 years of age compared to individuals >30 years of age (MNA & ELISA)

At Day 43, the GMT was 803.5 [95% CI: 748.5, 862.6] in participants aged 30 years and older. In comparison, GMT at Day 43 in the <30 years age group was 1043.4 [95% CI: 926.6, 1174.9]. This difference was statistically significant, with a GMT ratio of 1.3 [95% CI: 1.1, 1.5], p=0.0008.

Non-inferiority of the <30 years age group in terms of GMT was confirmed as the lower limit of the CI was above the predefined NI margin value of 0.67.

Table 21: Geometric Mean Titre of SARS-CoV-2 Neutralising Antibodies at Day 1 and Day 43 (Primary Population: Immunogenicity Analysis Set Excluding Participants with COVID-19 Infection)

	Statistic	VLA2001 <30 years (N=200)	VLA2001 ≥30 years (N=492)
Visit 1 - Day 1			
	Geometric Mean	31.0	31.0
	[95% CI] GM	[31.0, 31.0]	[31.0, 31.0]
	SD(log10)	0.00	0.00
	Mean	31.0	31.0
	SD	0.00	0.00
	Median	31.0	31.0
	Q1 / Q3	31.0 / 31.0	31.0 / 31.0
	Min / Max	31.0 / 31.0	31.0 / 31.0
	n	200	492
	n(log10)	200	492
Visit 4 - Day 43			
	Geometric Mean	1043.4	803.5
	[95% CI] GM	[926.6, 1174.9]	[738.3, 874.4]
	SD(log10)	0.37	0.41
	Mean	1456.4	1250.8
	SD	1363.00	1484.28
	Median	1118.5	867.0
	Q1 / Q3	657.0 / 1841.0	438.5 / 1520.0
	Min / Max	87.0 / 11036.0	31.0 / 12800.0
	n	200	492
	n(log10)	200	492

In terms of seroconversion, for the IAS population (excluding participants with COVID-19 infection), 98.5% [95% CI: 95.7, 99.7] of participants aged <30 years and 97.0% [95% CI: 95.0, 98.3] of participants aged ≥30 years met the definition of seroconversion. Non-inferiority for the <30 years age group was confirmed with a lower bound of the 95% CI for the difference between age groups of -1.5%.

Table 22: Proportion of Participants with Seroconversion of SARS-CoV-2 neutralising antibodies from Day 1 to Day 43 for IAS (Excluding Participants with COVID-19 Infection)

	VLA2001 <30 Years N=200	VLA2001 ≥30 Years N=492	Rate Difference % (CI) [b]
Participants with seroconversion at Day 43			
n (%)	197 98.5%	477 97.0%	1.5
95% CI [a]	95.7, 99.7	95.0, 98.3	[-1.5, 3.8]

CI=confidence interval; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2.
[a] Two-sided 95% CIs calculated according to Clopper-Pearson for seroconversion rate.
[b] Two-sided 95% CI calculated according to Miettinen-Nurminen for the difference in seroconversion rates
Note: Seroconversion was defined as ≥4-fold increase (i.e., participants Day 43 value divided by the Day 1 value) in SARS-CoV-2 neutralizing antibody levels between Day 1 and Day 43.
In case of missing values (missing at Day 1 or Day 43), fold-increase and seroconversion were not calculated.
Non-inferiority was claimed if the lower bound of the two-sided 95% CI for the difference is greater than -5%

Immunogenicity data in seropositive individuals ≥ 30 years of age (MNA and ELISA)

Table 23: GMT of SARS-CoV-2 neutralising antibodies at Day 1 and Day 43 in Participants age < 30 years who were MNA baseline seropositive

	Statistic	VLA2001 <30 years (N=67)
Visit 1 - Day 1		
	Geometric Mean	418.3
	[95% CI]	[340.9, 513.2]
	SD(log10)	0.36
	Mean	637.0
	SD	937.19
	Median	440.0
	Q1 / Q3	269.0 / 640.0
	Min / Max	67.0 / 6884.0
	n	67
	n(log10)	67
Visit 4 - Day 43		
	Geometric Mean	2425.7
	[95% CI] GM	[2072.6, 2839.0]
	SD(log10)	0.28
	Mean	2999.3
	SD	2307.02
	Median	2400.0
	Q1 / Q3	1702.0 / 3356.0
	Min / Max	440.0 / 12800.0
	n	67
	n(log10)	67

CI=confidence interval; GMT=geometric mean titre; Max=maximum; Min=minimum, n=number of participants with non-missing result; Q=quartile; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2.
Note: Values below the quantitation limit of the MNA (62) are replaced by 31. Values below the lower dilution limit are also replaced by 31. Values above the upper dilution limit are replaced by the upper dilution limit.
The Baseline Seropositive Analysis Set <30 years consists of all vaccinated participants <30 years of age who were seropositive at Day 1 and have at least one evaluable antibody titre measurement after vaccination.

Table 24: GMT of SARS-CoV-2 S-protein IgG ELISA at Day 1 and Day 43 in Participants age < 30 years who were ELISA Baseline Seropositive

Visit Statistic	VLA2001 <30 Years N=68
Visit 1 - Day 1	
n	68
GMT (95% CI)	628.4 (479.2, 824.1)
Median	615.2
Q1, Q3	289.3, 1166.6
Min, Max	51.0, 10856.3
Visit 4 - Day 43	
n	68
GMT (95% CI)	5174.9 (4555.0, 5879.1)
Median	4958.4
Q1, Q3	3862.1, 7632.8
Min, Max	1240.2, 15798.0

CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; ELU=ELISA laboratory units; GMT=geometric mean titre; IgG=immunoglobulin G; Max=maximum; Min=minimum, n=number of participants with non-missing result; Q=quartile; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2; S-protein=spike-protein.

Note: Values below the quantitation limit of the ELISA (50.3 ELU/mL) are replaced by 25 ELU/mL. If present, values above the quantitation limit (>15798) are replaced by the quantitation limit (15798).
The Baseline Seropositive Analysis Set <30 years consists of all vaccinated participants <30 years of age who were seropositive at Day 1 and have at least one evaluable antibody titre measurement after vaccination.
Source: Table 14.25

Immunogenicity data in seropositive individuals ≥ 30 years of age (MNA and ELISA)

Table 25: GMT of SARS-CoV-2 neutralising antibodies (ND50) - Day 43 (MNA baseline seropositive)

Visit	VLA2001 (N=84)
	Overall
Day 1	
n	84
GMT (95% CI) [B]	269.2 (226.4, 320.0)
Median	279.0
Min, Max	62, 6738
Day 43	
n [A]	81
GMT (95% CI) [B]	1478.6 (1245.6, 1755.1)
Median	1494
Min, Max	85, 12800

CI=confidence interval; GMT: Geometric Mean Titre
A Eligible is defined as having a sample available for Day 43.
B CI calculated using a two-sided t-test applied to log10 transformed data.
Source: Table 14.3.2.4b.

Table 26: Immune responses as measured by IgG antibodies to SARS-CoV-2 S-protein: MNA-Baseline positive population (everyone with MNA ND50 results)

Age Group: Overall

Visit	Statistic	VLA2001 (N=84)
Day 1	Participants Assessed At Visit	
	n	82
	GMT (95% CI)	212.8 (163.02, 277.75)
	Median	268.3
	Min, Max	25.0, 11629.6
Day 8	Participants Assessed At Visit	
	n	1
	GMT (95% CI)	1051.1 (0.00, 0.00)
	Median	1051.1
	Min, Max	1051.1, 1051.1
Day 29	Participants Assessed At Visit	
	n	80
	GMT (95% CI)	953.3 (673.95, 1348.55)
	Median	2048.0
	Min, Max	25.0, 15798.0
Day 43	Participants Assessed At Visit	
	n	81
	GMT (95% CI)	2892.5 (2350.47, 3559.41)
	Median	3444.1
	Min, Max	25.0, 15798.0
Day 71	Participants Assessed At Visit	
	n	79
	GMT (95% CI)	2803.3 (2296.93, 3421.32)
	Median	2954.8
	Min, Max	25.0, 15798.0

GMT: Geometric Mean Titre, CI: Confidence Interval

Data Sources: ADSL, ADIS
Data Cut-Off Date: Up to and including 14OCT2021.
Program Location: E:\Projects\1232Valneva\Stats\Programs\T_14_3_2_8b.sas Date: 21FEB2022:08:09

Table 27: Proportion of Participants with Seroconversion in Terms of Neutralising Antibodies MNA-Baseline Positive Population (Everyone with MNA ND50 result)

Age Group: Overall

Visit	VLA2001 (N=84)
Day 43	
Number of Patients With Eligible Samples at Visit	81
Participants with seroconversion	
n(%)	53 (65.4)
95% CI [1]	(54.04,75.66)
Participants with ≥ 4-fold increase	68 (84.0)
Participants with ≥ 10-fold increase	19 (23.5)
Participants with ≥ 20-fold increase	8 (9.9)

Immunogenicity data in seronegative individuals ≥30 years of age by age (MNA)

The following analyses have been provided to better characterise both the age distribution within the immunogenicity subset for the primary analysis as well as potential age-mediated effects:

Figure 6: Histogram of age distribution VLA2001-301 (IMM Population, 1 of 2)

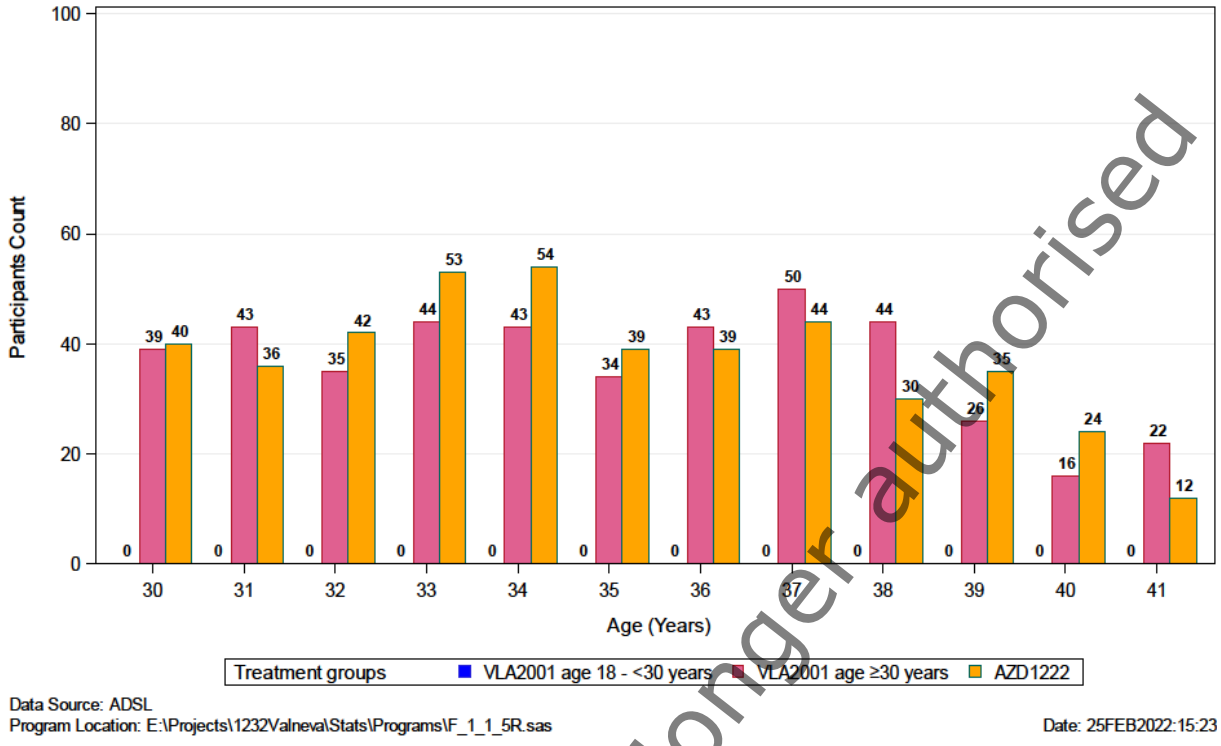


Figure 7: Histogram of age distribution VLA2001-301 (IMM Population, 2 of 2)

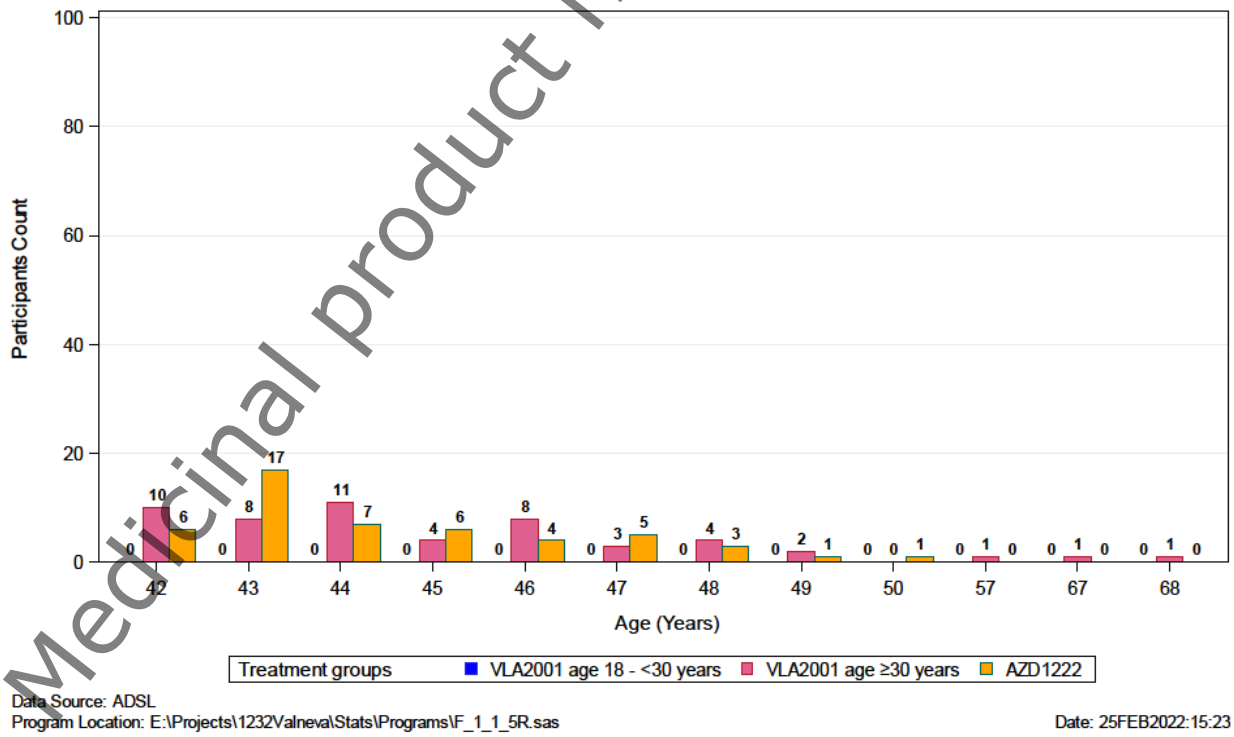


Figure 8: Scatter plot of nAb versus age VLA2001-301 (IMM population) with simple linear regression for each treatment group (log10 transformed)

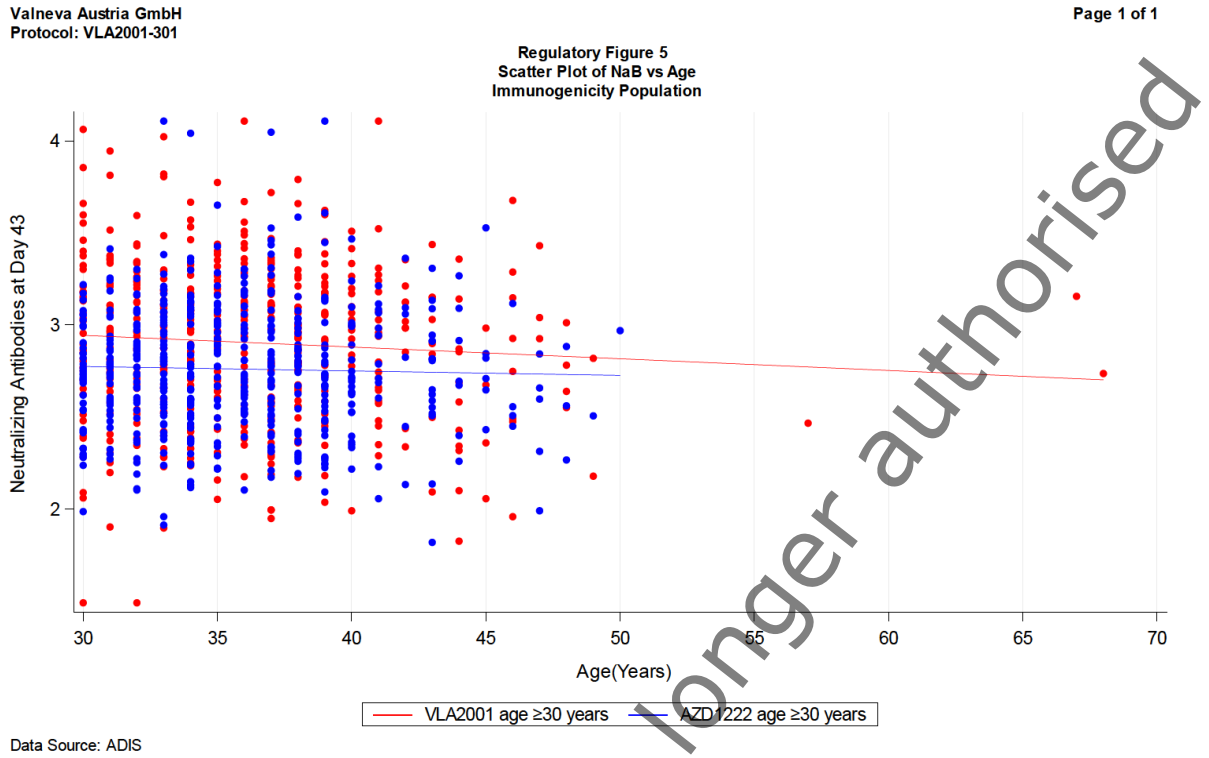
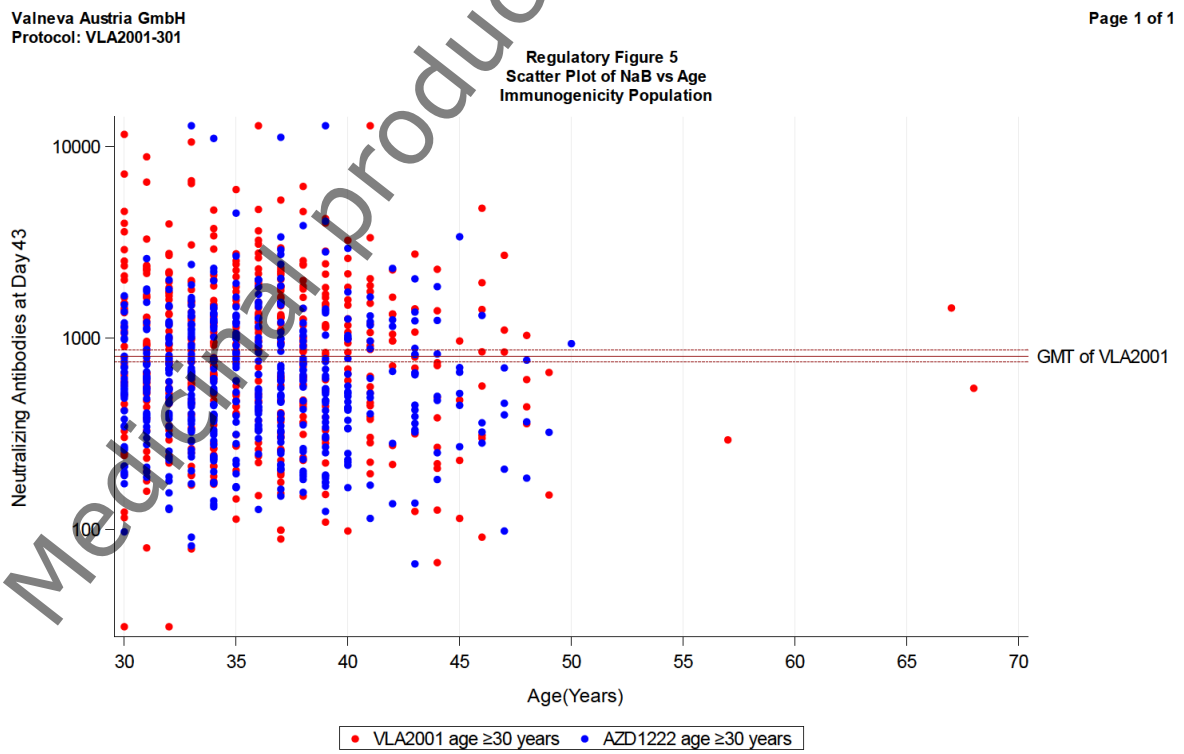


Figure 9: Scatter plot of nAb versus age VLA2001-301 (IMM population)



- **Summary of main immunogenicity results**

The following tables summarise the immunogenicity 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 28: Summary of immunogenicity for trial VLA2001-301

Title: A Randomized, Observer-blind, Controlled, Superiority Study to Compare the Immunogenicity Against COVID-19, of VLA2001 Vaccine to AZD1222 Vaccine, in Adults		
Study identifier	VLA2001-301 ClinicalTrials.gov Identifier: NCT04864561	
Design	Randomized, observer-blind, multicentre, controlled, superiority study to compare the immunogenicity against COVID-19, of VLA2001 vaccine to AZD1222 vaccine, in adults	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Approximately 13 months Maximum of 7 days Not applicable
Hypothesis	Superiority was tested on the Day 43 GMT ratio VLA2001/AZD1222. The null hypothesis was that the ratio is equal to 1, and the alternative hypothesis was that the ratio is not equal to 1. Testing was done at a 2-sided significance level of 5%. Superiority of VLA2001 was postulated in case of a statistically significant test with a Day 43 GMT ratio >1. Seroconversion was defined as ≥ 4-fold increase in SARS-CoV-2-specific neutralising antibody titre levels between Day 1 and Day 43. The fold increase is defined as a participant's post-Baseline titre at a visit divided by the baseline (Day 1) titre. The number and proportion of participants with seroconversion in terms of neutralising antibodies on Day 43 was be presented along with exact 95% Clopper-Pearson CI for both study arms and overall.	
Treatments groups	VLA2001 (age ≥30)	VLA2001 (Inactivated, SARS-CoV-2 vaccine adjuvanted with CpG and Alum (33 antigen units/dose) administered by intramuscular injection) Two vaccinations administered 28 days apart, on Day 1 and Day 29 1978 participants randomized
	AZD1222 (age ≥30)	AZD1222 (Recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 S surface glycoprotein administered by IM injection) Two vaccinations administered 28 days apart, on Day 1 and Day 29 997 participants randomized
	VLA2001 (age <30)	VLA2001 (Inactivated, SARS-CoV-2 vaccine adjuvanted with CpG and Alum (33 antigen units/dose) administered by intramuscular injection) Two vaccinations administered 28 days apart, on Day 1 and Day 29 1042 participants allocated (non-random)

Title: A Randomized, Observer-blind, Controlled, Superiority Study to Compare the Immunogenicity Against COVID-19, of VLA2001 Vaccine to AZD1222 Vaccine, in Adults			
Study identifier	VLA2001-301 ClinicalTrials.gov Identifier: NCT04864561		
Endpoints and definitions	Co-Primary endpoint	GMT of neutralising antibodies at day 43	Immune response measured after completion of a 2-dose immunization schedule, as determined by the GMT of SARS-CoV-2-specific neutralising antibodies at Day 43
	Co-Primary endpoint	Seroconversion of neutralising antibodies at day 43	Immune response measured after completion of a 2-dose immunization schedule, as determined by the Seroconversion (defined as a 4-fold increase from baseline) of SARS-CoV-2-specific neutralising antibodies at Day 43
	Secondary endpoint	Seroconversion on Day 8 (age 55+ only), Day 29, Day 43, Day 71 and Day 208	Proportion of participants with seroconversion on Day 8 (age 55+ only), Day 29, Day 43, Day 71 and Day 208. Seroconversion is defined as ≥4-fold increase in SARS-CoV-2 neutralising antibody titre and S-protein binding IgG levels between Day 1 and post-vaccination time points
	Secondary endpoint	GMT of neutralising antibodies on Day 8 (age 55+ only), Day 29, Day 71 and Day 208	Immune response on Day 8 (age 55+ only), Day 29, Day 71 and Day 208, as determined by the GMT of SARS-CoV-2- specific neutralising antibodies
	Secondary endpoint	GMT of IgG antibodies to SARS CoV-2 S-protein Day 8 (age 55+ only), Day 29, Day 43, Day 71 and Day 208	Immune response on Day 8 (age 55+ only), Day 29, Day 43, Day 71 and Day 208 , as determined by the GMT of IgG antibodies to SARS CoV-2 S-protein
	Secondary endpoint	T-cell responses after in vitro stimulation with SARS-CoV-2 antigens	Assessment of T-cell responses (Th1/Th2 polarization) from peripheral blood mononuclear cells on selected time points in a subset of participants after in vitro stimulation with SARS-CoV-2 antigens using e.g., ELISpot (IFNγ) or intracellular cytokine staining (interleukin-2, IL-4, IL-5, IL 13, tumour necrosis factor α, IFNγ)
	Exploratory endpoint	COVID-19 cases	Number of COVID-19 cases per treatment group
Database lock	The study is ongoing. The CSR is based on a datacut up to the data cut point of 11 August 2021 for the primary analysis of efficacy.		

Results and Analysis

Analysis description	**Co-Primary Analysis: SARS-CoV-2 Neutralising Antibody Titres**		
Analysis population and time point description	Immunogenicity population Day 43		
Descriptive statistics and estimate variability	Treatment group	VLA2001 Age ≥30 years	AZD1222 Age ≥30 years
	Number of subject	492	493
	GMT	803.5	576.6
	95% CI	748.48, 862.59	543.59, 611.66
	Median	867.0	553.0

Title: A Randomized, Observer-blind, Controlled, Superiority Study to Compare the Immunogenicity Against COVID-19, of VLA2001 Vaccine to AZD1222 Vaccine, in Adults				
Study identifier	VLA2001-301 ClinicalTrials.gov Identifier: NCT04864561			
	Min, Max	31, 12800	66, 12800	
Effect estimate per comparison	Co-Primary endpoint	Comparison groups	VLA2001 (≥30 years) AZD1222 (≥30 years)	
		GMT ratio	1.39	
		95% CI	1.25, 1.56	
		P-value (2-sided t-test applied to log10 transformed data)	<0.0001	
Notes	-			
Analysis description	**Co-Primary Analysis: Proportion of Participants with Seroconversion in Terms of Neutralising Antibodies**			
Analysis population and time point description	Per protocol population Day 43			
Descriptive statistics and estimate variability	Treatment group	VLA2001 Age ≥30 years	AZD1222 Age ≥30 years	
	Number of subjects	456	449	
	Seroconversion, n (%)	444 (97.4)	444 (98.9)	
	95% CI	0.954, 0.986	0.974, 0.996	
	Participants with			
	≥2-fold increase, n (%)	454 (99.6)	449 (100.0)	
	≥10-fold increase, n (%)	381 (83.6)	356 (79.3)	
	≥20-fold increase, n (%)	280 (61.4)	204 (45.4)	
Effect estimate per comparison	Co-Primary endpoint	Comparison groups	VLA2001 (≥30 years) AZD1222 (≥30 years)	
		Difference in proportions	-0.015	
		95% CI	-0.033, -0.002	
		P-value (2-sided t-test)	0.0911	

- **Cross-neutralisation potential of VLA2001 vaccine against SARS-CoV-2 VoC**

The subsequent is based on data generated as part of the Phase 1/2 study VLA2001-201 (report 'VIE-DR-0166').

The study was aimed to describe cross-neutralisation potential of nAb found in sera from recipients of two doses of the VLA2001 COVID-19 vaccine. Sera were tested for neutralising activity using a live-virus (micro)neutralisation assay (MNA_{PHE} and MNA_{VLA}) and a pseudotyped virus neutralisation assay (PNA) against several SARS-CoV-2 variants.

A two dose series of VLA-2001 vaccination induced neutralising antibodies against all tested SARS-CoV-2 VoCs (Alpha, Beta, Gamma, Delta). Compared to neutralising titres (GMTs) on day 36 against the Wuhan strain:

- Neutralising titres against the Alpha variant declined by 12.5-fold (MNA_{PHE}), 1.8-fold (PNA) and 2.2-fold (MNA_{VLA});
- Neutralising titres against the Beta variant GMTs declined by 21.1-fold (MNA_{PHE}), 4.5-fold (PNA), 7.3-fold (MNA_{VLA});
- Neutralising titres against the Gamma GMTs declined by 1.6-fold (PNA only).

Neutralising titres against the Wuhan/Victoria strain declined approx. 2.5-to 3-fold over time from day 36 to 106 (in both MNA_{PHE} and PNA). GMTs against all tested variants at day 106 were lower by a factor of 12 (Alpha), 8 (Beta) and 10 (Delta) compared to Victoria strain (MNA_{PHE}). These differences were less pronounced in the PNA assay and in the 1.0-2.5-fold decline range for Alpha, Beta and Gamma compared to Wuhan.

The Applicant provided novel data on SARS-CoV-2 pseudovirus neutralisation in individuals who received 3 doses of VLA2001 (primary schedule + booster 7-8 months thereafter in Phase 1/2 study). Neutralising activity against Omicron was about 6% compared to wt. Neutralising activity against Delta was about 37% of wt.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme is based on an immunobridging strategy that compares the experimental VLA2001 vaccine with the authorized AZD1222 vaccine of known efficacy. No efficacy studies were planned as they were considered not feasible. This was agreed by the CHMP in a previous EMA Scientific Advice procedure (Case No.: EMA/SA/0000064690).

The Applicant has requested the approval for primary series for the target population 18-55 years of age, instead of the initially planned population ≥18 yoa. This was due to delays in data analysis in the population >55 years of age.

The MAA is currently based on the interim results of two clinical trials: the FIH Phase 1/2 study VLA2001-201 and the pivotal Phase 3 study VLA2001-301. Both clinical studies are still ongoing. All clinical trials are being conducted in the UK in compliance with Good Clinical Practice.

Dose finding

Study VLA2001-201 is a first-in-human, Phase 1/2, dose finding trial on safety and immunogenicity to select the VLA2001 dose for further clinical trials (Day 36 and Day 106 interim analyses currently available, Day 208 [i.e. EoS] data not yet). Three doses were investigated: low (3 AU/dose), medium (7 AU/dose), and high (35 AU/dose) in study subjects aged from 18 to 55.

A 21-day interval between the first and second dose administration was chosen. In contrast, the pivotal Phase 3 applied a 28 day period to match the authorized 28-84 days interval of the EU-authorized comparator Vaxzevria (AZD1222 vaccine). The difference in dosing intervals between Phase 1/2 and 3 is not considered optimal as it impedes inter-study comparisons and somewhat limits further extrapolation to the clinically relevant dosing schedule. However, to inform dose decision, this appears not concerning.

The chosen endpoints are mostly in line with those of the Phase 3 trial, which had been agreed to by the CHMP in the EMA Scientific Advice (Case No.: EMA/SA/0000064690) and are thus adequate. Sampling time points seem to be reasonable and are assumed to appropriately allow evaluation of endpoints.

The study plan envisages that study participants who have completed the primary immunization schedule (two vaccinations), will be invited to participate in a Booster Phase to investigate the immunogenicity and safety of a booster dose with VLA2001. This is endorsed and requested as recommendation post-authorisation in case of approval of the primary immunization schedule (**Clinical efficacy recommendation 1**).

Main Study

The pivotal study VLA2001-301 is a Phase 3, superiority trial on the immunogenicity and safety of VLA2001 compared to the already licensed vaccine AZD1222 (Day 43 interim analysis currently available). The immunogenicity data obtained from the pivotal study VLA2001-301 are considered as the main evidence for this MAA. The assessment of immunogenicity to infer vaccine efficacy is based on the interim clinical study report v1.0, as the clinical trial is on-going. The final CSR for study VLA2001-301 should be provided by 30 June 2023 (**Clinical efficacy recommendation 4**). The immunobridging strategy employs a comparison of immune responses induced by VLA2001 or AZD1222 in vaccine-naïve adults ≥30 years of age. Subjects received two doses of either vaccine 28 days apart with the primary analysis (based on humoral immune responses) conducted on day 43 (i.e. approx. 2 weeks post-dose 2). In addition, within this study, the immunogenicity of VLA2001-vaccinated subjects 18-29 years of age was evaluated in comparison to VLA2001-vaccinated subjects ≥ 30 years of age. No (active) comparator data were generated for this younger age group.

A rapid antigen test was performed at baseline before randomization and vaccination in order to check if a participant was infected with SARS-CoV-2. This testing was implemented as additional safety precaution to prevent vaccination of currently sick/infected participants. Although this precautional measure *per se* is considered reasonable, a PCR-based test would have been preferable. This would have enabled higher sensitivity particularly in a presumably mainly asymptomatic population, as PCR is considered as the gold-standard for SARS-CoV-2 detection. Therefore, the true rate of enrolled subjects with asymptomatic COVID-19 might have been underestimated, which is not considered as ideal. However, no further issue is made as this is not expected to impact on the primary analysis.

As it has been discussed in the EMA-SA (Case No.: EMA/SA/0000064690) rather than using AZD1222 as a comparator, it would have been preferable to base the immunobridging approach on a comparison to a mRNA vaccine. This would have ensured the better comparability to VLA2001 as regards the vaccination schedule and type of immune response. Nonetheless, AZD1222 is an approved COVID-19 vaccine and therefore considered acceptable. Moreover, enrolment of a comparator group for subjects 18-29 years of age would have been possible with an mRNA vaccine for whom AZD1222 had been precluded at the time of study conduct. Close to the study start, it was recommended not to use AZD1222 in that age group in the UK. A change of comparator in that age group to another control vaccine would have resulted in a pronounced delay of study start. Although the decision to leave this age group without control group is not regarded optimal, given the development and the justification provided, it is considered acceptable.

Overall, inclusion and exclusion criteria were adequately defined and allowed for representative enrolment of the target population with the highest risk for COVID-19 including elderly above 65 years. While subjects with comorbidities (e.g. obesity, chronic pulmonary diseases, diabetes, cardiovascular diseases) at particular risk for COVID-19 were not enrolled at a certain targeted frequency, the defined inclusion and exclusion criteria would allow for their recruitment which is considered acceptable. Subjects with allergy against any vaccine component were excluded. The explicit exclusion of immunocompromised subjects, as well as pregnant or breast-feeding women limits conclusions regarding immunogenicity (and thus efficacy) as well as safety in these participants. This is, however, adequately reflected in the SmPC.

Subjects who had received medications and/or vaccinations intended to prevent COVID-19 were excluded. In contrast, subjects with a history of COVID-19 were not specifically excluded. While this may introduce heterogeneity in the study sample, the primary analysis was performed in subjects who were seronegative at baseline which is considered adequate.

The defined primary study objectives (superiority of neutralising geometric mean titres of VLA2001 compared to AZD1222 as well as non-inferiority of the seroconversion rate) are considered appropriate for the intended purpose of immunobridging in adults 30 years of age and older. The approach to further infer efficacy in VLA2001-vaccinated individuals 18-29 yoa by comparing humoral immune responses to VLA2001-vaccinated individuals ≥30 yoa is acceptable. Objectives to determine durability of immune responses up to one year which allow for evaluation of longer-term responses are endorsed. Evaluation of booster responses have not been specified as specific objectives but are recommended to be conducted post-authorisation in case of approval of the primary immunisation schedule. In this regard, it is also recommended to investigate the neutralisation activity against VoCs after 3 doses of VLA2001 (**Clinical efficacy recommendation 2**).

The co-primary endpoints in adults ≥30 yoa were defined as the immune response measured after completion of a 2-dose immunisation schedule, determined by geometric mean titre and seroconversion (defined as 4-fold increase from baseline) of SARS-CoV-2-specific neutralising antibodies on Day 43. The primary and secondary immunogenicity endpoints (comprising measures of both humoral and cellular immunity) are considered adequate to address corresponding objectives and deliver meaningful data as basis of the immunobridging strategy to infer VLA2001 efficacy in this age group. The exploratory efficacy endpoint which evaluates the number of COVID-19 cases per treatment group is acceptable in the context of the overall clinical approach.

In the age group 30 years and above, approximately 3000 participants were randomized in a 2:1 ratio, to receive either VLA2001 or AZD12222, respectively. In addition, for the immunogenicity analyses, 1200 participants were randomized 1:1 based on seronegative status (rapid antibody test) at screening. Thus, the non-immunogenicity subset was randomized at a 7:2 ratio in order to reach the overall sample size of the study and an overall ratio of 2:1. This is acceptable. Participants aged 18-29 years receiving VLA2001 were not randomized.

The baseline factors seem to be balanced between the treatment groups. Randomization was stratified by age, but not by site. This is acceptable.

Study subjects were selected as planned. The group of subjects <30 years (not included in the primary immunogenicity and blinded safety analysis) is relatively large (about 1/3 of those given VLA2001) whereas the most relevant target group for the vaccine are people of advanced age who are almost absent from the study 301. The study included mostly younger adults, only 0.6% were older than 55 years.

The Phase 3 study was designated as an observer-blind study. While participants aged 30 years and above were blinded as they received either VLA2001 or AZD1222, it is understood that the term"observer-blind" is derived from the fact that participants aged 18-29 years were placed in a non-randomized treatment group and only received VLA2001 without a control. Although it is not regarded optimal that there was no control group for this age cohort, the process of unblinding these participants is understood and accepted. Furthermore, members of the DSMB, the pharmacist preparing the dose of the 2 vaccine, and the CRA monitoring the vaccine inventory were unblinded. This is also acceptable.

Statistical methods and analysis groups were adequately planned. The method used to compute confidence intervals for the difference in response rates was clarified. An alternative calculation based on the Agresti and Min method was also provided.

Immunogenicity/ Efficacy data and additional analyses

Dose-finding (Phase 1/2)

Based on the results of all so far provided analyses available (Day 36 and Day 106 interim analyses; cut-off date June 30th 2021) a clear dose-dependent effect of the study vaccine on immunogenicity was observed and therefore, taking into account that there was no significant dose-dependent effect pertaining safety, the Applicant's decision to continue with the high dose (35 AU/dose) for the pivotal Phase 3 study is understood.

Notably, a considerable waning of immune responses was observable when comparing Day 36 (14 days after the second vaccination) and Day 106 (84 days after the second vaccination) data. In this regard, the final CSR with analyses of Day 208 samples, which represents the end-of-study visit, are considered of high interest to inform about long-term immunogenicity.

In contrast to the antigen content determined at 35 AU/dose for the high (and clinically relevant) dose in Phase 1/2, the batch used in Phase 3 was determined at 33 AU/dose. Considering the nature of the potency assay (i.e. ELISA) and that the results fall within the method variability, these doses can be regarded comparable.

Main study

A participant flow has been provided for study VLA2001-301. A total of 4181 subjects were screened and 4017 were randomized to receive VLA2001 or AZD1222 (allocation to VLA2001 in subjects 18-29 years of age non-random; "safety population"). The Applicant explained that a total of 164/4181 screened participants were not randomized to the study. Amongst those 164 participants, 153 were recorded as screen failures and 11 participants were not randomized for other reasons. In addition, according to the Applicant, 207 participants were unblinded during the study ("74 randomized to AZD1222 and 133 to VLA2001 groups"). The main reason for unblinding was related to administration of another licensed COVID-19 vaccine in addition to study vaccination. According to the Applicant this was due to lack of recognition/acceptance of an "investigational vaccine" by governmental bodies (e.g. for travel purposes). This was regarded acceptable.

Recruitment occurred in a timely manner in a population that is of relevance to the EU target population. As per 11th August 2021 a total of 26 sites across the UK had contributed to the recruitment.

The definition of analysis sets is acceptable. There were only 3 participants excluded in the PP population compared to the IMM population because of not having received a second vaccination. In addition, 82 participants were excluded from the PP population at the Day 43 timepoint, because of having received a deployed or approved COVID-19 vaccine outside the study or not having been within the time window for visit 3 (second vaccination) or day 43 visit. The details on number and reasons for exclusion from IMM and PP set were provided and can be followed.

Generally, retention in the study is high up to the latest cut-off with a limited follow-up duration which is acceptable given the challenging circumstances of SARS-COV-2 pandemic as a minimum requirement to establish benefit. The current follow-up duration cannot deliver any meaningful data on persistence of immune responses, yet longer-term results are expected post-authorisation.

According to the Applicant, the Phase 3 study was conducted according to GCP Guidelines and current version of the Declaration of Helsinki. All protocol versions have been provided.

In general, the baseline demographics (age, BMI, sex and ethnicity) of participants aged ≥30 years are well balanced across the treatment arms VLA2001 and AZD1222. In both safety and immunogenicity

population the mean/median age was approx. 35 yoa, indicating that only a minority of subjects from the upper end of the sought indication (55 yoa) contributed to the primary analysis.

There is a difference in the COVID-19 test results at screening with 5.5% of participants being seropositive in the VLA2001 group and 3.2% of participants being positive in the AZD1222 group. As these subjects were not involved in the primary analysis group, no implications are expected for the co-primary and secondary efficacy endpoints. However, the exploratory analysis of COVID-19 cases comprised all participants. The Applicant explained that the discrepant baseline distribution of participants being seropositive (5.5% in the VLA2001 group and 3.2% in the AZD1222 group) might represent a chance finding. Incidence rates of COVID-19 cases for the VLA2001 and AZD1222 groups were provided, both when analysing the total population or the seronegative population. Overall, the incidence rates were comparable and therefore, it is agreed that the different baseline distribution of seropositive subjects does not seem to have implications on the exploratory endpoint analysis.

Similar to the safety population, also in the IMM subset the baseline demographics of participants aged ≥30 years are generally well balanced across the treatment arms VLA2001 and AZD1222. For the IMM subset about 25% of subjects across groups had risk factors for COVID-19- almost entirely due to obesity. The number of subjects with a cardiac risk factor was seven times higher in the VLA2001 group (7/492; 1.4%) compared to the AZD1222 group (1/498; 0.2%). However, this imbalance is not considered to impact on the primary immunogenicity evaluation.

For the safety population aged 30 and above, the comorbidities were equally distributed between the VLA2001 and AZD1222 group, with about 25% of subjects having a risk factor. In the VLA2001 group aged 18-29, the comorbidities were generally lower (16.8% of subjects having a risk factor), which is a result of less subjects being obese in this age group (16.1%) compared to the age group above 30 (25%). No concern arises from this finding.

Based on the rapid antibody test at screening samples from 1,200 participants were randomized to the IMM. Of these 1,200 samples, 210 were actually seropositive at baseline as assessed by a microneutralisation assay (MNA (ND50)) and thus were eventually excluded from the IMM analysis population (considered seronegative).

The intend to use the rapid antibody test was as a tool to monitor the rough extent of pre-exposure at the time of screening to prevent potential excess recruitment of pre-exposed individuals. The evaluation of the serostatus for the respective primary analysis would be based on the MNA. Nevertheless, a few participants being MNA positive at Visit 1 had also immunogenicity samples taken and the results of these participants were also presented which is considered acceptable.

Both co-primary endpoints were met in the pivotal Phase 3 study evaluated in adults ≥30 yoa.

The results for the GMT of neutralising antibodies in the IMM population were as follows. GMTs of neutralising antibodies (ND50) on day 1 in seronegative participants ≥30 years of age were 31.0 for both VLA2001 and AZD1222 groups. GMTs (95% CI) by day 43 were 803.5 (748.5; 862.6) and 576.6 (543.6, 611.7) in seronegative participants who received VLA2001 (n=492) and AZD1222 (n=493), respectively. However, the number of subjects >55 years of age in the immunogenicity population was too low to draw any conclusions (VLA2001 n=3 subjects vs. AZD1222 n=0 subjects). Thus, according to the Applicant, superiority for the co-primary endpoint at Day 43 was confirmed with a GMT ratio (95% CI) of 1.39 (1.25, 1.56) in participants 30-55 years of age. Similar results were observed in the PP population. This is supported by reverse cumulative distribution functions.

The Applicant reports seroconversion rates (defined as ≥4-fold increase in SARS-CoV-2-specific neutralising antibody titre levels between Day 1 and post-vaccination sample collection time points) on day 43 for the Per Protocol Population as 97.4% (444/456) and 98.9% (444/449) in participants who received VLA2001 and AZD1222 respectively. According to the Applicant NI was confirmed (lower

bound of 95% CI for the difference between treatment groups of -3.3%). Similar seroconversion rates for the Immunogenicity Population were reported.

Conversely, numerically higher rates of participants with ≥10-fold increase in neutralising antibody titres were reported in the VLA2001 group (83.6%) compared to the AZD1222 group (79.3%). This tendency was also seen when comparing ≥20-fold increase in neutralising antibody titres (61.4% vs. 45.4% in VLA2001 and AZD1222 groups, respectively). Overall, NI objectives for seroconversion rates when comparing VLA2001 to AZD1222 were met. Again, this applies only to subjects 30-55 years of age, as the number of subjects >55 years of age in the immunogenicity population was too low to draw any meaningful conclusions.

For VLA2001 vaccinated subjects 18-29 yoa (n=200), at day 43 the nAb GMT was 1043.4 [95% CI: 926.6, 1174.9] compared to individuals ≥30 yoa (n=492) for whom the nAb GMT was 803.5 [95% CI: 748.5, 862.6]. A statistically significant difference (GMT-ratio of 1.3) was reported and NI criteria (18-29 vs. ≥30 yoa) were met. This was seen in the primary analysis population (immunogenicity analysis set excluding participants with COVID-19 infection). Subjects were randomly chosen, had a median (range) age of 25 (18-29) years and 55% were males. Likewise, at day 43 seroconversion rates in this 18-29 yoa individuals were 98.5% [95% CI: 95.7, 99.7] compared to 97.0% [95% CI: 95.0, 98.3] in participants aged ≥30 years, thus NI criteria were also met for this parameter (lower bound of the 95% CI for the difference between age groups of -1.5%.) Results were consistent across other analysis populations (also including a subset of subjects with prior COVID-19 infection).

Clinically relevant subgroup analyses were limited to obese subjects (30-55 yoa) as numbers of subjects with other risk factors (e.g. COPD, cardiac, diabetes) were too low to draw any meaningful conclusions.

On day 29 (i.e. before second vaccination) GMTs (IgG ELISA) in VLA2001 vaccinated subjects were lower compared to IgG titres in AZD1222 subjects. On day 43 results were more comparable between groups. This implies different kinetics of the generation of immune responses between the two vaccines with lower titres induced by the VLA2001 primary vaccination compared to AZD1222.

Of note, binding antibodies were tested against full length S-protein, no data on subunit binding (e.g. S-protein RBD) were generated. Likewise, no data on binding antibodies regarding other SARS-CoV-2 proteins (e.g. M, N) were generated. Such data would have been of value to further understand the likely more holistic mode of action of VLA2001 as opposed to authorised COVID-19 vaccines in the EU that selectively target the S-protein. However, absence of this data does not compromise the overall conclusions.

Similar to IgG GMTs seroconversion rates (≥ 4 fold increase from baseline) in terms of S-protein specific IgGs on day 29 were lower in VLA2001 vaccinated subjects compared to AZD1222 vaccinated subjects. Again, on day 43 seroconversion rates were more comparable between groups, yet still higher in AZD1222 vaccinated subjects. Of note, rates of participants with ≥10 or ≥20 fold rise in IgGs were ≥90% for both groups as opposed to the results obtained for ≥10 or ≥20 fold increase rates based on neutralising titres. The biological relevance of these findings is unknown.

Analysis of T-cell responses against S-protein (full protein) based on ELISPOT showed that there was a numerically higher cellular immune response against S-protein in AZD1222 compared to VLA2001 vaccinated individuals, both on day 29, day 43 and day 71. Similar to results seen for humoral immunity, VLA2001 cellular immune responses against S protein peaked at day 43 with slower kinetics compared to AZD1222. Conversely, cellular immune responses against nucleocapsid and membrane proteins were higher in VLA2001 compared to AZD1222 vaccinated individuals on days 43 and 71, in line with the distinct SARS-CoV-2 antigen content for the two vaccines. Again, induction of cellular

immune responses against these proteins did not seem to occur before day 43 in VLA2001 vaccinated individuals.

A secondary analysis on T-spot reactivity based on the (arbitrary) definition of reactivity against stimulation panels on normalised spot forming units ≥6 showed similar results. There was a higher reactivity in AZD12222 vaccinated individuals against S-protein N terminus, S-protein C terminus and S-protein full sequence, while the reactivity against N and M protein was higher in VLA2001 vaccinated subjects. Again, this depicts the distinct mode of action between the two vaccines and provides further support of the induction of cellular immune responses by VLA2001 (but not AZD1222) against SARS-CoV-2 proteins other than S-protein. In how far this translates into clinical efficacy is, however, unknown.

While co-primary immunogenicity objectives in individuals ≥30 yoa as well as 18-29 yoa were met, the data on neutralising activity of VLA2001 are currently too limited to reliably infer vaccine efficacy across the entire intended age range of 18-55 years. About 85% of all subjects contributing to the primary immunogenicity analysis in Phase 3 were 30-40 yoa. Only about 15% of subjects were >40 yoa (and within this age group the majority being 41-45 yoa). In the VLA2001 group the oldest subject within the sought age-restricted indication (18-55 yoa) was 49 yoa, no subjects 50-55 yoa were recruited. One subject each 57, 67, and 68 yoa received VLA2001 and had immunogenicity data available. Likewise, the data in individuals >40 yoa who received the clinically most relevant 35 AU dose in Phase 1/2 is very sparse.

Furthermore, when considering also the scatterplot analysis of neutralising antibodies by age for VLA2001 and AZD1222, it appears that the difference in neutralising antibodies induced by both vaccines is higher in younger individuals (e.g. 30-35 yoa) compared to older (e.g. >40 yoa) individuals. However, it appears that the AZD1222 induced humoral immunity is more stable across the age groups compared to VLA2001 induced humoral immunity (albeit acknowledging that the highest GMTs induced by AZD1222 in individuals e.g. 30-35 yoa are lower compared to VLA2001). Nevertheless, due to the limited amount of data generated in individuals >40 yoa it is difficult to estimate whether VLA2001-induced neutralising GMTs can still be considered as superior to AZD1222 for this age group. Additionally, no data in VLA2001 vaccinated individuals 50-55 yoa of age are available and two of the three data points from individuals >55 yoa show neutralising GMTs at a level that is substantially lower when compared to all VLA2001 vaccinated individuals >30 yoa. Combined these aspects constitute a significant uncertainty for the intended upper age range of the sought indication. A comprehensive characterisation of immune responses across different age strata is currently not observed for individuals ≥50 yoa. The Applicant agreed to this restriction.

In terms of persistence of immune responses, the data are currently limited and based on preliminary results from Phase 1/2 and some data on cellular immunity. In order to better understand the VLA2001- compared to AZD1222- induced immune responses, additional humoral immunogenicity data evaluating both neutralising and binding activity at day 71 post-primary vaccination from both groups should be provided (**Clinical efficacy recommendation 3**). The currently available data on S-protein binding antibodies show declining GMTs from Day 43 towards Day 71 with waning of approx. 55-65% of Day 43 levels (no neutralising data from Day 71 available yet). While the data on binding GMTs over time are appreciated, they are regarded as supportive as inferring of efficacy is based on neutralising antibodies.

Additional data in a limited set of individuals SARS-CoV-2 seropositive at baseline have been provided (evaluated in individuals 18-29 yoa and in individuals ≥30 years of age by MNA and ELISA). Overall, as expected, a more pronounced humoral immune response in individuals seropositive at baseline who received VLA2001 compared to individuals seronegative at baseline became apparent.

COVID-19 cases were evaluated as part of an exploratory efficacy analysis. The frequency of participants who tested COVID-19 positive after the first vaccination was comparable across treatment groups. COVID-19 incidence rates were approx. 1.5-fold-higher in individuals 18-29 years of age vaccinated with VLA2001 compared to individuals ≥30 yoa vaccinated with either VLA2001 or AZD1222. However, confidence intervals were wide and overlapping for all groups. Thus, it remains unclear whether the substantially larger incidence rate in subjects 18-29 yoa may have been due to population differences (possibly also related to the lack of blinding in the younger age cohort), or due to a differential treatment effect between age cohorts. Importantly, due to the lack of a comparator group in the younger age cohort, it is unclear whether a potential differential treatment effect would similarly apply to either treatment.

No severe COVID-19 cases were reported. At the time of the interim analysis samples from 109 COVID-19 cases have been successfully processed, in 60 samples sequencing resulted in successful strain identification and exclusively strains of the Delta variant have been identified with no meaningful differences with regards to the distribution of SARS-CoV-2 variants across treatment groups.

No data in patients with renal or hepatic impairment have been generated.

Cross-neutralisation of SARS-CoV-2 variants of concern (VOCs) was evaluated using selected serum samples from Phase 1/2 in 3 different neutralisation assays (NB: different dosing schedule compared to Phase 3). Deficiencies considering validation of applied methods and imputation rules were identified. Therefore, the following needs to be interpreted with caution. Neutralisation of strains representative of the SARS-CoV-2 lineages Wuhan/ Victoria, Alpha and Beta was evaluated in all three assays, whereas neutralisation of Gamma was evaluated only in the PNA assay and neutralisation of Delta only in the MNA (PHE) assay. Unfortunately, no data on Delta neutralisation were generated earlier than Day 106 post primary vaccination.

Based on the provided results the following preliminary conclusions can be drawn (emphasizing that deficiencies considering validation of applied methods and imputation rules were identified):

- A two dose series of VLA-2001 vaccination induced neutralising antibodies against all tested SARS-CoV-2 VoCs (Alpha, Beta, Gamma, Delta).
- Compared to neutralising titres (GMTs) on day 36 against the Wuhan strain, neutralising titres against the Alpha variant declined by 12.5-fold (MNA_{PHE}), 1.8-fold (PNA) and 2.2-fold (MNA_{VLA}); neutralising titres against the Beta variant GMTs declined by 21.1-fold (MNA_{PHE}), 4.5-fold (PNA), 7.3-fold (MNA_{VLA}); neutralising titres against the Gamma GMTs declined by 1.6-fold (PNA only).
- Neutralising titres against the Wuhan/Victoria strain declined approx. 2.5-to 3-fold over time from day 36 to 106 (in both MNA_{PHE} and PNA). GMTs against all tested variants at day 106 were lower by a factor of 12 (Alpha), 8 (Beta) and 10 (Delta) compared to Victoria strain (MNA_{PHE}). These differences were less pronounced in the PNA assay and in the 1.0-2.5-fold decline range for Alpha, Beta and Gamma compared to Wuhan.
- Depending on the test lab and assay used, large variability was observed as regards the decline in neutralisation of VoCs.
- As no human convalescent reference sera were included in the variant testing, it is unknown in how far these results align with the natural course of disease.
- The Applicant provided novel data (from Phase 1/2) on SARS-CoV-2 pseudovirus neutralisation in individuals who received 3 doses of VLA2001 (primary schedule + booster 7-8 months thereafter). The data are considered as research grade and need to be interpreted with caution, as the assay has not been validated. Still, the data show a substantial reduction in

neutralising activity against Omicron even after receipt of 3 doses of VLA2001 as neutralising activity against Omicron was only about 6% compared to wt. Neutralising activity against Delta was about 37% of wt. Based on current evidence with other COVID-19 vaccines it is reasonable to assume that this substantial reduction in neutralising titres against Omicron will be paralleled by a reduction in clinical efficacy/effectiveness against this VoC. This is recommended to be evaluated in further detail in the post-marketing setting **(Clinical efficacy recommendation 2**).

In light of the studies performed and available data, in the context of this clinical development programme for this vaccine which is based on an immunobridging strategy that compares the experimental VLA2001 vaccine with the authorized AZD1222 vaccine of known efficacy, the data package is considered comprehensive vis-à-vis the dossier requirements for a vaccine authorisation based on immunobridging. Still, there are uncertainties that need to be addressed.

2.5.7. Conclusions on the clinical efficacy

VLA2001 was shown to be immunogenic in individuals 18-50 years of age. Co-primary endpoints evaluating neutralising antibody responses in the ≥30 yoa group compared to individuals vaccinated with AZD1222 were met. In addition, non-inferiority criteria for VLA2001 vaccinated subjects 18-29 yoa compared to VLA2001 vaccinated subjects ≥30 yoa were met. With regards to the sought indication of protection against COVID-19 in individuals 18-55 years of age the upper age limit was restricted to 50 years as the data were considered too limited to reliably infer vaccine efficacy for the upper age segment >50 yoa.

The CHMP considers the following measures necessary to address the clinical efficacy issues.

Description of post-authorisation measures
Clinical efficacy recommendations
1. The study plans of clinical trials VLA2001-201 and VLA2001-301 envisage that study participants who have completed the primary immunisation schedule (two vaccinations), will be invited to participate in a Booster Phase to investigate the immunogenicity and safety of a booster dose with VLA2001. This is endorsed and the applicant is recommended to provide these data post-authorisation.
2. Based on current evidence with other COVID-19 vaccines it is reasonable to assume that there is substantial reduction in neutralising titres against Omicron with a parallel reduction in clinical efficacy/effectiveness against this VoC. The applicant is recommended to investigate neutralisation activity of VLA2001 against VoCs in further detail in the post-marketing setting.
3. The applicant should provide data on neutralising antibodies at day 71 from study VLA2001-301 by 31 August 2022.
4. The applicant should provide the final CSR for study VLA2001-301 by 30 June 2023.

2.5.8. Clinical safety

Initially, two clinical studies were submitted evaluating VAL2001 vaccine related safety and tolerability:

- Study VLA2001-201, a phase 1/2 dose finding study with 3 dose groups and total of 153 enrolled subjects (n=51 subjects per dose group, i.e. 3 AU/dose, 7 AU/dose and 35 AU/dose) in the age of 18 to 55 years.
- Study VLA2001-301, a phase 3 study with one VLA2001 vaccine dose group (i.e. 33 AU/dose) in two age groups (i.e. 18-30 years and ≥30 years), as well as one active comparator group that received the licensed COVID-19 vaccine AZD1222 (all subject of this group were ≥30 years). In total 4012 subjects received at least one vaccine and 3017 adult subjects received at least one dose of the study drug (n=1040 18-30 years and n=1977 ≥30 years).

Data from vaccine studies comprise local and systemic safety events after first and second vaccination. Additionally, solicited adverse events were recorded for 7 consecutive days post vaccination (after first and second vaccination) and unsolicited adverse events were recorded throughout the submitted observation period. Data are available for up to 106 days after 2nd vaccination in study VLA2001-201 (interim analysis from cut off data June 2021) and for at least 4 weeks after 2nd vaccination in study VLA2001-301 (mean follow-up time of 151.4 days after the first vaccine dose across treatment groups, for the currently available submission up to data cut-off on October 14th 2021, also referred to as "entire study"). However, both studies are still ongoing. Safety analysis was performed in the safety population which included all participants who received at least one dose of VLA2001 (or comparator in case of study VLA2001-301).

Table 29: Safety of VLA2001 available from studies VLA2001-201 and VLA2001-301

	Study VLA2001-201 Phase 2	Study VLA2001-301 Phase 3
Solicited AEs	In the period of 7 consecutive days starting on the day of each vaccination	In the period of 7 consecutive days starting on the day of each vaccination
Unsolicited AEs	Up to Day 36 (2 weeks after 2nd vaccination) • First interim analysis (cut off 10 March 2021) • Second interim analysis (cut off 30 June 2021)	Up to Day 43 (2 weeks after 2nd vaccination; referred to as "Day 43") • First interim analysis (cut off 11 August 2021)
	Up to Day 106 (3 months after 2nd vaccination) • Second interim analysis (cut off 30 June 2021)	*At least* 4 weeks after 2nd vaccination (referred to as "entire study" period)* • First interim analysis (cut off 11 August 2021)

Of note, while the Applicant applied for an indication including only individuals between 18 and 55 years of age, safety data from study VLA2001-304, including data from individuals 56 years of age and older, was requested to further characterise the safety profile in this population, since off-label use is not unlikely.

Of note, while the Applicant applied for an indication including only individuals between 18 and 55 years of age, safety data from study VLA2001-304, including data from individuals 56 years of age, to understand the safety profile in the elderly population, since off-label use in subjects above 55 is not unlikely.

The preliminary safety report for study VLA2001-304 was provided. This is an on-going, multicentre, open-label, single arm study to assess the safety, tolerability, and immunogenicity of VLA2001 in participants aged 56 years or older. Approximately 300 participants aged 56 years or older were planned to be enrolled in a non-randomised manner to receive VLA2001 at the recommended dose level, with 2 doses given 28 days apart, on Days 1 and 29. Immunogenicity (neutralising and binding antibody titres) and safety are being assessed up to Month 12 after the first vaccination. All participants were observed for immediate adverse events (AEs) and/or reactogenicity for at least 30 minutes after the administration of the vaccine. Participants were provided with an electronic Diary (e-

Diary) and trained to record specifically solicited systemic and local symptoms daily for 7 days following each vaccination (starting on the day of vaccination), as well as any additional AEs during the follow-up period after each of the 2 vaccinations up to the next visit to the site, until the Day 43 visit had been completed.

Besides the clinical studies evaluating the safety profile of the study vaccine, also the CSRs as well as a summary of two clinical phase 1 studies were submitted evaluating safety and tolerability of the novel excipient recombinant human albumin (study CE1245/1001 and CE1245/1002).

Two double-blind, randomised clinical phase I studies were conducted to evaluate the safety and tolerability of the novel recombinant human albumin (rHA) excipient after repeated i.m (study CE1245/1001) and i.v. (study CE1245/1002) administration. It is recognised that no relevant increase in tested antibody levels was detected in those subjects without known allergies. Also, regarding symptoms of potentially allergic events as well as other safety assessments (haematology, clinical chemistry, urinalysis and vital signs), no striking differences were detected for rHA compared to a commercial HSA product. However, for both studies only subjects with "*no known history of allergic reactions to Saccharomyces cerevisiae or any other yeast products and with no history of anaphylactic or severe systemic response to human plasma proteins were selected*". Complete study reports for non-clinical studies CPG/011, AES/034, CPG/013, PG/012, PSK 01/99, CPG/014, REG 03/99, PT99-01 as well as clinical studies CE1245/1001 and CE1245/1002 were provided.

No clinical study was performed to assess the safety and tolerability of the excipient CpG 1018. CpG 1018 is also included as an adjuvant in Heplisav B, a recombinant hepatitis B vaccine authorised in the European Union since February 2021 (EMEA/H/C/005063). Therefore, CpG 1018 is not considered a novel excipient per definition (Guideline on Excipients in the Dossier Application Marketing Authorisation of a Medicinal Product - Revision 2, dated 19 June 2007, Doc. Ref. EMEA/CHMP/QWP/396951/2006). It is reassuring that only one third of the CpG 1018 amount that is included in Heplisav B (3mg/0.5ml) is included in the Valneva vaccine (1mg/0.5ml), but it is also noted that the combination with aluminium hydroxide (0.5 mg/ Al^{3+}/dose) is unknown. Altogether, the use of the relatively new adjuvant CpG 1018 in combination with aluminium hydroxide comprises an uncertainty with respect to potentially related safety events. In relation to the risk of acute myocardial infarction, a concern with Heplisav-B at the time of marketing authorisation, post-marketing surveillance study HBV-25 (from Heplisav-B) provided compelling and reassuring evidence that there is no increased cardiovascular risk with CpG 1018 adjuvant. In addition, there were no AMI risks detected across Valneva's VLA2001 program and with other CpG 1018 adjuvanted COVID-19 investigational vaccine products studied recently. During the initial MA procedure of Heplisav B, a theoretical risk of occurrence of 'Potentially immune-mediated disorders (including inflammatory disorders)' and 'Exacerbation of potentially immune-mediated disorders (including inflammatory disorders) was identified due to TLR9 activation by CpG1018. The risk of immune-mediated events has been evaluated across the large post-marketing safety study HBV-26 (from Heplisav-B). There was no signal detected across Heplisav-B clinical program for immune-mediated AEs and the rates were similar between Heplisav-B and Engerix-B. In addition, there was no immune-mediated adverse events risk detected across Valneva's VLA2001 program and with other CpG 1018 adjuvanted COVID-19 investigational vaccine products studied recently. Nevertheless, while immune-mediated disorders remain a hypothetical risk, the RMP includes a list with AESI that may be considered related to CpG1018, which will be monitored in the post-marketing phase.

2.5.8.1. Patient exposure

The safety analysis sets include all participants who received at least one dose of vaccine (VLA2001 for VLA-2001-201 and VLA2001-301) or AZD1222 (VLA2001-301). Safety analysis sets and exposure of participants included in the trials VLA2001-201 and VLA2001-301 are summarised in the below tables.

Study VLA2001-201

In study VLA2001-201, 153 participants aged 18 to 55 years were randomly assigned to receive VLA2001 vaccination on Day 1 and Day 22, distributed on three dose groups (51 per group). All participants were included in the safety analysis as all received at least one dose of VLA2001. No vaccinee terminated the study up to Day 106. However, 3 participants did not receive the second vaccination (2 participants in the medium dose group and 1 participant in the high dose group).

Table 30: Safety analysis set and exposure in study VLA2001-201 (Day 36 / Day 106)

	VLA2001-201 dose		
Number of participants	3 AU/dose	7 AU/dose	35 AU/dose
Participants (enrolled/ randomised)	51	51	51
Safety analysis set[1]: n	51	51	51
Participants vaccinated overall, n	51	51	51
Participants vaccinated once (1 dose), n	51	51	51
Participants vaccinated twice (2 doses), n	51	49	50
Early terminated, n	Day 36: 0 Day 106: 0	Day 36: 0 Day 106: 0	Day 36: 0 Day 106: 0

1: all participants who received at least 1 dose of trial vaccine
Source: VLA2001-201 interim CSR, 1.0, 10 Sept 2021, Table 14.1.1,

Study VLA2001-301

Study population and safety analysis set

In study VLA2001-301, a total of 4181 participants were screened in this study and 4017 participants were randomised and distributed to different groups according to age group and randomised or allocated to treatment with VLA2001 or AZD1222: 1042/4017 participants (25.9%) in the VLA2001 (age 18-29 years) group, 1978/4017 participants (49.2%) in the VLA2001 (age ≥30 years) group; and 997/4017 participants (24.8%) in the AZD1222 group. A total of 4012 were included in the safety analysis population: 1040 participants in the age group 18 to <30 years who received VLA2001, 1977 participants in the age group ≥30 years who received VLA2001 and 995 in the age group ≥30 years who received AZD1222. Only a small and similar percentage in each treatment and age group terminated the study early as of the cut-off date 11 August 2021 and no further imbalances of significance were noted after the extended data cut-off on 14 October 2021.

Overall, 4012 of 4181 screened participants (96.0%) received at least 1 vaccination, and the majority of participants (3216/4181, 76.9%) received 2 vaccinations within the scheduled 29 days. The percentages of participants who received at least 1 vaccination were similar in all groups. Likewise, the percentages of participants who received 2 vaccinations within the scheduled 29 days or after the scheduled 29 days was similar between groups.

Participant disposition was also comparable in the following subgroups: by age (18-29; and 30-55 years), baseline serostatus (positive/negative), and obesity (Yes/No) (VLA2001-301 interim CSR, 1.0, 17 Nov 2021). Notably, subjects >55 years are not included in the finally requested indication and the numbers of participants in the subgroup over 55 years of age is too small (24 participants) relative to the other age subgroups to make meaningful comparisons.

Table 31: Disposition and safety analysis set (VLA2001-301), data cut-off 11 Aug 2021

Number of Participants:	VLA2001 Age <30 years N=1042 n (%)	VLA2001 Age ≥30 years N=1978 n (%)	AZD1222 N=997 n (%)	All Participants N=4181 n (%)
Screened	--	--	--	4181
Visits				
Screening (Visit 0)	--	--	--	4181 (100.0)
Visit 1 Day 1	--	--	--	4057 (97.0)
Visit 2 Day 8	--	--	--	1143 (27.3)
Visit 3 Day 29	--	--	--	3978 (95.1)
Visit 4 Day 43	--	--	--	3907 (93.4)
Visit 5 Day 71	--	--	--	3820 (91.4)
Visit 6 Day 208	--	--	--	1 (0.0)
Visit 7 Day 365	--	--	--	0
Visit Early Termination	--	--	--	16 (0.4)
Covid-19 Illness Visit	--	--	--	633 (15.1)
Screen Failure [A]	--	--	--	153 (3.7) [B]
Randomized	1042	1978	997	4017
Vaccinated [C]	1040 (99.8)	1977 (99.9)	995 (99.8)	4012 (96.0)
Randomized but not vaccinated [C]	2 (0.2)	1 (0.1)	2 (0.2)	5 (0.1)
Randomized with at least 1 vaccination [C]	1040 (99.8)	1977 (99.9)	995 (99.8)	4012 (96.0)
Randomized with 2 vaccinations (second vaccine was given within 29 days) [C]	856 (82.1)	1557 (78.7)	804 (80.6)	3216 (76.9)
Randomized with 2 vaccinations (second vaccine was given after 29 days) [C]	170 (16.3)	392 (19.8)	185 (18.6)	748 (17.9)
Early terminated	55 (5.3)	72 (3.6)	25 (2.5)	153 (3.6)
Reason for Early Termination				
Adverse event	0	0	0	0
Positive pregnancy test during study drug treatment	1 (0.1)	1 (0.1)	0	2 (0.0)
Early termination from the study	2 (0.2)	0	0	2 (0.0)
Withdrawal due to individual stopping criterion (protocol section 11.5)	5 (0.5)	5 (0.3)	0	10 (0.2)
Withdrawal of consent due to AE	1 (0.1)	1 (0.1)	0	2 (0.0)
Withdrawal of consent not due to AE	14 (1.3)	23 (1.2)	11 (1.1)	48 (1.1)
Moved from study area	4 (0.4)	4 (0.2)	3 (0.3)	11 (0.3)
Lost to follow-up	26 (2.5)	35 (1.8)	10 (1.0)	71 (1.7)
Death	0	0	0	0
Contacted study team and requested withdrawal from study, want NHS vaccine for travel	1 (0.1)	0	0	1 (0.0)
Lost faith in trial	1 (0.1)	0	0	1 (0.0)
Needs to travel regularly, can no longer attend visits	0	1 (0.1)	0	1 (0.0)
Participant requested to withdraw, could no longer attend visits due to financial difficulties	0	0	1 (0.1)	1 (0.0)
Participant unwilling to have trial mandated procedures, namely phlebotomy	0	1 (0.1)	0	1 (0.0)
Participant did not attend visit and has not responded, withdrawn from trial	0	1 (0.1)	0	1 (0.0)

Note: Percentages are computed based on number of randomized participants except where indicated.
'N' for overall column presents the count of all participants that signed informed consent.

A Percentages are computed based on number of screened participants.

B In total, 164 of the 4181 screened participants were not randomized. Of these, 153 participants were screen failures. Of the remaining 11 participants, 8 participants did not show up to the randomization visit, 1 participant has conflicting information and was therefore not counted as a screen failure and 2 participants were screen failures but mistakenly randomized and withdrawn from the study before a study vaccine had been administered to them.

C Percentages are computed based on number of participants randomized to the treatment group. Percentages in the overall column are based on the number of screened participants. Two subjects who failed inclusion/exclusion criteria were mistakenly randomized but withdrawn from the study based on Investigator/Sponsor recommendation and are not counted in the "randomized but not vaccinated row."

Exposure

As by definition of the safety population, all participants in each group received the first vaccination [all 4012 participants (100.0%)], and almost all in each group received the second vaccination: 98.7% in the VLA2001 (age 18-29 years) group, 98.6% in the VLA2001 (age ≥30 years) group, and 99.4% in the AZD1222 group.

Overall, 3017 participants received at least one dose of VLA2001 in the pivotal phase 3 clinical trial VLA2001-301 (1040 in the age group 18-29 years and 1977 participants in the age group 30 years and above).

The mean (SD) duration of exposure, i.e., days between first and second study vaccination, and follow-up time after first dose were comparable between groups. Up to October 14th 2021, the mean follow-up time after first dose was 151.4 days (SD 19.3) across all groups. The minimum number of days after the first vaccination was 8 days in both VLA2001 treatment groups (due to the few participants only receiving the first vaccination) and 28 days in the AZD1222 treatment group. The maximum number duration is 170 days after first vaccination for all treatment groups.

Table 32: Treatment exposure for study VLA2001-301 (safety population) until data cut on October 14th 2021

Characteristics	VLA2001 Age <30 years N=1040 n (%)	VLA2001 Age ≥30 years N=1977 n (%)	AZD1222 N=995 n (%)	All Participants N=4012 n (%)
Received first vaccination	1040 (100.0)	1977 (100.0)	995 (100.0)	4012 (100.0)
Received second vaccination	1026 (98.7)	1949 (98.6)	989 (99.4)	3964 (98.8)
Time between vaccination 1 and 2 (days)				
n	1026	1949	989	3964
Mean (SD)	29.3 (1.79)	29.4 (2.40)	29.4 (1.99)	29.4 (2.15)
Median	29.0	29.0	29.0	29.0
Min, Max	27, 50	23, 64	26, 54	23, 64
Follow up time after first dose until 14 Oct 2021 (days)				
n	1040	1977	995	4012
Mean (SD)	152.1 (22.45)	149.7 (18.86)	154.2 (15.81)	151.4 (19.27)
Median	156.0	153.0	157.0	155.0
Min, Max	8, 170	8, 170	28, 170	8, 170

Max=maximum; Min=minimum; SD=standard deviation
Note: Time between vaccination 1 and 2 was calculated as: ([date of vaccine 2 – date of vaccine 1] + 1).
Follow up time after first dose until 14 Oct 2021 was calculated as [(14 Oct 2021 – date of first dose of study drug)

Study VLA2001-304 (preliminary safety report)

Overall, 334 participants were screened in this study and 306 participants were enrolled (i.e. vaccinated). The mean (SD) age at the time of informed consent was 62.1 (5.43) years with a range of 56 to 87 years. 76 participants (22.8%) were above 65 years of age. The majority of study participants were European (271/306 (88.6%). Overall, 146/306 participants (47.7%) were male, and 160/306 participants (52.3%) were female. Only 2 participants (1.3 %) were of childbearing potential.

Medical history included 5.9% (18/306) participants with a medical history of Renal and urinary disorders, 10.1% (31/306) with a medical history of Cardiac disorders and 20.3% (62/306) with a medical history of Respiratory, thoracic and mediastinal disorders. Participants had a mean Body Mass Index (BMI) at screening [kg/m²] at screening of 27.0. Overall, 306 participants (91.6%) received both the first and second vaccination.

The table below summarizes the time of follow-up after the 1st and 2nd vaccination, respectively, which is referred to as "entire observation period" (i.e. up to a data cut-off on December 27, 2021). The follow-up time after the second vaccination ranges from 77 to 109, with a mean of 94 days.

Table 33: follow-up of participants in the analysis (i.e. until data cut-off on 27 December 2021)

	Statistic	Cohort 1 VLA2001-304 (N=334)
Screened	N	334
Received 1st vaccination	n (%)	306 (91.6)
Received 2nd vaccination	n (%)	306 (91.6)
Time of follow-up after 1st vacc. [days]		
	Mean	122.1
	SD	8.95
	Median	123.0
	Min / Max	104 / 137
Time of follow-up after 2nd vacc. [days]		
	Mean	94.0
	SD	9.09
	Median	94.5
	Min / Max	77 / 109
n...number of participants, percentages are based on number screened (N) *Percentages are based on vaccinated subjects.		

2.5.8.2. Adverse events

Study VLA2001-201

A comparison of the reactogenicity (local and systemic AEs) between the three doses evaluated (3 AU, 7 AU, 35 AU per dose) did not reveal a dose-dependent difference. The Applicant provided a comparison of the local and systemic reactogenicity in the phase III trial (VLA2001-301) vs. the high dose group in the phase II trial (VLA2001-201) and no meaningful difference was noted. However, the comparability is limited, due to the small number of subjects (n=51) who received the relevant dose in the phase II trial.

The number of participants with at least one unsolicited AE until both data cut-offs was comparable between the low (Day 36: 47.1%, Day 106: 49.0%) and the high (Day 36: 43.1%, Day 106: 45.1%) dose groups, while the reporting rate was lower for participants who received the medium dose (Day 36: 35.3%, Day 106: 37.3%). Regarding vaccine-related AEs until Day 106, a similar outcome was reported with the most reported events in the low dose group (incidence 25.5%) and the fewest events in the medium dose group (incidence 13.7%). The incidence in the high dose group was 19.6%. These data suggest that there was no dose-dependent increase in unsolicited AEs. This should be interpreted with caution, due to small number of subjects included (n=51 per group). There was one mild (grade 1) event of chilblains (redness and swelling of toes) 4 days after the first vaccination in the medium dose group. This event was reported as an AESI and SAE as per protocol. A COVID-19 test was negative. The event was considered as not related by the investigator and the subject received the second vaccine. No other SAE or AESI has been reported.

Study VLA2001-301

Solicited local reactions

After any injection, at least one solicited injection site reaction was reported in less participants in the two VLA2001 treatment groups (80.9% in the group 18-29 years; 73.2% in the group ≥30 years)

compared with the AZD1222 group (91.1%). An overview of solicited local ARs in study VLA2001-301 is presented in the Table below (for vaccinations 1 and 2 separately). After the first vaccination, the reporting rates of solicited local reactions were lower for all events in both VLA2001 age groups, compared to the AZD1222 group. The differences between the vaccines were statistically significant (p <0.0001, comparison includes participants 30 years of age and above). After the second vaccination, the frequencies of local reactions were comparable for both vaccines and there was no statistically significant difference for any event.

Table 34: Solicited Injection Site Reactions within 7 days after first and second vaccination (safety population, study VLA2001-301)

Age group (years) **Group allocation**	**18 to <30,** **open label**	**≥30,** **randomised**	**≥30,** **randomised**	**Overall** **(≥18 years)**
Vaccine	**VLA2001**	**VLA2001**	**AZD1222**	**NA**
Dose /treatment group **Participants with**	**33 AU/dose** **N=1,040 n (%)**	**33 AU/dose** **N=1,977 n (%)**	**As by label[§]** **N=995 n (%)**	**Overall** **N=4,012 n (%)**
After first vaccination				
at least one solicited Injection Site Reaction				
n (%)	696 (66.9)	1,180 (59.7)	877 (88.1)	2,753 (68.6)
95% CI [1]	(63.97, 69.78)	(57.49, 61.86)	(85.97, 90.08)	(67.16, 70.05)
p value [2]	--	--	--	**<0.0001**
Injection Site Tenderness				
n (%)	631 (60.7)	1025 (51.8)	831 (83.5)	2487 (62.0)
95% CI [1]	(57.63, 63.66)	(49.62, 54.07)	(81.06, 85.77)	(60.47, 63.49)
p value [2]	--	--	--	**<0.0001**
Injection Site pain				
n (%)	398 (38.3)	597 (30.2)	622 (62.5)	1617 (40.3)
95% CI [1]	(35.30, 41.30)	(28.18, 32.27)	(59.42, 65.53)	(38.78, 41.84)
p value [2]	--	--	--	**<0.0001**
Injection Site itching				
n (%)	41 (3.9)	60 (3.0)	64 (6.4)	165 (4.1)
95% CI [1]	(2.84, 5.31)	(2.32, 3.89)	(4.99, 8.14)	(3.52, 4.77)
p value [2]	--	--	--	**<0.0001**
Injection Site induration				
n (%)	12 (1.2)	29 (1.5)	40 (4.0)	81 (2.0)
95% CI [1]	(0.60, 2.01)	(0.98, 2.10)	(2.89, 5.43)	(1.61, 2.50)
p value [2]	--	--	--	**<0.0001**
Injection Site swelling				
n (%)	11 (1.1)	21 (1.1)	39 (3.9)	71 (1.8)
95% CI [1]	(0.53, 1.88)	(0.66, 1.62)	(2.80, 5.32)	(1.38, 2.23)
p value [2]	--	--	--	**<0.0001**
Injection Site redness				
n (%)	10 (1.0)	11 (0.6)	40 (4.0)	61 (1.5)
95% CI [1]	(0.46, 1.76)	(0.28, 0.99)	(2.89, 5.43)	(1.16, 1.95)
p value [2]	--	--	--	**<0.0001**
After second vaccination				
at least one solicited Injection Site Reaction				
n (%)	667 (65.0)	1,102 (56.5)	548 (55.4)	2,317 (58.5)
95% CI [1]	(62.00, 67.93)	(54.31, 58.76)	(52.25, 58.54)	(56.90, 59.99)
p value [2]				**0.5589**
Injection Site Tenderness				
n (%)	608 (59.3)	982 (50.4)	490 (49.5)	2,080 (52.5)
95% CI [1]	(56.18, 62.28)	(48.14, 52.63)	(46.38, 52.71)	(50.90, 54.04)
p value [2]	--	--	--	**0.6670**
Injection Site pain				
n (%)	398 (38.8)	605 (31.0)	288 (29.1)	1,291 (32.6)

95% CI [1]	(35.80, 41.85)	(28.99, 33.15)	(26.30, 32.06)	(31.11, 34.05)
p value [2]	--	--	--	**0.2847**
Injection Site itching				
n (%)	30 (2.9)	61 (3.1)	30 (3.0)	121 (3.1)
95% CI [1]	(1.98, 4.15)	(2.40, 4.00)	(2.06, 4.30)	(2.54, 3.64)
p value [2]	--	--	--	**0.8866**
Injection Site induration				
n (%)	10 (1.0)	20 (1.0)	7 (0.7)	37 (0.9)
95% CI [1]	(0.47, 1.79)	(0.63, 1.58)	(0.29, 1.45)	(0.66, 1.28)
p value [2]	--	--	--	**0.3928**
Injection Site swelling				
n (%)	6 (0.6)	28 (1.4)	13 (1.3)	47 (1.2)
95% CI [1]	(0.21, 1.27)	(0.96, 2.07)	(0.70, 2.24)	(0.87, 1.57)
p value [2]	--	--	--	**0.7896**
Injection Site redness				
n (%)	9 (0.9)	15 (0.8)	10 (1.0)	34 (0.9)
95% CI [1]	(0.40, 1.66)	(0.43, 1.27)	(0.49, 1.85)	(0.59, 1.20)
p value [2]	--	--	--	**0.5007**

CI: confidence interval.
§: dose of AZD1222 as by approved SmPC in the UK and EU
[1] Exact 95% Clopper-Pearson confidence interval for proportion.
[2] P value compares VLA2001 group (above 30 years of age) with the AZD1222 group.
Source VLA2001-301 interim CSR, 1.0, 17 Nov 2021, Table 14.2.1.2

Table 35: Solicited injection site reactions within 7 days after any vaccination by preferred term and treatment group (safety population) (study VLA2001-301)

Age group (years) Group allocation	18 to <30, open label	≥30, randomised	≥30, randomised	Overall (≥18 years)
Vaccine	VLA2001	VLA2001	AZD1222	NA
Dose /treatment group Participants with	33 AU/dose N=1040 n (%)	33 AU/dose N=1977 n (%)	As by label§ N= 995 n (%)	Overall N=4012 n (%)
at least one solicited Injection Site Reaction				
n (%)	841 (80.9)	1,448 (73.2)	906 (91.1)	3,195 (79.6)
95% CI [1]	(78.34, 83.21)	(71.23, 75.18)	(89.11, 92.76)	(78.36, 80.87)
p value [2]				<0.0001
Injection Site Tenderness				
n (%)	795 (76.4)	1,320 (66.8)	871 (87.5)	2,986 (74.4)
95% CI [1]	(73.74, 78.99)	(64.64, 68.84)	(85.32, 89.53)	(73.05, 75.77)
p value [2]				<0.0001
Injection Site pain				
n (%)	550 (52.9)	900 (45.5)	671 (67.4)	2,121 (52.9)
95% CI [1]	(49.80, 55.95)	(43.31, 47.75)	(64.43, 70.34)	(51.31, 54.42)
p value [2]				<0.0001
Injection Site itching				
n (%)	64 (6.2)	107 (5.4)	89 (8.9)	260 (6.5)
95% CI [1]	(4.77, 7.79)	(4.46,6.50)	(7.24, 10.89)	(5.74,7.29)
p value [2]				0.0003
Injection Site induration				
n (%)	20 (1.9)	45 (2.3)	44 (4.4)	109 (2.7)
95% CI [1]	(1.18, 2.95)	(1.66, 3.03)	(3.23, 5.89)	(2.24, 3.27)
p value [2]				0.0012
Injection Site swelling				
n (%)	16 (1.5)	40 (2.0)	46 (4.6)	102 (2.5)
95% CI [1]	(0.88, 2.49)	(1.45, 2.75)	(3.40, 6.12)	(2.08, 3.08)
p value [2]				<0.0001
Injection Site redness				
n (%)	17 (1.6)	25 (1.3)	48 (4.8)	90 (2.2)
95% CI [1]	(0.96, 2.60)	(0.82, 1.86)	(3.58, 6.35)	(1.81, 2.75)
p value [2]				<0.0001

CI: confidence interval
§: dose of AZD1222 as by approved SmPC in the UK and EU (see also section 2.5.1.5.3)
[1] Exact 95% Clopper-Pearson confidence interval for proportion.
[2] P value compares VLA2001 group (above 30 years of age) with the AZD1222 group.
Source VLA2001-301 interim CSR, 1.0, 17 Nov 2021, Table 14.2.1.2

Among all reported local ARs for each group, the majority were either mild (VLA 2001 18 to <30: 91.1%, ≥30: 93.2%; AZD1222 ≥30: 79.0%) or moderate (VLA 2001 18 to <30: 8.9%, ≥30: 6.8%; AZD1222 ≥30: 20.1%) in severity. Severe (grade 3) local ARs did occur in one participant (0.1%) of the VLA2001 group (injection site pain), compared to 8 participants (0.9%) in the AZD1222 group (including injection site pain, tenderness, induration, swelling, and redness).

The mean [SD] duration of local ARs was shorter in the VLA2001 groups, compared to the AZD1222 group (VLA 2001 18 to <30: 1.9 [1.18] days, ≥30: 1.9 [1.38] days; AZD1222 ≥30: 2.8 [1.68] days). The median duration was either 1 or 2 days for all local events in the VLA2001 group, or 1 to 3 days for the events in the AZD1222 group.

Solicited systemic reactions

After any injection, at least one solicited systemic reaction was reported in less participants in the two VLA2001 treatment groups (76.9% in the group 18-29 years; 70.2% in the group ≥30 years) compared with the AZD1222 group (91.1%). An overview of solicited systemic ARs is shown in Table

40 (for vaccinations 1 and 2 separately). After the first vaccination, the incidences of solicited systemic reactions were lower for all events in both VLA2001 age groups, compared to the AZD1222 group. Again, the differences between the vaccines were statistically significant (p <0.0001, comparison includes participants 30 years of age and above). After the second vaccination, the reporting rates were overall more similar between VLA2001 and AZD1222. When comparing the two groups including only participants ≥30 years of age only, statistically significant differences were noted for the events of fatigue, headache and fever/body temperature.

Table 36: Solicited Systemic Reactions within 7 days after first and second vaccination (safety population, study VLA2001-301)

Age group (years) **Group allocation**	**18 to <30, open label**	**≥30, randomised**	**≥30, randomised**	**Overall (≥18 years)**
Vaccine	**VLA2001**	**VLA2001**	**AZD1222**	**NA**
Dose /treatment group	**33 AU/dose N=1,040 n (%)**	**33 AU/dose N=1,977 n (%)**	**As by label[8] N= 995 n (%)**	**Overall N=4,012 n (%)**
After first vaccination				
at least one solicited Systemic Reaction				
n (%)	**699 (67.2)**	**1,187 (60.0)**	**876 (88.0)**	**2,762 (68.8)**
95% CI [1]	(64.26, 70.06)	(57.84, 62.21)	(85.86, 89.99)	(67.38, 70.27)
p value [2]	--	--	--	**<0.0001**
Fatigue				
n (%)	**477 (45.9)**	**802 (40.6)**	**711 (71.5)**	**1,990 (49.6)**
95% CI [1]	(42.80, 48.95)	(38.39, 42.77)	(68.54, 74.25)	(48.04, 51.16)
p value [2]	--	--	--	**<0.0001**
Headache				
n (%)	**325 (31.3)**	**627 (31.7)**	**620 (62.3)**	**1,572 (39.2)**
95% CI [1]	(28.44, 34.17)	(29.67, 33.82)	(59.22, 65.33)	(37.67, 40.71)
p value [2]	--	--	--	**<0.0001**
Muscle pain				
n (%)	**360 (34.6)**	**541 (27.4)**	**593 (59.6)**	**1,494 (37.2)**
95% CI [1]	(31.72, 37.60)	(25.41, 29.39)	(56.47, 62.66)	(35.74, 38.76)
p value [2]	--	--	--	**<0.0001**
Nausea / Vomiting				
n (%)	**115 (11.1)**	**168 (8.5)**	**189 (19.0)**	**472 (11.8)**
95% CI [1]	(9.22, 13.12)	(7.31, 9.81)	(16.60, 21.57)	(10.78, 12.80)
p value [2]	--	--	--	**<0.0001**
Fever/ Body temperature				
n (%)	**4 (0.4)**	**17 (0.9)**	**143 (14.4)**	**164 (4.1)**
95% CI [1]	(0.10, 0.98)	(0.50, 1.37)	(12.25, 16.71)	(3.50 ,4.75)
p value [2]	--	--	--	**<0.0001**
After second vaccination				
at least one solicited Systemic Reaction				
n (%)	**526 (51.3)**	**908 (46.6)**	**501 (50.7)**	**1935 (48.8)**
95% CI [1]	(48.16, 54.37)	(44.35, 48.83)	(47.49, 53.82)	(47.25, 50.38)
p value [2]	--	--	--	0.0369
Fatigue				
n (%)	**355 (34.6)**	**597 (30.6)**	**340 (34.4)**	**1292 (32.6)**
95% CI [1]	(31.69, 37.60)	(28.59, 32.73)	(31.42, 37.43)	(31.13, 34.08)
p value [2]	--	--	--	0.0395
Headache				
n (%)	**235 (22.9)**	**392 (20.1)**	**255 (25.8)**	**882 (22.3)**
95% CI [1]	(20.37, 25.60)	(18.35, 21.96)	(23.08, 28.63)	(20.96, 23.58)
p value [2]	--	--	--	0.0005
Muscle pain				
n (%)	**257 (25.0)**	**410 (21.0)**	**224 (22.6)**	**891 (22.5)**

95% CI [1]	(22.42, 27.82)	(19.25, 22.91)	(20.07, 25.39)	(21.19, 23.81)
p value [2]	--	--	--	0.3153
Nausea / Vomiting				
n (%)	**63 (6.1)**	**106 (5.4)**	**66 (6.7)**	**235 (5.9)**
95% CI [1]	(4.75, 7.79)	(4.47, 6.54)	(5.20, 8.41)	(5.21, 6.71)
p value [2]	--	--	--	0.1779
Fever/ Body temperature				
n (%)	**7 (0.7)**	**12 (0.6)**	**15 (1.5)**	**34 (0.9)**
95% CI [1]	(0.27, 1.40)	(0.32, 1.07)	(0.85, 2.49)	(0.59, 1.20)
p value [2]	--	--	--	0.0156

§: dose of AZD1222 as by approved SmPC in the UK and EU
[1] Exact 95% Clopper-Pearson confidence interval for proportion.
[2] P value compares VLA2001 group (above 30 years of age) with the AZD1222 group.
Source VLA2001-301 interim CSR, 1.0, 17 Nov 2021, Table 14.2.1.3

Table 37: Solicited systemic reactions within 7 days after any vaccination by preferred term and treatment group (safety population) (study VLA2001-301)

Age group (years) Group allocation	18 to <30, open label	≥30, randomised	≥30, randomised	Overall (≥18 years)
Vaccine	**VLA2001**	**VLA2001**	**AZD1222**	**NA**
Dose /treatment group **Participants with**	**33 AU/dose** **N=1,040** **n (%)**	**33 AU/dose** **N=1,977** **n (%)**	**As by label§** **N= 995** **n (%)**	**Overall** **N=4,012** **n (%)**
at least one solicited Systemic Reaction				
n (%)	**800 (76.9)**	**1,387 (70.2)**	**906 (91.1)**	3,093 (77.1)
95% CI [1]	(74.24, 79.45)	(68.09, 72.17)	(89.11, 92.76)	(75.76, 78.39)
p value [2]	--	--	--	**<0.0001**
Fatigue				
n (%)	**596 (57.3)**	**1,012 (51.2)**	**767 (77.1)**	2,375 (59.2)
95% CI [1]	(54.24, 60.34)	(48.96, 53.41)	(74.35, 79.66)	(57.66, 60.72)
p value [2]	--	--	--	**<0.0001**
Headache				
n (%)	**422 (40.6)**	**787 (39.8)**	**674 (67.7)**	1,883 (46.9)
95% CI [1]	(37.57, 43.63)	(37.64, 42.00)	(64.73, 70.64)	(45.38, 48.49)
p value [2]	--	--	--	**<0.0001**
Muscle pain				
n (%)	**458 (44.0)**	**732 (37.0)**	**639 (64.2)**	1,829 (45.6)
95% CI [1]	(40.99, 47.12)	(34.89, 39.20)	(61.15, 67.20)	(44.04, 47.14)
p value [2]	--	--	--	**<0.0001**
Nausea / Vomiting				
n (%)	**154 (14.8)**	**231 (11.7)**	**227 (22.8)**	612 (15.3)
95% CI [1]	(12.70, 17.11)	(10.30, 13.18)	(20.24, 25.55)	(14.15, 16.40)
p value [2]	--	--	--	**<0.0001**
Fever/ Body temperature				
n (%)	**11 (1.1)**	**29 (1.5)**	**154 (15.5)**	194 (4.8)
95% CI [1]	(0.53, 1.88)	(0.98, 2.10)	(13.28, 17.88)	(4.19, 5.55)
p value [2]	--	--	--	**<0.0001**

§: dose of AZD1222 as by approved SmPC in the UK and EU (see also section 2.5.1.5.3)
[1] Exact 95% Clopper-Pearson confidence interval for proportion.
[2] P value compares VLA2001 group (above 30 years of age) with the AZD1222 group.
Note: After 1st vaccination: all solicited systemic reactions show significant difference. After 2nd vaccination: significance overall, as well as for fatigue, muscle pain, headache; not for nausea/ vomiting, fever/ body temperature.
Source VLA2001-301 interim CSR, 1.0, 17 Nov 2021, Table 14.2.1.3

The majority of the reported systemic events was mild (VLA2001 18 to <30: 76.4%, ≥30: 75.1%; AZD1222 ≥30: 51.4%) or moderate (VLA 2001 18 to <30: 23.0%, ≥30: 23.5%; AZD1222 ≥30: 43.5%) in severity. Severe (grade 3) events were reported in 24 participants who received VLA2001 (18 to <30: 0.6%, ≥30: 1.4% of all reported events), compared to 46 participants who received the AZD1222 vaccine (5.1% of all reported events). One serious solicited event of headache was reported during the trial (AZD1222 group, 3 days after 2nd vaccination). The event was moderate in severity, but met the criteria of a serious event due to hospitalisation.

The mean duration of systemic reactions was comparable between the groups (VLA 2001 18 to <30: 2.0 [1.66] days, ≥30: 2.0 [1.63] days; AZD1222 ≥30: 2.1 [1.56] days). The median duration was 1 day for all systemic ARs in the VLA2001 groups, and either 1 or 2 days in the AZD1222 group.

Figures below represent a visual comparison of all solicited ARs after the first and second vaccinations. Of note, as the AZD1222 vaccine was not administered to participants below the age of 30, only the age group between 30-55 years is shown.

Figure 10: Solicited Adverse Events within 7 days after first vaccination – safety population (N=2984)

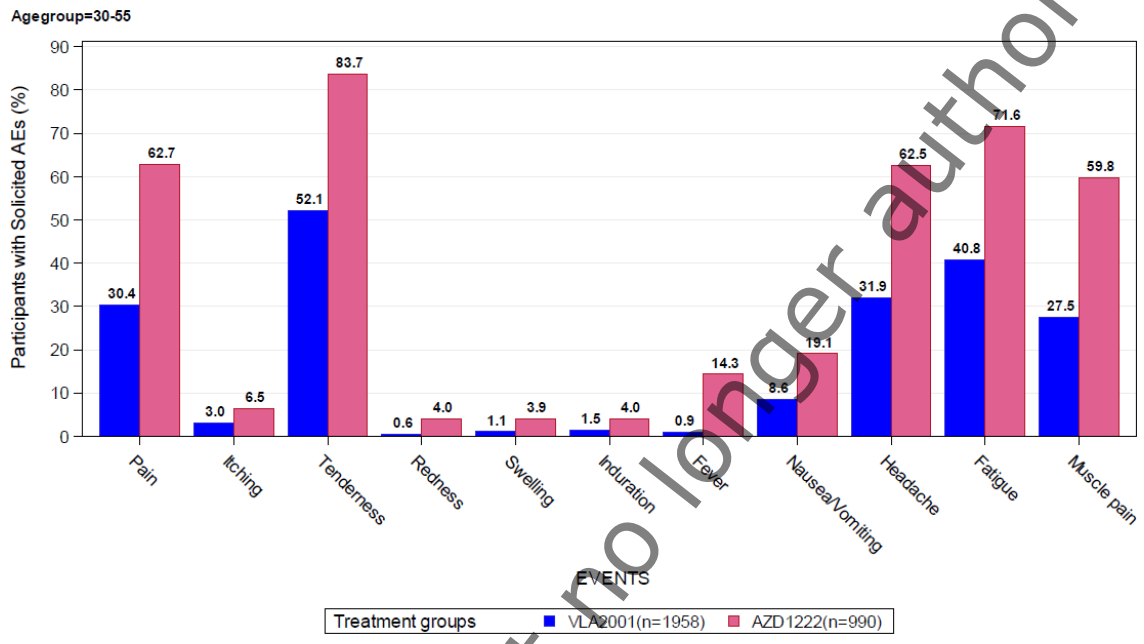
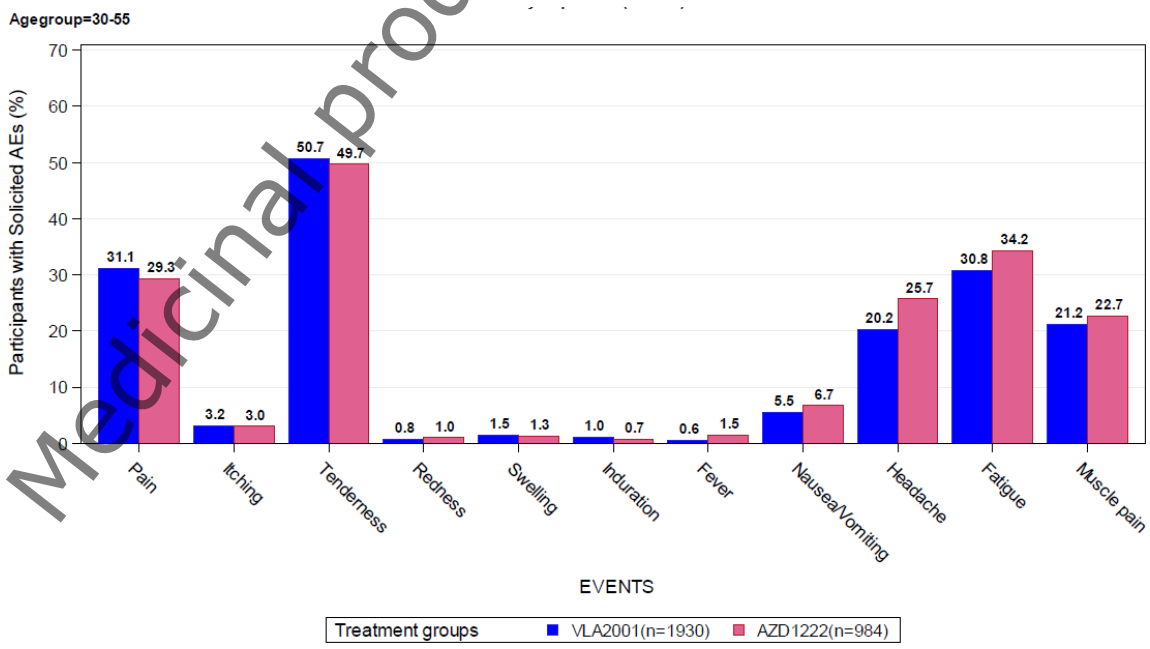


Figure 11: Solicited Adverse Events within 7 days after second vaccination – safety population (N=2914)



Unsolicited adverse events

The overall summary of unsolicited AEs is presented in the following table.

Table 38: Overall Summary of Unsolicited Adverse Events (Safety Population)

Number of	VLA2001 Age <30 years N=1040	VLA2001 Age ≥30 years N=1977	AZD1222 N=995	Overall N=4012
Participants with any unsolicited AE until Day 43				
n (%)	300 (28.8)	566 (28.6)	349 (35.1)	1215 (30.3)
95% CI [A]	(26.11, 31.70)	(26.64, 30.68)	(32.11, 38.13)	(28.86, 31.73)
p-value [B]	–	–	–	0.0003
Participants with any unsolicited AE for the entire study				
n (%)	423 (40.7)	793 (40.1)	443 (44.5)	1659 (41.4)
95% CI [A]	(37.67, 43.73)	(37.94, 42.31)	(41.40, 47.67)	39.82, 42.89)
p-value [B]	–	–	–	0.0213
Participants with any serious unsolicited AE until Day 43				
n (%)	2 (0.2)	6 (0.3)	3 (0.3)	11 (0.3)
95% CI [A]	(0.02, 0.69)	(0.11, 0.66)	(0.06, 0.88)	(0.14, 0.49)
p-value [B]	–	–	–	0.9936
Participants with any serious unsolicited AE for the entire study				
n (%)	7 (0.7)	14 (0.7)	10 (1.0)	31 (0.8)
95% CI [A]	(0.27, 1.38)	(0.39, 1.19)	(0.48, 1.84)	(0.55, 1.09)
p-value [B]	–	–	–	0.3934
Participants with any unsolicited AESI until Day 43				
n (%)	2 (0.2)	1 (0.1)	2 (0.2)	5 (0.1)
95% CI [A]	(0.02, 0.69)	(0.00, 0.28)	(0.02, 0.72)	(0.04, 0.29)
p-value [B]	–	–	–	0.2230
Participants with any unsolicited AESI for the entire study				
n (%)	3 (0.3)	4 (0.2)	2 (0.2)	9 (0.2)
95% CI [A]	(0.06, 0.84)	(0.06, 0.52)	(0.02, 0.72)	(0.10, 0.43)
p-value [B]	–	–	–	0.9940
Participants with any treatment related unsolicited AE until Day 43				
n (%)	110 (10.6)	218 (11.0)	177 (17.8)	505 (12.6)
95% CI [A]	(8.77, 12.61)	(9.68, 12.49)	(15.46, 20.31)	(11.58, 13.65)
p-value [B]	–	–	–	<.0001
Participants with any medically attended unsolicited AE until Day 43				
n (%)	75 (7.2)	137 (6.9)	68 (6.8)	280 (7.0)
95% CI [A]	(5.71, 8.96)	(5.85, 8.14)	(5.35, 8.58)	(6.21, 7.81)
p-value [B]	–	–	–	0.9277
Participants with any treatment related unsolicited AE for entire study period				
n (%)	113 (10.9)	227 (11.5)	178 (17.9)	518 (12.9)
95% CI [A]	(9.04, 12.92)	(10.11, 12.97)	(15.56, 20.42)	(11.89, 13.99)
p-value [B]	–	–	–	<.0001
Participants with any medically attended unsolicited AE for entire study period				
n (%)	132 (12.7)	243 (12.3)	114 (11.5)	489 (12.2)
95% CI [A]	(10.73, 14.87)	(10.88, 13.82)	(9.54, 13.60)	(11.19, 13.24)
p-value [B]	–	–	–	0.5092

AE=adverse event; AESI=adverse event of special interest; CI=confidence interval Note: Follow up time after first dose until data cut point (e.g., 14 October 2021) is referred to as "Entire Study" in this analysis
A Exact 95% Clopper-Pearson CI for proportion.
B p-value is based on a Wald Test for the difference in proportions between VLA2001 age 30 and above and AZD1222.
Source: 14.2.1.6

The frequency of unsolicited AEs until day 43 was nearly identical between the two VLA2001 groups (age 18-29 years: 28.8%, age ≥30 years: 28.6%), and higher in the AZD1222 group (35.1%). The difference between the two vaccines was statistically significant (p=0.0003, comparing age ≥30 years). Until the data cut-off (mean 151.4 days after the first vaccination), this difference was reduced (VLA2001 18 to <30: 40.7%, ≥30: 40.1%; AZD1222 ≥30: 44.5%), but still significant (p=0.0213).

The most commonly reported unsolicited AEs until day 43 were oropharyngeal pain (VLA2001 18 to <30: 3.0%, ≥30: 3.2%; AZD1222 ≥30: 4.1%) and headache (incidence of 2.8% for all three treatment groups).

The difference between the VLA2001 and AZD1222 groups (comparing age ≥30 years) was mainly caused by adverse events in the SOCs of General disorders and administration site conditions (4.5% vs. 9.9%), Musculoskeletal and connective tissue disorders (4.6% vs. 6.4%), and Gastrointestinal disorders (4.1% vs. 5.6%). Regarding AEs on the PT level, notable imbalances were seen for the AEs of chills (0.3% vs. 3.3%), diarrhoea (1.4% vs. 2.7%), dizziness (1.7% vs. 2.5%), vaccination site pain (0.6% vs. 1.3%), arthralgia (0.7% vs. 1.5%), and oropharyngeal pain (3.2% vs. 4.1%, respectively).

Similar results were reported for vaccine-related unsolicited AEs until day 43 (VLA 2001 18 to <30: 10.6%, ≥30: 11.0%; AZD1222 ≥30: 17.8%) and the differences between VLA2001 and AZD1222 were again significant (p<0.0001). For the vaccine-related AEs, the statistical significance also remained until the later data cut-off.

A review of all vaccine-related AEs until Day 43 revealed that differences in reporting rates between VLA2001 and AZD1222 were mainly caused by events in the SOCs of General disorders and administration site conditions (2.5% vs. 7.2%), Musculoskeletal and connective tissue disorders (1.7% vs. 3.4%), Skin and subcutaneous tissue disorders (0.7% vs. 1.9%), and Investigations (0.3% vs. 1.2%). On the PT level, notable differences were seen for the events of chills (0.2% vs. 3.1%), vaccination site pain (0.5% vs. 1.1%), and arthralgia (0.2% vs. 1.1%).

The following vaccine-related AEs were reported that may have been caused by virus reactivation following vaccination: herpes zoster/shingles (2 AEs in the VLA2001 groups, none in the AZD1222 group), oral herpes (1 AE in the VLA2001 groups, none in the AZD1222 group), genital herpes simplex (1 AE in the VLA2001 groups, none in the AZD1222 group), mouth ulceration (2 AEs in the VLA2001 groups, none in the AZD1222 group), gingival ulceration (1 AE in the VLA2001 groups, none in the AZD1222 group), lip ulceration (1 AE in the VLA2001 groups, none in the AZD1222 group), and tongue ulceration (1 AE in the VLA2001 groups, none in the AZD1222 group). See also reported cases from study 304 below.

There were two mild (grade 1) events of thrombophlebitis in the VLA2001 group (calf in both cases). The events occurred in close temporal relationship with the first vaccination (2 and 3 days after) and were considered as possibly related by the investigator (and the sponsor). Both events resolved and the participants received the second vaccination. For one subject, safety lab data was captured to rule out deep vein thrombosis (D-dimer: 0.4 µg/mL, platelet counts within normal range [315 10^9/L]). A diagnosis of a superficial thrombophlebitis of the lower limb was given.

There were reports of various menstrual disorders during the trial, which were considered related to treatment by the Investigator.

Table 39: Summary of treatment related unsolicited AEs for entire study (safety population)

Age Group: Overall

System Organ Class/ Preferred Term	VLA2001 Age Under 30 (N=1040) n (%)	VLA2001 Age 30 and Above (N=1977) n (%)	AZD1222 (N=995) n (%)	Overall (N=4012) n (%)
Reproductive system and breast disorders	9 (0.9)	9 (0.5)	10 (1.0)	28 (0.7)
Menstruation irregular	1 (0.1)	3 (0.2)	3 (0.3)	7 (0.2)
Heavy menstrual bleeding	3 (0.3)	1 (0.1)	1 (0.1)	5 (0.1)
Menstruation delayed	1 (0.1)	1 (0.1)	2 (0.2)	4 (0.1)
Vaginal haemorrhage	1 (0.1)	1 (0.1)	2 (0.2)	4 (0.1)
Dysmenorrhoea	2 (0.2)	1 (0.1)	0	3 (0.1)
Menstrual disorder	0	0	2 (0.2)	2 (0.0)
Intermenstrual bleeding	0	1 (0.1)	0	1 (0.0)
Polymenorrhoea	1 (0.1)	0	0	1 (0.0)
Premenstrual syndrome	1 (0.1)	0	0	1 (0.0)
Testicular pain	0	1 (0.1)	0	1 (0.0)

Overall, the incidences were balanced between the two vaccines (slightly lower frequency in the VLA2001 group). It is acknowledged that with the present study design without a placebo group it is hardly possible to determine whether there is an elevated risk for menstrual disorders following vaccination, especially considering that menstrual disorders are common in general. So far the PRAC concluded that there is no evidence of a causal relationship of menstrual disorders with AZD1222 or other vaccines against COVID-19. Taking all of this into account, even though some of the events were considered as possibly related to vaccination by the investigator, there is not sufficient evidence to add these as adverse reaction into the SmPC. It is noted that there are recent publications (doi: 10.1136/bmj.o142) suggesting that changes to the menstrual cycle do occur following vaccination, but they are small compared with natural variation and quickly reverse. Therefore, this topic needs to be monitored post-marketing. The Applicant suggested to monitor and report on menstrual disorders as AESIs in aggregate reporting, which is supported.

A SMQ analysis for hypersensitivity & angioedema events for the first interim report (cut-off 11 August 2021) was provided. Within 10 days post vaccination, 24 participants (0.8%) in the VLA2001 group (with a total of 24 potential hypersensitivity-indicating AEs) compared to 11 participants (1.1%) in the AZD1222 group (reporting a total of 12 AEs) reported AEs matching hypersensitivity & angioedema SMQs. A similar trend was seen within 42 days post vaccination (VLA2001: 40 participants [1.3%] with 41 AEs; AZD1222: 15 participants [1.5%] with 16 AEs). The most common hypersensitivity event was the AE "rash". Two events of generalized urticaria (both grade 2, related) have been reported following vaccination with VLA2001.

The majority of participants reported AEs which were mild (grade 1, 1013/1659 participants, 61.1%) or moderate (grade 2, 569/1659 participants, 34.3%) in intensity with comparable rates across treatment groups. Similarly, the rate of severe unsolicited AEs was comparable between treatment groups; a total of 73/1659 participants (4.4%) reported unsolicited AEs that were severe (grade 3). Two participants in the VLA2001 (age ≥30 years) group and one participant in the AZD1222 group reported unsolicited AEs that were potentially life threatening (grade 4):

- One participant had a potentially life threatening (Grade 4) perforated appendicitis. The event was a serious, medically attended event, which resolved within 14 days and was considered unrelated to the vaccination.
- The second participant had 3 potentially life threatening (Grade 4) events: sepsis, embolism, and Mallory-Weiss syndrome. All these events were serious, medically attended events, which were considered unlikely related to the vaccination and all of the events were resolved with sequelae at the time of the data interim retrieval in October 2021.
- A participant in the AZD1222 group had a potentially life threatening (Grade 4) subarachnoid haemorrhage. This was a serious, medically attended event which resolved in 11 days and was considered unrelated to the vaccination.

Myocarditis and pericarditis can occur following COVID-19 infection. Further, myo- and pericarditis are confirmed very rare adverse events of mRNA vaccines (described in sections 4.4 and 4.8 of the respective SmPCs), with increased frequencies in young (and male) vaccine recipients. For the comparator vaccine (AZD1222) of the phase 3 trial VLA2001-301, these adverse events have not been confirmed. According to the provided data, so far no AEs of myocarditis or pericarditis have been reported for VLA-2001 or AZD1222. The provided clinical trials are likely not large enough to detect rare adverse events. A Table with all adverse events that may be indicative for potential mild forms of myo- or pericarditis (shortness of breath, chest pain [any form], palpitations, arrhythmias) was provided. Another table was submitted, comparing the severity of potential cardiac symptoms. No meaningful differences were noted between the vaccines regarding frequency or severity of these

symptoms. There were two notable subjects reporting more than one AE which may represent symptoms indicative for myo-/pericarditis:

One subject (50-59 year-old) reported several symptoms such as shortness of breath, different forms of chest pain (pleuritic chest pain, non-cardiac chest pain, and musculoskeletal chest pain), bilateral leg swelling, hot flush, headache and dizziness (all symptoms in close temporal relationship to either the first or second vaccination). The participant was admitted to accident & emergency department one day after 2nd vaccination and different clinical investigations were performed (ECG, vital signs, safety lab), but without significant findings. All events resolved within 1-3 days.

One subject (20-29 year-old) experienced shortness of breath (grade 2, 7 days after 2nd vaccination, duration 1 day) and chest discomfort, palpitations (grade 1, starting a few days later). During study visit 4 onsite (16 days after second vaccination), an ECG was performed in this participant due to chest discomfort and palpitations AEs and the results appeared normal per PI. Other results available from this visit are HR 81.6 beats/min., regular saturation (97%) on room air. The PI has noted that heart sounded normal during this examination, no murmur warm and well perfused, CRT was less than 2 s. Chest auscultation finding was normal, no added sounds.

Narratives of the other subjects did not reveal noticeable findings, usually only single (transient) symptoms were reported. There was no diagnosis of myocarditis or pericarditis during the trial.

Study VLA2001-304 (preliminary safety report)

Solicited local reactions

Overall, 193 (63.1%) study participants reported 433 solicited injection site reactions after any vaccination. The incidences were nearly identical between the first (48.0%) and the second vaccination (48.2%). The most commonly reported solicited injection site reactions were tenderness (58.8%) and pain (25.5%) at the injection site. The other solicited local reactions were induration/hardening (9.2%), redness (8.2%) and swelling (5.2%).

Solicited systemic reactions

173 (56.5%) participants reported 392 systemic reactions after any vaccination. The incidence of any systemic reaction was slightly higher after the first vaccination (45.2%), compared to the second vaccination (40.6%). The most common systemic reactions were fatigue (35.9%), headache (28.1%) and muscle pain (25.8%). The other solicited systemic reactions were nausea (9.8%), fever (1.6%), and vomiting (1.0%).

Nearly all solicited AEs were either mild (participant incidence 55.9%) or moderate (18.6%) in severity. There was one severe event of muscle pain on days 6 and 7 after vaccination.

The median duration of all solicited local or systemic reactions in study VLA2001-304 was either 1 or 2 days, which confirms the results from study VLA2001-301.

Unsolicited Adverse Events

Table 40: Adverse Events up to Day 43 (Safety Analysis Set, study VLA2001-304)

	Overall (N=306) n (%) Obs [95% CI]
Any AE	247 (80.7) 1007 [75.8, 85.0]
Any related AE	234 (76.5) 871 [71.3, 81.1]
Any severe AE	2 (0.7) 3 [0.1, 2.3]

Any severe related AE	1 (0.3) 1 [0.0, 1.8]
Any medically attended AE	49 (16.0) 73 [12.1, 20.6]
Any related medically attended AE	14 (4.6) 17 [2.5, 7.6]
Any serious AE	1 (0.3) 1 [0.0, 1.8]
Any solicited AE	230 (75.2) 825 [69.9, 79.9]
Any severe solicited AE	1 (0.3) 1 [0.0, 1.8]
Any solicited injection site reaction	193 (63.1) 433 [57.4, 68.5]
Any solicited systemic reaction	173 (56.5) 392 [50.8, 62.2]
Any solicited AE ongoing beyond 6th day after vaccination	16 (5.2) 20 [3.0, 8.4]
Any unsolicited AE	103 (33.7) 182 [28.4, 39.3]
Any related unsolicited AE	33 (10.8) 46 [7.5, 14.8]
Any severe unsolicited AE	1 (0.3) 2 [0.0, 1.8]
Any severe related unsolicited AE	0 (0.0) 0 [0.0, 1.2]
Any serious unsolicited AE	1 (0.3) 1 [0.0, 1.8]
Any medically attended unsolicited AE	46 (15.0) 66 [11.2, 19.5]
Any related medically attended unsolicited AE	9 (2.9) 10 [1.4, 5.5]
Any AE of Special Interest	0 (0.0) 0 [0.0, 1.2]

The interim analysis snapshot includes unsolicited AEs only until Day 43, except for SAE/AESI, which were reported until the data cut-off (mean of 122.1 days after first vaccination). The next version of the CSR will include all unsolicited AEs.

The highest incidences (≥2%) of unsolicited AEs up to Day 43 were reported within the SOCs of Infections and infestations (10.1%), Musculoskeletal and connective tissue disorders (6.9%), Gastrointestinal disorders (4.9%), General disorders and administration site conditions (4.9%), Injury, poisoning and procedural complications (4.6%), Nervous system disorders (3.6%), Respiratory, thoracic and mediastinal disorders (3.3%), and Skin and subcutaneous tissue disorders (3.3%).

The most commonly reported (>1%) AEs by PT were arthralgia (2.0%), diarrhoea (2.0%), fatigue (1.6%), headache (1.6%), neck pain (1.6%), upper respiratory tract infection (1.6%), and oropharyngeal pain (1.3%). Most of these events are already included in section 4.8 of the SmPC, except for neck pain (covered by myalgia) and upper respiratory infection (6 events in 5 participants does not seem unusually high).

Among the study participants, 33 subjects (10.8%) reported 46 AEs, which were considered related by the Investigator. Related and medically attended AEs were documented for 14 subjects (4.6%, 17 events).

Two vaccine-related and medically attended events of herpes, Herpes Simplex (HSV-1) and Herpes Zoster (Shingles), were reported. The case of HSV-1 occurred 13 days after the first vaccination and the event of Shingles 2 days after the second vaccination.

There was one vaccine-related event of thrombophlebitis (medically attended).

Three events of palpitations occurred in study VLA2001-304 (two of them were medically attended and considered related).

2.5.8.3. Serious adverse events, deaths, and other significant events

Study VLA2001-301

For the entire study (until data cut date of 14 October 2021), 31 of 4012 participants (0.8%) reported at least 1 serious unsolicited AE: 7 participants (0.7%) in the VLA2001 (age 18-29 years) group, 14 (0.7%) in the VLA2001 (age ≥30 years) group and 10 (1.0%) in the AZD1222 group. The most common serious unsolicited AEs reported for the entire study were intervertebral disc protrusion (2 participants in the VLA2001 [age ≥30] group), headache (2 participants in the AZD1222 group), and migraine (2 participants in the AZD1222 group).

Until the data cut of 14 October 2021, 34 serious unsolicited AEs were reported (by preferred term):

- VLA2001 (18 to <30 years of age): gastroenteritis viral, diabetes mellitus type 1, intestinal abscess, viral meningitis, pyelonephritis, vestibular migraine, ovarian cyst,
- VLA2001 (≥30 years of age): appendicitis perforated, gastroenteritis, migraine, cerebrospinal fluid leakage, idiopathic intracranial hypertension, nerve compression, abdominal pain, Hypercalcaemia, food allergy (nuts), dyspnoea, Mallory-Weiss syndrome, embolism, sepsis, road traffic accident, nephrolithiasis, intervertebral disc protrusion (2x),
- AZD1222 (≥30 years of age): gastroenteritis salmonella, pelvic inflammatory syndrome, migraine/headache (2x), inflammatory bowel disease (flare), non-cardiac chest pain, accidental overdose, renal colic, subarachnoid haemorrhage, and anaemia.

None of these events were considered related by the investigator (see discussion for more details about some of the events). Some events were mild or moderate in severity, but met the criteria for seriousness due to hospitalization.

During the assessment, narratives for additional SAEs were submitted, which occurred after the data cut-off (14th October 2022):

VLA2001 group: intentional escitalopram overdose, laparoscopic cholecystectomy (elective), classical Hodkin Lymphoma, mesenteric adenitis, Covid-19, viral infection (non-Covid-19), atrial fibrillation, miscarriage (2x), multiple sclerosis, elective sterilization, appendicitis, arachnoid cyst causing obstruction cerebral, seizures (2x), infected sinus tract arm, and ankle fracture.

AZD1222 group: coeliac disease, diverticulitis, intestinal obstruction due to parastomal hernia, hip osteoarthritis, ischiorectal infection, Covid-19, pelvic inflammatory disease (abdominal pain).

The Investigator assessed all SAEs as not related. Of note, both miscarriage events occurred within the first trimester (within ~4-5 weeks of estimated conception).

Up to the cut date of 14 October 2021, overall, 0.2% (9/4012) of participants reported in total 11 AESIs during the entire observed study period:

- VLA2001 (18 to <30 years of age): ageusia, anosmia, diabetes mellitus type 1 (SAE),

- VLA2001 (≥30 years of age): ageusia (2x), anosmia, alopecia areata, psoriasis, embolism (SAE),
- AZD1222 (≥30 years of age): facial paralysis, pruritic rash (initially classified as chilblains).

After the data cut-off, one AESI of trigeminal neuralgia (grade 2, ongoing) was reported for a subject who received VLA2001. The AE was documented on visit day 208 according to the patient, which seems to be the reason why it was not yet included at the data cut-off (14 October 2021), although the symptoms (pain, sensitive teeth) appeared months earlier. The patient cannot recall whether the first symptoms started prior or after vaccination with VLA2001. The symptoms got worse around October 2021 (4 months after the vaccination), the general practitioner then diagnosed trigeminal neuralgia and started the participant on Carbamazepine, which the participant still uses. Considering the available information, a potential relationship to vaccination cannot be clearly confirmed or denied. Therefore, the Investigator assessed the event as possibly related.

Further additional AESI were reported and provided during the assessment, which occurred after the data cut-off (14th October 2022): psoriasis flare up (VLA2001), reactive arthritis (VLA2001), atrial fibrillation (SAE, VLA2001), Raynaud's phenomenon (1x VLA2001, 1x AZD1222), and coeliac disease (SAE, AZD1222).

Except for the events of trigeminal neuralgia and psoriasis flare up (possibly related), no AESI in the VLA2001 groups was assessed to be treatment related by the investigator. One participant in the AZD1222 group had AESIs that were considered related to study vaccination (facial paralysis [mild; resolved]). Besides one allergic reaction to nuts (suspected anaphylaxis 4 days after vaccination), no anaphylactic reaction was reported. There was no death in any of the clinical trials.

Study VLA2001-304

Eight serious AE were reported. The events (by reported PT) were: atrial fibrillation, legionella pneumonia, leg fracture, a transient ischaemic attack, urosepsis, ureteric calculus, hemiplegic migraine, and stroke. None of them was considered related to the study medication.

Of note, the SAE of stroke (grade 2, 60-69 year-old) occurred ~3.5 months after second vaccination. The event resolved with sequelae (specified as dyspraxia) on the same day and the subject was released from hospital on the following day.

No AESI, no anaphylactic reaction and no death was reported in study VLA2001-304.

2.5.8.4. Laboratory findings

The strategy for the assessment of laboratory findings, vital signs and physical examination was comparable in studies VLA2001-201 and VLA2001-301.

Blood and urine samples were obtained for assessment of clinical laboratory parameters and parameters were analysed by central laboratories according to the applicable laboratory SOP.

Laboratory analysis included clinical chemistry (Creatinine, sodium, potassium, calcium, aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, and C-reactive protein (CRP)), a haematology panel (Haemoglobin, haematocrit, erythrocyte count, WBC count, differential WBC count (basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelets, erythrocyte sedimentation rate (ESR)), a coagulation panel (Small blood coagulation (prothrombin time, activated partial thromboplastin time and fibrinogen), urinalysis (Standard urine dipstick for determining pH-value, specific gravity, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, erythrocytes) and a pregnancy test.

Vital signs included body temperature (°C) measured digitally and orally according to National Health Service method, pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg) while seated and at rest.

At the screening (Visit 0), a full physical examination included, but was not limited to, assessment of height and weight, general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological system. A symptom-driven physical examination was performed at all study visits and on vaccination visits before the vaccination was given, except the screening visit (Visit 0), i.e., only if the participant reported a symptom.

Available data do not indicate an increased risk of abnormal measures from vaccination with VLA2001 as compared to the effects of AZD1222, also for the age subgroups 18 to <30 years and ≥30 to <55 years.

2.5.8.5. Safety in special populations

For study VLA2001-301 data on safety events were separately reported for three potential risk factors (age, obesity and SARS-CoV-2 baseline status) with six dedicated subgroups (age: 18-29 years, age: 30-55 years, obesity: yes, obesity: no, SARS-CoV-2 baseline status: seropositive and SARS-CoV-2 baseline status: seronegative). Further summary tables on subgroups were provided for AEs overall (age, serostatus, obesity, COPD, cardiovascular risk, diabetes and sex), unsolicited AEs (age, serostatus, obesity, cardiovascular risk, diabetes and sex) and solicited AEs (age, serostatus and sex).

No meaningful differences regarding incidences of solicited adverse reactions within 7 days after any vaccination, medically attended AEs, unsolicited AEs, vaccine-related unsolicited AEs or serious adverse events were observed. Some subgroup analyses suffered from low patient numbers (e.g., cardiovascular risk, diabetes).

In summary, no particular safety pattern of concern was identified for the presented subgroups.

2.5.8.6. Safety related to drug-drug interactions and other interactions

No interaction studies have been performed. Concomitant administration of VLA2001 with other vaccines has not been studied.

A list of concomitant NSAID/paracetamol intake for the 7-day periods starting from the day of vaccination and separately for vaccination 1 and 2, as well as a combined. During the study period, the use of NSAIDs and/or paracetamol was almost twice as high in the AZD1222 group compared to both VLA2001 groups. This is in line with the higher reactogenicity observed in the ADZ1222 group, especially after the first vaccination (supported by a more than 3-times higher use in the AZD1222 group compared to both VLA2001 groups during 7 days after the first vaccination).

2.5.8.7. Discontinuation due to adverse events

In total 119 discontinuations were recorded across all treatment groups of study VLA2001-301. Of those subjects n=69 missed the day 43 visit (n=20 in VLA2001 <30 years, n=35 in VLA2001 ≥30years and n=14 in AZD1222) and from those subjects 30 also discontinued before the second vaccination (n=11 in VLA2001 <30 years, n=15 in VLA2001 ≥30years and n=4 in AZD1222). The remaining 50 subjects discontinued after the day 43 visit (n=15 in VLA2001 <30 years, n=20 in VLA2001 ≥30years and n=15 in AZD1222).

The most frequent causes for discontinuation were lost to follow-up in n=70 subjects (n=21 in VLA2001 <30 years, n=34 in VLA2001 ≥30years and n=15 in AZD1222), withdrawal of consent not due to AE in n=28 subjects (n=5 in VLA2001 <30 years, n=12 in VLA2001 ≥30years and n=11 in AZD1222), moved from study area in n=10 subjects (n=2 in VLA2001 <30 years, n=6 in VLA2001 ≥30years and n=2 in AZD1222) and withdrawal due to individual stopping criterion in n=7 subjects (n=4 in VLA2001 <30 years, n=3 in VLA2001 ≥30years and none in AZD1222).

Other reasons for discontinuation were recorded in individual subjects only (lost faith in trial: n=1 in VLA2001 <30 years, participant requested to withdrawal, could no longer attend visit : n=1 in AZD1222, positive pregnancy test during study drug treatment: n=1 in VLA2001 <30 years, withdrawal of consent due to AE: n=1 in VLA2001 <30 years).

At the updated data from cut-point (October 14th 2021) in total n=153 subjects (of 4017 randomized and 4012 vaccinated subjects) terminated early across all treatment groups of study VLA2001-301, n=30 subjects discontinued before the second vaccination (n=11 in VLA2001 <30 years, n=15 in VLA2001 ≥30years and n=4 in AZD1222).

2.5.8.8. Post marketing experience

There are no post-marketing data of the vaccine.

2.5.9. Discussion on clinical safety

The current data package comprises two clinical studies evaluating the safety profile of the study vaccine VLA2001 in subjects 18-55 years of age after first and second vaccination (28 days apart). The general strategy of safety evaluation, including the assessment of solicited and unsolicited as well as local and systemic AEs is supported. Baseline demographics in study VLA2001-301 appear to be well balanced for the comparison between VLA2001 and AZD1222.

Additionally, besides the clinical studies evaluating the safety profile of the study vaccine, also the CSRs as well as a summary of two clinical phase 1 studies were submitted evaluating safety and tolerability of the novel excipient recombinant human albumin. No relevant increase in tested antibody levels was detected in those subjects without known allergies. Also, regarding symptoms of potentially allergic events as well as other safety assessments, no striking differences were detected for rHA compared to a commercial HSA product. However, for both studies only subjects with "*no known history of allergic reactions to Saccharomyces cerevisiae or any other yeast products and with no history of anaphylactic or severe systemic response to human plasma proteins were selected*". Hypersensitivity to traces of yeast-derived residues (i.e. yeast DNA, yeast antigens and mannosylated rHA) was therefore added as a contraindication in section 4.3 as well as the specification that rHA is produced in yeast (Saccharomyces cerevisiae) to section 6.1 of the SmPC.

No clinical study was performed to assess the safety and tolerability of the excipient CpG 1018. CpG 1018 is also included as an adjuvant in Heplisav B, a recombinant hepatitis B vaccine authorised in the European Union since February 2021 (EMEA/H/C/005063). It is reassuring that only one third of the CpG 1018 amount that is included in Heplisav B (3mg/0.5ml) is included in the Valneva vaccine (1mg/0.5ml), but it is also noted that the combination with aluminium hydroxide (0.5 mg/ Al^{3+}/dose) is unknown. Altogether, the use of the relatively new adjuvant CpG 1018 in combination with aluminium hydroxide comprises an uncertainty with respect to potentially related safety events. In relation to the risk of acute myocardial infarction, a concern with Heplisav-B at the time of marketing authorisation, post-marketing surveillance study HBV-25 ((from Heplisav-B) provided compelling and reassuring evidence that there is no increased cardiovascular risk with CpG 1018 adjuvant. Moreover,

in relation to the risk of immune-mediated events has been evaluated across the large post-marketing safety study HBV-26 (from Heplisav-B). There was no signal detected across Heplisav-B clinical program for immune-mediated AEs and the rates were similar between Heplisav-B and Engerix-B. While immune-mediated disorders remain a hypothetical risk, the RMP includes a list with AESI that may be considered related to CpG1018, which will be monitored in the post-marketing phase.

Exposure

Data are available for up to 106 days after 2nd vaccination in study VLA2001-201 (interim analysis from cut off data June 30th 2021) and for at least 4 weeks after 2nd vaccination in study VLA2001-301 (mean follow up time of 151.4 days after the first dose for the available interim analysis from cut-off date 14th October 2021, in the current submission also referred to as "entire study"). Study duration appears sufficient to evaluate early vaccine related effects, including the pre-defined solicited events (i.e. expected early effects within 7 days after vaccination that were obliged to be recorded in a patient e-diary). However, rare events and potentially late occurring vaccine responses (beyond the immediate vaccine response, e.g. the defined AESI of vaccine associated increased disease) might not be detected in both studies. Both studies are still ongoing and further safety data will be submitted as they become available and are expected to cover a longer time period after vaccination (especially referring to the phase 3 study VLA2001-301, safety data from visits for Day 71 and Day 208 are awaited). Still, currently the provided data set for the phase 3 study includes the Day 43 visit (93.4% of enrolled participants) and data until cut-point (October 14th 2021), which carries some uncertainty regarding potential late effects and rare events. This uncertainty is based on the relatively short observation period currently available, but also related to the relatively low subject number included in both clinical trials.

In total 4012 subjects were included in the safety population of study VLA2001-301, all of which received the first dose of their randomised vaccine (n=1040 for VLA2001 18-<30 years, n=1977 for VLA2001 ≥30 years and n=995 for AZD1222 ≥30 years). In study VLA2001-201 153 subjects received the first dose of their randomised vaccine concentrations (n=51 for 3 AU/dose, 7 AU/dose and 35 AU/dose).

The rate of patients that did not receive the second dose of the vaccine or had a delayed second vaccination (past 29 days after first vaccination) was comparable across treatment groups in study VLA2001-301 and no concerns derive from the general pattern of early study termination. Importantly, data from both clinical studies cover only adult patients ≥18 years. More precisely, sufficient numbers for the evaluation of the vaccines safety profile are available only for subjects 18-55 years. No comparator treatment is provided for the age group 18 to <30 years, which hampers the interpretation of safety results for adult subjects <30 years.

Solicited Adverse Events

Phase 3 trial (VLA2001-301)

Solicited Local Adverse Reactions

During both trials (VLA2001-201 and VLA2001-301), the participants were asked to report the local adverse reactions of tenderness, pain, itching, induration, swelling or redness at the injection site by using an eDiary for a period of 7 consecutive days starting on the day of each vaccination. These events represent typical local adverse events that may occur following vaccination. The most common ARs after any vaccination were injection site tenderness (VLA 2001 18 to <30: 76.4%, ≥30: 66.8%; AZD1222 ≥30: 87.5%) and injection site pain (VLA 2001 18 to <30: 52.9%, ≥30: 45.5%; AZD1222 ≥30: 67.4%). After the first vaccination in study VLA2001-301, the reporting rates of solicited local reactions were lower for all events in both VLA2001 age groups, compared to the AZD1222 group. The differences between the vaccines were statistically significant (p <0.0001, comparison of only the

participants 30 years of age and above). After the second vaccination, the frequencies of local reactions were comparable for both vaccines and there was no statistically significant difference for any event.

The local ARs were mostly mild or moderate in severity. Severe (grade 3) local ARs did occur in one participant (0.1%) of the VLA2001 group (injection site pain), compared to 8 participants (0.9%) in the AZD1222 group (injection site pain, tenderness, induration, swelling, and redness).

The mean duration of local ARs was shorter in the VLA2001 groups, compared to the AZD1222 group. The median duration was either 1 or 2 days for all local events in the VLA2001 group, or 1 to 3 days for the events in the AZD1222 group.

Solicited Systemic Adverse Reactions

The solicited systemic ARs were fever/body temperature, fatigue, headache, nausea/vomiting, and muscle pain. For the comparator vaccine AZD1222, the AR of chills is a known commonly reported event following vaccination, especially after the first vaccination. Reasons for the lack of recording are unclear, but data do not appear crucial considering the availability of other relevant measures for systemic ARs (all of which indicating comparable or higher incidences for AZD1222). Chills was reported as unsolicited AE and a clearly lower incidence was noted for the VLA group (VLA2001: 0.2% vs. AZD1222: 3.0%).

The following systemic ARs were reported with the frequency of "very common" (> 1/10 participants) for both vaccines after any injection: fatigue (VLA2001 18 to <30: 57.3%, ≥30: 51.2%; AZD1222 ≥30: 77.1%), headache (VLA2001 18 to <30: 40.6%, ≥30: 39.8%; AZD1222 ≥30: 67.7%), muscle pain (VLA2001 18 to <30: 44.0%, ≥30: 37.0%; AZD1222 ≥30: 64.2%), and nausea/vomiting (VLA2001 18 to <30: 14.8%, ≥30: 11.7%; AZD1222 ≥30: 22.8%). The AR of fever/body temperature was less frequent in the VLA2001 groups (VLA2001 18 to <30: 1.1%, ≥30: 1.5%), but very common in the AZD1222 group (AZD1222 ≥30: 15.5%).

Similar to the local reactions, the incidences of solicited systemic reactions after the first vaccination were lower for all events in both VLA2001 age groups, compared to the AZD1222 group. The differences were again highly significant for all events (p <0.0001). After the second vaccination, the reporting rates were overall comparable between VLA2001 and AZD1222.

The majority of the reported systemic events was also mild or moderate in severity. Severe (grade 3) events were reported in 24 participants who received VLA2001 (18 to <30: 0.6%, ≥30: 1.4% of all reported events), compared to 46 participants who received the AZD1222 vaccine (5.1% of all reported events). One serious solicited event of headache was reported during the trial (AZD1222 group, 3 days after 2nd vaccination). The event was moderate in severity, but met the criteria of a serious event due to hospitalisation.

The mean duration of systemic reactions was comparable between the groups. The median duration was 1 day for all systemic ARs in the VLA2001 groups, and either 1 or 2 days in the AZD1222 group.

A total of 53/4012 participants (1.3%) had solicited AEs ongoing beyond the diary period of 7 days: 1.3% in the VLA2001 (age 18-29 years) group, 1.1% in the VLA2001 (age ≥30 years) group, and 1.9% in the AZD1222 group. Mostly vaccination site reactions, headache, fatigue and myalgia persisted beyond 7 days.

In study VLA2001-201, a comparison of the reactogenicity between the three doses evaluated (3 AU, 7 AU, 35 AU per dose) did not reveal a relevant difference. A comparison of the local and systemic reactogenicity in the phase 3 trial (VLA2001-301) vs. the high dose group in the phase 2 trial (VLA2001-201) was provided and no meaningful difference was noted. However, the comparability is

limited, due to the small number of subjects (n=51) who received the relevant dose in the phase 2 trial.

The reactogenicity after vaccination with VLA2001 was milder in terms of frequency and severity compared to the authorised AZD1222, particularly after the first vaccination. For the comparator vaccine (AZD1222) it is known that the reactogenicity is more pronounced following the first vaccination. This finding was confirmed by the VLA2001-301 trial.

Among the participants who received the VLA2001 vaccine, the number of subjects reporting solicited local or systemic reactions was higher in the younger age group (local: 80.9%, systemic: 76.9%), compared to the older age group (local: 73.2%, systemic: 70.2%). A stronger reactogenicity following vaccination in younger subjects is not unexpected. One factor that might have contributed to these differences (to some extent) is the fact that participants between 18 to <30 years of age were not blinded, which might favour reporting of potential adverse reaction. Thus, the lack of comparator (and consequently non-blinded study conduct) for subjects 18 to <30 also limits the comparability of safety data between these age groups.

The solicited adverse reactions after vaccination with VLA2001 were mostly mild or moderate in severity and resolved within 1 or 2 days. Overall, the reactogenicity profile of VLA2001 can be considered as acceptable.

Phase 3 trial (VLA2001-304)

Overall, 193 (63.1%) study participants reported 433 solicited injection site reactions after any vaccination. The incidences were nearly identical between the first (48.0%) and the second vaccination (48.2%). The most commonly reported solicited injection site reactions were tenderness (58.8%) and pain (25.5%) at the injection site. The other solicited local reactions were induration/hardening (9.2%), redness (8.2%) and swelling (5.2%).

173 (56.5%) participants reported 392 systemic reactions after any vaccination. The incidence of any systemic reaction was slightly higher after the first vaccination (45.2%), compared to the second vaccination (40.6%). The most common systemic reactions were fatigue (35.9%), headache (28.1%) and muscle pain (25.8%). The other solicited systemic reactions were nausea (9.8%), fever (1.6%), and vomiting (1.0%).

Nearly all solicited AEs were either mild (participant incidence 55.9%) or moderate (18.6%) in severity. There was one severe event of muscle pain on days 6 and 7 after vaccination. Overall, the incidences of most solicited adverse events in subjects above the age of 55 (study VLA2001-304) were either lower or comparable (fever) to the rates reported in younger individuals in study VLA2001-301. The local reactions of injection site redness, swelling, and induration/hardening were more frequently reported in participants above 55 years of age. This should however be interpreted with caution, since the two trials conducted in different study centres and countries (301: UK, 304: New Zealand) may not be fully comparable.

Unsolicited adverse events

Phase 3 trial (VLA2001-301)

The total numbers of unsolicited AEs and unsolicited vaccine-related AEs until the data cut-off (11 August 2021) were provided. In the phase 3 trial, the frequency of unsolicited AEs until day 43 was nearly identical between the two VLA2001 groups (age 18-29 years: 28.8%, age ≥30 years: 28.6%), and higher in the AZD1222 group (35.1%). The difference between the two vaccines was statistically significant (p=0.0003, comparing age ≥30 years). Until the data cut-off (mean 151.4 days after the first vaccination), this difference was reduced (VLA2001 18 to <30: 40.7%, ≥30: 40.1%; AZD1222 ≥30: 44.5%) but still significant (p=0.0213).

The most commonly reported unsolicited AEs until day 43 were oropharyngeal pain (VLA2001 18 to <30: 3.0%, ≥30: 3.2%; AZD1222 ≥30: 4.1%) and headache (incidence of 2.8% for all three treatment groups). The difference between the VLA2001 and AZD1222 groups (comparing age ≥30 years) was mainly caused by adverse events in the SOCs of General disorders and administration site conditions (4.5% vs. 9.9%), Musculoskeletal and connective tissue disorders (4.6% vs. 6.4%), and Gastrointestinal disorders (4.1% vs. 5.6%). Regarding AEs on the PT level, notable imbalances were seen for the AEs of chills (0.3% vs. 3.3%), diarrhoea (1.4% vs. 2.7%), dizziness (1.7% vs. 2.5%), vaccination site pain (0.6% vs. 1.3%), arthralgia (0.7% vs. 1.5%), and oropharyngeal pain (3.2% vs. 4.1%, respectively).

Similar results were reported for vaccine-related unsolicited AEs until day 43 (VLA 2001 18 to <30: 10.6%, ≥30: 11.0%; AZD1222 ≥30: 17.8%) and the differences between VLA2001 and AZD1222 were again significant ($p<0.0001$). For the vaccine-related AEs, the statistical significance remained until the later data cut-off.

A review of all vaccine-related AEs until Day 43 revealed that differences in reporting rates between VLA2001 and AZD1222 were mainly caused by events in the SOCs of General disorders and administration site conditions (2.5% vs. 7.2%), Musculoskeletal and connective tissue disorders (1.7% vs. 3.4%), Skin and subcutaneous tissue disorders (0.7% vs. 1.9%), and Investigations (0.3% vs. 1.2%). On the PT level, notable differences were seen for the events of chills (0.2% vs. 3.1%), vaccination site pain (0.5% vs. 1.1%), and arthralgia (0.2% vs. 1.1%).

In study 301, there were two grade 1 events of thrombophlebitis in the VLA2001 group. The events occurred in close temporal relationship with the first vaccination (2 and 3 days after) and were considered as possibly related by the investigator (and the sponsor). Both events resolved and the participants received the second vaccination. Of note, such an event did also occur in one subject in study VLA2001-304 (medically attended and considered vaccine-related). As a result thrombophlebitis was added in section 4.8 of the SmPC.

There were reports of various menstrual disorders during the trial, which were considered related to treatment by the Investigator. Overall, the incidences were balanced between the two vaccines (slightly lower frequency in the VLA2001 group). So far the PRAC concluded that there is no evidence of a causal relationship of menstrual disorders with AZD1222 or other vaccines against COVID-19. The Applicant suggested to monitor and report on menstrual disorders as AESIs in aggregate reporting, which is supported.

A SMQ analysis for hypersensitivity & angioedema events showed comparable results between the vaccine groups. The most common hypersensitivity event was the AE "rash". Two events of generalized urticaria (both grade 2, related) have been reported following vaccination with VLA2001. The adverse events of urticaria and rash were therefore added to section 4.8 of the SmPC.

Vaccine-related AEs such as herpes zoster/shingles, oral herpes, and different reports of mouth/lip ulcerations were reported during the trials, a possible relationship with vaccination could not be excluded (virus reactivation), and such adverse events have been reported for other vaccines. The Applicant argued that there is no scientific evidence for a causal link between inactivated vaccines and virus reactivation. However, it should be mentioned that herpes zoster is included as an AE in the SmPC of FSME-IMMUN (tick-borne encephalitis vaccine, included due to postmarketing data). Further, a recent publication reports an excess of herpes zoster related hospitalizations following vaccination with other COVID-19 vaccines, including BNT162b2 (https://doi.org/10.1016/j.lanwpc.2022.100393), but the absolute risk was suggested to be very low. In the preliminary safety report for study VLA2001-304 (n=306 vaccinated participants) two vaccine-related and medically attended events of herpes, Herpes Simplex (HSV-1) and Herpes Zoster (Shingles), were reported in close temporal relationship to vaccination. As mentioned in the results section, other vaccine-related AEs occurred in

Study VLA2001-301 which may be causally related to virus reactivation: 2x herpes zoster, 1x genital herpes simplex, 1x oral herpes, 1x gingival ulceration, 1x lip ulceration, 1x tongue ulceration, 2x mouth ulceration. No such AE was reported for the AZD1222 group. It should however be considered that three times more participants were vaccinated with VLA2001 than AZD1222 in study VLA2001-301. Overall, it is acknowledged that a certain background incidence needs to be considered and the currently available evidence is too premature to establish a causal relationship with vaccination. The Applicant's proposal to closely monitor virus reactivation after a potential MA is therefore supported. The suggestion of reporting such events as AESI in aggregate reporting is agreed.

Myocarditis and pericarditis can occur following COVID-19 infection. Further, myo- and pericarditis are confirmed very rare adverse events of currently approved mRNA vaccines. For the comparator vaccine (AZD1222) of the phase 3 trial VLA2001-301, these adverse events have not been confirmed. There was no diagnosis of myocarditis or pericarditis during the trials for VLA2001. The provided clinical trials are likely not large enough to detect rare adverse events. Narratives for subjects who reported AEs that may be indicative for potential mild forms of myo- or pericarditis (shortness of breath, chest pain [any form], palpitations, arrhythmias) did not reveal noticeable findings; usually only single (transient) symptoms were reported. The RMP lists myopericarditis as AESI.

Phase 2 trial (VLA2001-201)

These data suggest that there was no dose-dependent increase in unsolicited AEs. The interpretability of these results is however limited, due to small number of subjects included (n=51 per group).

Phase 3 trial (VLA2001-304)

The data provided are preliminary. The clinical study report should be provided once available (**Clinical safety recommendation 1**)

The interim analysis snapshot includes unsolicited AEs only until Day 43, except for SAE/AESI, which were reported until the data cut-off (mean of 122.1 days after first vaccination). Until Day 43, 103 participants (33.7%; 182 events) reported any unsolicited AE. The highest incidences (≥ 2%) of unsolicited AEs up to Day 43 were reported within the SOCs of Infections and infestations (10.1%), Musculoskeletal and connective tissue disorders (6.9%), Gastrointestinal disorders (4.9%), General disorders and administration site conditions (4.9%), Injury, poisoning and procedural complications (4.6%), Nervous system disorders (3.6%), Respiratory, thoracic and mediastinal disorders (3.3%), and Skin and subcutaneous tissue disorders (3.3%).

The most commonly reported (>1%) AEs by PT were arthralgia (2.0%), diarrhoea (2.0%), fatigue (1.6%), headache (1.6%), neck pain (1.6%), upper respiratory tract infection (1.6%), and oropharyngeal pain (1.3%). Most of these events are already included in section 4.8 of the SmPC, except for neck pain (covered by myalgia) and upper respiratory infection (6 events in 5 participants does not seem unusually high).

Among the study participants, 33 subjects (10.8%) reported 46 AEs, which were considered related by the Investigator. Related and medically attended AEs were documented for 14 subjects (4.6%, 17 events). The reported adverse events are adequately represented in the SmPC.

The narratives for three events of palpitations that occurred in study VLA2001-304 were provided. Two of these cases were medically attended and considered related by the investigator. However, no firm conclusions can be drawn based on these 2 cases.

There was a medically-attended vaccine-related AE of superficial vein thrombosis. The Applicant included the PT of thrombophlebitis in section 4.8 of the SmPC due to two vaccine-related AEs in close temporal relationship to vaccination in study VLA2001-301.

Two events of herpes, Herpes Simplex (HSV-1, 13 days after the first vaccination) and Herpes Zoster (Shingles, 2 days after second infection), were reported. Since similar AEs also occurred in study 301, the Applicant suggested monitoring such events as AESI in aggregate reporting, which is supported. The currently available evidence is too premature to conclude on a causal relationship.

Serious adverse events (SAE)

Phase 3 trial (VLA2001-301)

Until the data cut-off (14 October 2021), 31 of 4012 participants (0.8%) reported at least one serious unsolicited AE: 7 participants (0.7%) in the VLA2001 (age 18-29 years) group, 14 (0.7%) in the VLA2001 (age ≥30 years) group and 10 (1.0%) in the AZD1222 group. In total, 34 serious unsolicited AEs were reported until the mentioned time point (VLA2001: gastroenteritis viral, diabetes mellitus type 1, intestinal abscess, viral meningitis, pyelonephritis, vestibular migraine, ovarian cyst, appendicitis perforated, gastroenteritis, migraine, cerebrospinal fluid leakage, idiopathic intracranial hypertension, nerve compression, abdominal pain, hypercalcaemia, food allergy (nuts), dyspnoea, Mallory-Weiss syndrome, sepsis, embolism, road traffic accident, nephrolithiasis, intervertebral disc protrusion (2x); AZD1222: gastroenteritis salmonella, pelvic inflammatory syndrome, migraine/headache (2x), inflammatory bowel disease (flare), non-cardiac chest pain, accidental overdose, renal colic, subarachnoid haemorrhage, and anaemia). During the assessment procedure, narratives for additional SAEs were submitted, which occurred after the data cut-off (VLA2001 group: intentional escitalopram overdose, laparoscopic cholecystectomy (elective), classical Hodgkin Lymphoma, mesenteric adenitis, Covid-19, viral infection (non-Covid-19), atrial fibrillation, miscarriage (2x), multiple sclerosis, elective sterilization, appendicitis, arachnoid cyst causing obstruction cerebral, seizures (2x), infected sinus tract arm, and ankle fracture; AZD1222 group: coeliac disease, diverticulitis, intestinal obstruction due to parastomal hernia, hip osteoarthritis, ischiorectal infection, Covid-19, pelvic inflammatory disease (abdominal pain).

None of the serious adverse events in study VLA2001-301 were considered related by the investigator. Based on the provided narratives for all SAES, this conclusion can be followed. Some events were mild or moderate in severity, but met the criteria for seriousness due to hospitalization.

Phase 3 trial (VLA2001-304)

Eight serious AE were reported. The events (by reported PT) were: Atrial fibrillation, Legionella pneumonia, leg fracture, transient ischaemic attack, stroke, urosepsis, ureteric calculus, and hemiplegic migraine. None of them was considered related to the study medication.

Adverse events of special interest (AESI)

Until the cut-off date (14 October 2021) in study VLA2001-301, 0.2% (9/4012) of participants reported in total 11 AESIs during the entire observed study period (VLA2001: 3x ageusia, 2x anosmia, diabetes mellitus type 1 [SAE], alopecia areata, psoriasis, embolism [SAE]; AZD1222: facial paralysis, pruritic rash [initially classified as chilblains]). Among the subjects who reported anosmia/ageusia, some had either concomitant COVID-19 infection or other upper respiratory infection. The AESI of psoriasis and alopecia areata (both grade 1) were reported by one participant who had a family history of psoriasis but has not been diagnosed in the past. The participant was diagnosed with alopecia areata by his general practitioner. The first noticed patch of hair loss was observed some days before the first vaccination. After the cut-off date, one AESI of trigeminal neuralgia (grade 2, ongoing) was reported. Considering the available information, a potential relationship to vaccination cannot be clearly confirmed or denied.

Further additional AESI were reported for the time period after the data cut-off: reactive arthritis (VLA2001), psoriasis flare up (VLA2001), atrial fibrillation (SAE, VLA2001), Raynaud's phenomenon (1x

VLA2001, 1x AZD1222), and coeliac disease (SAE, AZD1222). The case of psoriasis flare-up occurred in close temporal association with the vaccine and was assessed by the investigator as possibly related. However, there was only one additional case from study VLA-2001-301 apparent from the line-listings. Therefore, there is no need for closely monitoring for this AE as there isn't sufficient evidence in regards to this event.

Except for the events of trigeminal neuralgia and psoriasis flare up (possibly related), no AESI in the VLA2001 groups was assessed to be treatment related by the investigator. One participant in the AZD1222 group had an AESI that was considered related to study vaccination (facial paralysis [mild; resolved]).

Besides one allergic reaction to nuts (suspected anaphylaxis 4 days after the second vaccination), no anaphylactic reaction was reported. There was no death in any of the clinical trials.

Safety laboratory

The general strategy for the assessment of laboratory findings, vital signs and physical examination is acceptable for both clinical studies. No concerns arose from submitted listings for studies VLA2001-201 (haematology, biochemistry, urinalysis, coagulation, vital signs and physical examination) and VLA2001-301 (haematology, vital signs and physical examination).

Safety in special populations

Summary tables including information on AEs for subgroups were provided (age, serostatus, obesity, COPD risk, cardiovascular risk, diabetes and sex). No meaningful differences regarding incidences of solicited adverse reactions within 7 days after any vaccination, medically attended AEs, unsolicited AEs, vaccine-related unsolicited AEs or serious adverse events were observed. Some subgroup analyses suffered from low patient numbers (e.g., cardiovascular risk, diabetes).

In summary, no particular safety pattern of concern was identified for the presented subgroups.

Study discontinuations

Up to the available data cut-point (October 14th 2021) in total n=153 subjects (of 4017 randomized and 4012 vaccinated subjects) terminated early across all treatment groups of study VLA2001-301. In total, n=30 subjects discontinued before the second vaccination (n=11 in VLA2001 <30 years, n=15 in VLA2001 ≥30years and n=4 in AZD1222). Early discontinuations (before 2nd vaccination) do not appear to have been driven by safety events in these subjects. Lack of recognition of an investigational vaccine by governmental bodies (e.g. for cross-country travel) is considered a relevant factor that might have driven the reported imbalance in discontinued before the second vaccination across treatment groups.

Two subjects discontinued due to AEs (up to the available data-cut in October 2021). However, neither of both AEs that led to discontinuation ("worsening of anxiety" and "Incidental finding of hypercalcaemia") is considered to be caused by the physiological action of the vaccine itself and the general rate of reported "withdrawal of consent due to AE" is considered low.

2.5.10. Conclusions on clinical safety

The observed safety profile is considered favourable for subjects between 18 and 55 years of age. Longer-term safety data is awaited from the on-going clinical trials. The Applicant provided a preliminary safety report for study VLA2001-304, which recruited 306 subjects >55 years of age. The preliminary data from this additional trial did not reveal a new safety concern although the clinical study report for VLA2001-304 should be provided once available. This is considered a valuable

resource for the estimation of the safety profile in this age group, considering the potential of off-label use of the vaccine (**Clinical safety recommendation**).

Description of post-authorisation measures
Clinical safety recommendations
1. Although the data from study VLA2001-304 fall outside the scope of the initially sought indication, they are still regarded as very relevant and are recommended to be provided post-authorization

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns	
Important identified risks	-
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with unstable health conditions and co-morbidities, e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data

2.6.2. Pharmacovigilance plan

Study	**Summary of objectives**	**Safety concerns addressed**	**Milestones / Due dates**
Pregnancy Registry	To estimate the risk of the most common obstetric outcomes, i.e. pregnancy losses, placentation disorders, gestational diabetes, premature delivery, and COVID-19, neonatal outcomes, i.e. congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission, and COVID-19, among pregnant women exposed to COVID-19 Vaccine (inactivated, adjuvanted) Valneva from 30 days prior to the first day of the LMP to end of pregnancy and their offspring relative to a matched unexposed reference group.	Use in pregnancy and corresponding AESIs	Registration in the EU PAS Register 20 January 2021. Start of data collection of VLA2001 exposures 01 August 2022. Annual Reports: 31 August 2023 31 August 2024 31 August 2025 31 August 2026 Semiannual Reports: 28 February 2023

			29 February 2024 28 February 2025 28 February 2026 28 February 2027 Final Study Report: 31 August 2027
Post-Authorisation Safety Study	To estimate the incidence of adverse events of special interest (AESIs), including the potential risk of vaccine associated enhanced disease (VAED) and vaccine associated respiratory disease (VAERD), that are medically attended following the administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the real-world immunisation setting. A retrospective study using health care databases.	VAED and VAERD Use in immunocompromised patients Use in frail patients Use in patients with autoimmune or inflammatory disorders Long-term safety data	Study Protocol: June 2022 Registration in the EU PAS Register: upon protocol finalisation Request for data extraction: launch of VLA2001 in the EU Progress reports: 12 and 24 months after start of vaccination campaign. Final study report: 36 months after start of vaccination campaign.
Post-Authorisation Safety Study	To evaluate the risk of adverse events of special interest (AESIs) that are medically attended. A prospective multi-centre cohort study.	VAED and VAERD Use in immunocompromised patients Use in frail patients Use in patients with autoimmune or inflammatory disorders Long-term safety data	Study is expected to end 36 months after start of enrolment with delivery of the final study report (30 months for data collection and 6 months for database lock, data analysis, and study report).
Post-Authorisation Efficacy Study	To estimate effectiveness against hospitalization due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with COVID-19 Vaccine (inactivated, adjuvanted) Valneva.	VAED and VAERD	The interim and final analysis are anticipated to be triggered 6 and 12 months after initiation of use of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the participating countries assuming a constant COVID-19 attack rate. Therefore, the anticipated timelines for the interim and final reports are 9 and 16 months after study initiation.
Clinical Study VLA2001-201	To evaluate the tolerability, safety and immunogenicity of the inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001	Long-term safety data	Interim CSR submitted as part of licensure application Q4 2021.

	of a two-dose schedule in healthy adults aged 18 to 55 years.		Interim CSR including follow-up to Month 6 planned to be submitted mid-2022. Final CSR submission planned Q4 2022.
Clinical Study VLA2001-301	To demonstrate the superiority of VLA2001 (Wuhan strain) compared to AZD1222 in adults aged 30 years and older. To examine the immunogenicity of VLA2001 in adolescents aged ≥12 to <18 years compared to adults 18-29 years of age. To evaluate the safety and tolerability of VLA2001 in adults and adolescents aged ≥12 years and older.	Long-term safety data	CSR submitted as part of licensure rolling review procedure Q4 2021. Addendum CSR with extended immunogenicity and safety follow-up (including Day 71) planned to be submitted until 31 August 2022. Interim CSR report including primary endpoint in adolescents planned to be submitted Q3 2022. Final CSR submission planned Q2 2023.

2.6.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up Questionnaire. Additional pharmacovigilance activities: COVIDRIVE study. Post-authorisation safety studies.
Use in pregnancy and while breast feeding.	Routine risk minimisation measures: SmPC section 4.6, PL section 2. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up Questionnaire. Additional pharmacovigilance activities: Pregnancy registry.
Use in immunocompromised patients	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Sub-population in post-authorisation safety studies.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Sub-population in post-authorisation safety studies.
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Sub-population in post-authorisation safety studies.
Interaction with other vaccines	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Post-authorisation safety studies.
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Clinical study extension of VLA2001-201 and VLA2001-301. Post-authorisation safety studies.

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 request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.02.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

A justification for not performing an user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable, given the current public health need for rapid development and approval of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease, and because the product will always be administered by a healthcare professional.

The applicant is expected to thoroughly review and update the package leaflet in the light of the results from the user testing, especially as regards the section 'Information about storage and handling', and provide it as soon as possible.

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 labelling flexibilities described in the Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/689080/2020 rev.3) document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities.

Outer and immediate packaging in EN only:

Outer and immediate labelling will be provided in English only for all EU Member States (MSs), as well as Norway and Iceland. The labelling flexibility is granted until end of March 2023.

EN only printed package leaflet:

If required, EN printed package leaflet (PL) will be supplied to EU MSs, including Norway and Iceland. The applicant will discuss the provision of national language package leaflets with those countries that require it as per labelling Q&A. The applicant plans to provide electronic and downloadable national translations of the Package Leaflet for other Member States / languages via a QR code. The labelling flexibility is granted until end of March 2023.

Omission of the Blue Box information on the outer carton:

Due to the use of one unified EN packaging across all the EU countries, the Blue Box will not be displayed on the outer carton. The labelling flexibility is granted until end of March 2023. The information, normally provided in the market specific packaging Blue Box area of the carton, will be provided as an electronic version on the website (via the QR code/URL).

2.8.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable by all EU MSs, including Norway and Iceland. The following elements have been agreed to be provided through a QR code:

Statutory information:

- Approved regulatory information, including the patient information leaflet (PIL) and Summary of Product Characteristics (SmPC).

2.8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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. Benefit risk assessment

3.1.1. Therapeutic Context

3.1.2. 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.

3.1.3. Available therapies

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 recently authorised based on its ability to reduce the risk of COVID-19 infection. These therapies have shown variable efficacy depending on the severity and duration of illness as well as against different variants of concern.

There are 5 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) and Nuvaxovid (EMEA/H/C/005808).

3.1.4. Main clinical studies

The clinical programme to develop VLA2001 consists of several trials of which two have been submitted to support the use of this vaccine as primary series: the Phase 1/2 trial VLA2001-201 (dose finding and VoC neutralisation) and the pivotal Phase 3 trial VLA2001-301, assess the immunogenicity and safety of VLA2001. Preliminary results on a third study VLA2001-304 have also been provided to support the safety profile of the vaccine.

The Phase 3 study VLA2001-201 is considered as main evidence and was designed to bridge immunogenicity results of VLA2001 to AZD1222, an already registered COVID-19 vaccine with known efficacy. This study was designed to show superiority of VLA2001 in terms of inducing neutralising antibodies as well as non-inferiority for seroconversion rates of neutralising antibodies to infer vaccine efficacy in the absence of a currently established correlate of protection. The study consisted of three study arms: participants 18-29 years of age received VLA2001 (non-random) and participants ≥30 years of age were randomized to receive either VLA2001 or AZD1222. All vaccines were given in a two dose schedule four weeks apart (as authorised for AZD1222) to evaluate the primary outcomes two weeks after the second vaccination. No efficacy studies for VLA2001 have been performed.

3.2. Favourable effects

Superiority VLA2001/AZD1222 neutralising GMTs. Superiority for VLA2001 compared to AZD1222 for the co-primary endpoint at Day 43 was confirmed with a neutralising antibody GMT ratio (95% CI) of 1.39 (1.25, 1.56) in participants 30 years of age and older (strain Victoria/1/2020).

Non-inferiority VLA2001/AZD1222 seroconversion. Seroconversion was defined as a ≥4-fold increase in SARS-CoV-2-specific neutralising antibody titre levels between Day 1 and post-vaccination sample collection time points. At day 43, non-inferiority was confirmed with a lower bound of the 95% CI for the difference between the randomised groups of -3.3% in participants 30 years of age and older (strain Victoria/1/2020). These co-primary endpoints were supported by a numerically higher rate of participants with ≥10-fold and ≥20-fold increase in neutralising antibody titres in the VLA2001 group.

For both co-primary endpoints, similar results were achieved for the IMM and PP population.

Immunobridging to individuals 18-29 years of age. The neutralising GMT ratio of 18-29 year old individuals compared to individuals ≥ 30 years of age was 1.3, thus NI criteria were met. Likewise, NI criteria for seroconversion rates in individuals 18-29 vs. ≥30 yoa individuals were also met (lower bound of the 95% CI for the difference between age groups of -1.5%.).

Additional measures of humoral immunity. Primary outcomes based on neutralising antibodies are supported by secondary outcomes evaluating induction of S-protein specific binding IgGs (ELISA).

Additional measures of cellular immunity. Induction of T-cell responses against SARS-CoV-2 S-protein, N-protein and M-protein was demonstrated.

Immunity against (mainly historic) SARS-CoV-2 variants of concern. Samples from VLA2001 vaccinated participants in Phase 1/2 showed neutralising activity of varying extent against SARS-CoV-2 variants Alpha, Beta, Gamma and Delta.

Data in SARS-CoV-2 seropositive individuals. A more pronounced humoral immune response in a limited set of individuals seropositive at baseline who received VLA2001 compared to individuals seronegative at baseline became apparent.

Exploratory efficacy data. Efficacy for VLA2001 was evaluated as exploratory objective in the pivotal Phase 3 study. The frequency of participants who tested COVID-19 positive after the second vaccination up to the data cut (14 October 2021) in subjects ≥ 30 years vaccinated with VLA2001 (139/1977; 7%) was comparable to AZD1222 (60/995; 6%). The frequency of participants who tested COVID-19 positive after the second vaccination in subjects < 30 years vaccinated with VLA2001 was 8.4% (87/1040). All COVID-19 cases were reported as mild or moderate and based on currently available sequencing data were caused by the Delta variant.

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 VLA2001 to AZD1222 with known efficacy is therefore essential for the interpretation of a potential protective effect of VLA2001.

Immunity against (mainly historic) SARS-CoV-2 variants of concern. Results from Phase 1/2 are considered preliminary and currently not deemed sufficiently robust to draw final conclusions on the cross-neutralisation potential of VLA2001 vaccination against VoCs.

Immunity against currently predominant SARS-CoV-2 Omicron variant. Limited (research-grade) neutralisation data on VLA2001 induced neutralisation (after 2-dose prime + boost series) against the currently dominant SARS-CoV-2 Omicron variant have been provided (pseudovirus). The data indicate a substantial reduction in neutralising activity compared to wild type.

Persistence. Humoral immune response data from Phase 3 were provided up to Day 43 (neutralising GMTs) or Day 71 (binding GMTs) after the first vaccination (i.e. 2 weeks, or 6 weeks after second vaccination, respectively). Data from later time points have not been submitted yet. Additional data on neutralising responses on Day 71 are to be provided post-marketing. Humoral immune response data from Phase 1/2 up to Day 106 after the first vaccination (i.e. approx. 3 months after second vaccination) indicate waning immunity over time.

Need and timing of booster after primary vaccination series. No data on booster vaccinations have been provided but are recommended to be submitted post-authorisation.

Humoral immunity against non-S-protein targets. VLA2001 has the potential to induce humoral immunity against SARS-CoV-2 proteins, other than S-protein, owing to its nature as a whole virus inactivated vaccine. No data in humans were provided.

3.4. Unfavourable effects

Solicited local reactions. After the first vaccination in study VLA2001-301, the reporting rates of solicited local reactions were lower for all events in both VLA2001 age groups, compared to the AZD1222 group. The differences between the vaccines were statistically significant ($p < 0.0001$, comparison of only the participants 30 years of age and above). After the second vaccination, the frequencies of local reactions were comparable for both vaccines and there was no statistically significant difference for any event. The most common solicited local reactions were injection site tenderness and injection site pain. The local ARs were mostly mild or moderate in severity. Severe (grade 3) local ARs did occur in one participant (0.1%) of the VLA2001 group, compared to 8 participants (0.9%) in the AZD1222 group. The median duration was either 1 or 2 days for all local events in the VLA2001 group, or 1 to 3 days for the events in the AZD1222 group.

Solicited systemic reactions. The incidences of solicited systemic reactions after the first vaccination were lower for all events in both VLA2001 age groups, compared to the AZD1222 group. The differences were again highly significant for all events ($p < 0.0001$). After the second vaccination, the reporting rates were overall comparable between VLA2001 and AZD1222. After any injection, nearly all types of solicited systemic reactions (fatigue, headache, muscle pain, nausea/vomiting) were reported with a frequency of 'very common' (≥ 10%) for both vaccines. A clear difference in reporting rates between the vaccines was noted for fever (VLA2001: 1.1%; AZD1222: 15.5%). The majority of the reported systemic events was again mild or moderate in severity. The incidence of severe (grade 3)

evens was higher in the AZD1222 group. The median duration was 1 day for all systemic ARs in the VLA2001 groups, and either 1 or 2 days in the AZD1222 group.

Unsolicited adverse events. The frequency of unsolicited AEs until day 43 was nearly identical between the two VLA2001 groups, and higher in the AZD1222 group. The difference between the two vaccines was statistically significant (p=0.0003, comparing age ≥30 years). Until the data cut-off (mean 151.4 days after the first vaccination), this difference was reduced but still significant (p=0.0213). The most commonly reported unsolicited AEs until day 43 were oropharyngeal pain and headache. The difference between the VLA2001 and AZD1222 groups (comparing age ≥30 years) was mainly caused by adverse events in the SOCs of General disorders and administration site conditions (4.5% vs. 9.9%), Musculoskeletal and connective tissue disorders (4.6% vs. 6.4%), and Gastrointestinal disorders (4.1% vs. 5.6%). Regarding AEs on the PT level, notable imbalances were seen for the AEs of chills (0.3% vs. 3.3%), diarrhoea (1.4% vs. 2.7%), dizziness (1.7% vs. 2.5%), vaccination site pain (0.6% vs. 1.3%), arthralgia (0.7% vs. 1.5%), and oropharyngeal pain (3.2% vs. 4.1%, respectively).

Vaccine-related unsolicited adverse events. The incidence of vaccine-related AEs was significantly higher in the AZD1222 group (p<0.0001). A review of all vaccine-related AEs until Day 43 revealed that differences in reporting rates between VLA2001 and AZD1222 were mainly caused by events in the SOCs of General disorders and administration site conditions (2.5% vs. 7.2%), Musculoskeletal and connective tissue disorders (1.7% vs. 3.4%), Skin and subcutaneous tissue disorders (0.7% vs. 1.9%), and Investigations (0.3% vs. 1.2%). On the PT level, notable differences were seen for the events of chills (0.2% vs. 3.1%), vaccination site pain (0.5% vs. 1.1%), and arthralgia (0.2% vs. 1.1%).

There were two mild (grade 1) events of thrombophlebitis in the VLA2001 group, which occurred in close temporal relationship with the first vaccination (2 and 3 days after) and were considered as possibly related by the investigator (and the sponsor). Both events resolved and the participants received the second vaccination. As a result thrombophlebitis was included in section 4.8 of the SmPC. Of note, such an event did also occur in one subject in study VLA2001-304 (medically attended and considered vaccine-related).

Some vaccine-related AEs such as herpes zoster/shingles, oral herpes, and different reports of mouth/lip ulcerations occurred in studies VLA2001-301 and VLA2001-304. However, the currently available evidence is too premature to conclude on a causal relationship. The Applicant's proposal to closely monitor virus reactivation after a potential MA is therefore supported. The suggestion of reporting such events as AESI in aggregate reporting is agreed.

Serious adverse events (SAE). Until the data cut-off (14 October 2021), 31 of 4012 participants (0.8%) reported at least one serious unsolicited AE: 7 participants (0.7%) in the VLA2001 (age 18-29 years) group, 14 (0.7%) in the VLA2001 (age ≥30 years) group and 10 (1.0%) in the AZD1222 group. In total, 34 serious unsolicited AEs were reported until the data cut-off. During the assessment procedure, additional SAEs were reported for the time period after this data cut, 17 SAEs in the VLA2001 group and 7 SAEs in the AZD1222 group. None of the serious adverse events in study VLA2001-301 were considered related by the investigator. Based on the provided narratives, this conclusion can be followed.

Adverse events of special interest (AESI). Until the data cut-off (14 October 2021), 0.2% (9/4012) of participants reported in total 11 AESIs during the entire observed study period (VLA2001: 3x ageusia, 2x anosmia, diabetes mellitus type 1 [SAE], alopecia areata, psoriasis, embolism [SAE]; AZD1222: facial paralysis, pruritic rash). Among the subjects who reported anosmia/ageusia, some had either concomitant COVID-19 infection or other upper respiratory infection. After the data cut, additional AESI were reported: trigeminal neuralgia (VLA2001), reactive arthritis (VLA2001), atrial

fibrillation (SAE, VLA2011), psoriasis flare up (VLA2001), 2x Raynaud's phenomenon (1x VLA2001, 1x AZD1222), and coeliac disease (SAE, AZD1222). Except for the events of trigeminal neuralgia and psoriasis flare up (possibly related), no AESI in the VLA2001 groups was assessed to be treatment related by the investigators.

Besides one allergic reaction to nuts (suspected anaphylaxis 4 days after vaccination), no anaphylactic reaction was reported. There was no death in any of the clinical trials.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety. Long-term safety data are not yet available. Currently, the mean follow-up time after the first vaccination is 151.4 days. For trial VLA2001-301, all SAEs and AESIs will be analysed and presented by severity and relationship to study treatment up to the end of the study (Month 12). Potentially late occurring vaccine responses (beyond the immediate vaccine response, e.g. the defined AESI of vaccine associated enhanced disease) might not have been detected.

Subjects <30 years of age: No comparator treatment is provided for the age group 18 to <30 years, which hampers the interpretation of safety results for adult subjects <30 years.

Rare adverse events. The sample size of the clinical trial(s) is not large enough to detect rare or very rare adverse events.

Myocarditis/pericarditis. 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 VLA2001 studies. However, the trials are not large enough to detect such potential adverse events.

Potential adverse events related to the adjuvants (CpG 1018, Aluminium hydroxide). The adjuvant CpG 1018 is included in one EMA authorised vaccine (Heplisav B). During the clinical trials for Heplisav B, an imbalance for the AE of myocardial infarction was noted. However, post marketing safety data was sufficiently reassuring in this regard. This event was not observed during the VLA2001 trials. The contained dose of CpG 1018 in VLA2001 corresponds to only one third the dose, compared to Heplisav B. However, VLA2001 does additionally include Aluminium hydroxide as a second adjuvant (new combination). Myocardial infarction is considered as an AESI in the RMP.

Seropositive subjects. Only limited safety data in seropositive subjects is available (192 [4.8%] participants). The so far provided data does not suggest a clinically meaningful difference regarding reactogenicity.

Immunosuppressed/immune-deficient individuals. There are no safety data available for immunocompromised individuals. Safety data in individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressant medications will be investigated in a post-authorisation safety study (PASS).

Frail patients with co-morbidities. There are no safety data available for frail patients with co-morbidities. The Applicant will collect safety data in patients who are frail due to age or debilitating diseases in a PASS and through routine pharmacovigilance.

Interaction with other vaccines. There are no data available of concomitant administration of VLA2001 with other vaccines. The Applicant intends to study interactions with other vaccines in a PASS.

Pregnancy/breastfeeding. There are no clinical data available on the safety of VLA2001 in pregnant women (exclusion criterion). There was one positive pregnancy test during the trial (leading to

discontinuation of the participant from the trial). There are no data regarding breastfeeding. A post-authorisation pregnancy registry is planned.

Menstrual disorders. The incidence of menstrual disorders during study VLA2001-301 was similar to the comparator vaccine AZD1222. So far, the PRAC concluded that there is no evidence of a causal relationship of menstrual disorders with AZD1222 or other vaccines against COVID-19. However, there are recent publications suggesting that changes to the menstrual cycle do occur following vaccination, but they are small compared with natural variation and quickly reverse. The Applicant will monitor and report menstrual disorders as AESI in aggregate reporting.

Vaccine-associated enhanced disease (VAED). 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.

3.6. Effects Table

Table 41. Effects Table for COVID-19 Vaccine (inactivated, adjuvanted) Valneva (VLA2001) indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18-50 years of age.

Effect	Short Description	Unit	VLA2001	AZD1222	Uncertainties/ Strength of evidence	References
Favourable Effects (30-50 yoa)						
Immune response (co-primary)	Superiority SARS-CoV-2 Neutralisation	nAb GMT (95% CI)	803.5 (748.48, 862.59)	576.6 (543.59, 611.66)	Superiority of VLA2001 vs. AZD1222 based on limited age range; GMT ratio (95% CI) 1.39 (1.25, 1.56)	CSR V1.0 VLA2001-301
Immune response (co-primary)	Non-inferiority Seroconversion	n/ % (95% CI)	444/ 97.4 (0.954, 0.986)	444/ 98.9 (0.974, 0.996)	NI based on limited age range; lower bound 95% CI of -3.3%	CSR V1.0 VLA2001-301
Immune response (secondary)	S-protein binding Abs	IgG GMT	2361.7 (2171.08, 2569.11)	2126.4 (1992.42, 2269.45)	ELISA validation data to be provided post-approval	CSR V1.0 VLA2001-301
Immune response (secondary)	Cellular immunity	IFN-γ SFU	T cell responses against S-protein induced by both vaccines; VLA2001 induced T cell responses against M and N protein		Findings as expected due to different mechanism of action	CSR V1.0 VLA2001-301
Efficacy (exploratory)	COVID-19 cases after second vaccination	COVID-19 cases	≥30 yoa: 7% 18-29 yoa: 8.4%	≥30 yoa: 6%	Exploratory data	CSR V1.0 VLA2001-301

Effect	Short Description	Unit	VLA2001	AZD1222	Uncertainties/ Strength of evidence	References
Immune response (supportive)	Neutralisation VoCs	nAb GMT	Neutralisation of VoCs Alpha, Beta, Gamma, Delta, Omicron (reduced compared to Victoria/ Wuhan)	no data	Preliminary data; further data recommended to be provided post-marketing	Report VIE-DR-0166 (substudy from Phase 1/2),
Favourable effects (18-29 yoa)						
Immune response (co-primary)	Non-inferiority SARS-CoV-2 Neutralisation D43 GMTs 18-29 yoa vs. ≥30 yoa (VLA2001 only)	nAb GMT (95% CI)	18-29 yoa: 1043.4 [926.6, 1174.9] ≥30 yoa: 803.5 [748.5, 862.6] GMT ratio 1.3 [1.1, 1.5]	Not applicable	no active comparator	Addendum to CSR V2.0 VLA2001-301
Immune response (co-primary)	Non-inferiority Seroconversion D43 GMTs 18-29 yoa vs. ≥30 yoa (VLA2001 only)	n/ % (95% CI)	18-29 yoa: 197/ 98.5% (95.7, 99.7) ≥30 yoa: 477/ 97.0% (95.0, 98.3)	Not applicable	no active comparator	Addendum to CSR V2.0 VLA2001-301
Unfavourable Effects						
Injection site pain	Incidence	%	45.5	67.4	Transient events, majority mild to moderate intensity	Study VLA2001-301 Safety set (incidence vs. comparator shown for subjects ≥30 years of age) VLA2001
Injection site tenderness	Incidence	%	66.8	87.5		
Fatigue	Incidence	%	51.2	77.1		
Headache	Incidence	%	39.8	67.7		

Effect	Short Description	Unit	VLA2001	AZD1222	Uncertainties/ Strength of evidence	References
Muscle pain	Incidence	%	37	64.2		(≥30 years of age n=1,977) AZD1222 (n=995)
Nausea/ vomiting	Incidence	%	11.7	22.8		
Fever/ Body temperature increased	Incidence	%	1.1	15.5		

Abbreviations: CI… confidence interval; CSR… clinical study report; GMT…geometric mean titre; nAb… neutralising antibodies; SFU…spot forming unit; VoC…variant of concern; yoa…years of age
Notes: none

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

This application relies on establishing an immunological bridge between the vaccine VLA2001 and the authorised vaccine AZD1222 with known protective efficacy against COVID-19 in order to obtain a MA in individuals 18-55 years of age. In addition, supportive efficacy data have been submitted as an exploratory endpoint. While no correlate of protection has been identified to date, the key role of neutralising antibodies to protect against COVID-19 has been demonstrated by numerous studies. Thus, this approach is generally acceptable and largely in line with respective EMA guidance and previous scientific advice.

The main evidence from the VLA2001 clinical development program comes from the pivotal Phase 3 study in participants 18 years of age and above, although the immunological comparison comprises adults age between 30 to 55 years of age. The co-primary endpoints were evaluated after a two dose vaccination series (with vaccinations 4 weeks apart) at day 43 post-primary vaccination. Both were met: superior neutralising GMTs were induced by VLA2001 vaccination compared to AZD1222 vaccination and, non-inferiority for seroconversion rates. Furthermore, neutralising GMTs and seroconversion rates in VLA2001-vaccinated individuals 18-29 yoa were non-inferior compared to VLA2001-vaccinated individuals ≥30 yoa.

While immunologic success criteria have been met in individuals ≥30 yoa, a large fraction of the analysis population was 30-40 yoa, with only limited immunogenicity data derived from individuals > 40 yoa and lack of immunogenicity data in individuals >50 yoa. Therefore, vaccine efficacy across the entire intended age range cannot be inferred and the indication was restricted to individuals 18-50 yoa.

The co-primary endpoints are supported by additional measures of humoral immunity, such as numerically higher rate of participants with ≥10-fold and ≥20-fold increase in neutralising antibody titres in the VLA2001 group, as well as comparable S-protein binding IgG titres (ELISA) between both groups. Furthermore, induction of T cell responses against S-protein was demonstrated following both VLA2001 and AZD1222 vaccination, whereas nucleocapsid and matrix protein specific T-cell responses were selectively demonstrated after VLA2001 vaccination owing to its distinct (whole virus, inactivated) composition. This might be of particular value for (future) SARS-CoV-2 strains with novel S-protein mutations that could evade immunity. Therefore, while the potential of VLA2001 to induce a more holistic type of (humoral and/or cellular) immunity against SARS-CoV-2 is considered of interest,

further data (particularly in terms of humoral immunity against non-S-protein targets) would be needed to substantiate this.

Furthermore, exploratory efficacy data support the primary immunogenicity findings, as numbers of individuals with COVID-19 were comparable between individuals ≥30 years of age between VLA2001 and AZD1222, with all cases being mild or moderate in severity. On the contrary, COVID-19 cases occurred at a higher frequency in subjects 18-29 years vaccinated with VLA2001. As no comparator was evaluated for this age group, this finding is difficult to interpret. However, when considering the exploratory nature of this finding and the provided immunogenicity data in this population the benefits are considered positive.

Limited data from Phase 1/2 suggest waning immunity after VLA2001 vaccination against the Wuhan/Victoria strain over time (evaluated until Day 106 post primary immunization). Similarly, waning of binding titres in Phase 3 was reported (Day 71), however, data on neutralisation at this time point are still missing and need to be provided post-marketing in order to further enhance the understanding of VLA2001 vs. AZD1222 induced immunity over time.

The data from Phase 1/2 further indicate that VLA2001 can neutralize (now mainly historic) VoCs SARS-CoV-2 Alpha, Beta, Gamma and Delta to varying, but compared to the initial Wuhan/Victoria strain, generally greatly reduced extent (with further waning immunity against VoCs over time). Notably, these data need to be interpreted with caution as deficiencies considering validation of applied methods and imputation rules were identified. As seen for other authorised vaccines, it is reasonable to expect that this reduced neutralisation capacity will also result in reduced VLA2001 efficacy/effectiveness. However, the extent of this reduction and thus clinical impact cannot be estimated by the provided data, particularly with regards to extrapolation to the Omicron variant. Data on Omicron (and Delta) neutralisation following a third dose of VLA2001 show a substantial reduction in neutralising activity of VLA2001 against these VoCs (particularly against Omicron) with unknown clinical translatability of these findings. For now, no final conclusions can be drawn in these regards and additional data are recommended to be collected in the post-marketing setting.

With increased vaccination efforts and currently unprecedentedly high SARS-CoV-2 infection rates in Europe due to the Omicron variant, it is expected that within the next months, the majority of the European population will have become SARS-CoV-2 seropositive. While it is understood that at the time of initiation of VLA2001 clinical studies this situation was completely different, it still needs to be taken into account that target population characteristics have changed since. Limited data in SARS-CoV-2 seropositive individuals (recovered from COVID-19) who received VLA2001 indicate a generally more pronounced humoral immune response compared to the seronegative counterparts. These results are considered as preliminary reassuring for the recovered population. In how far the same holds true for subjects who had received another licensed COVID-19 vaccine remains to be shown (acknowledging that this is not part of the current submission).

The short-term safety of VLA2001 is considered sufficiently well characterised in subjects between 18-55 years of age. The preliminary safety report for study VLA2001-304, which recruited 306 subjects in subjects >55 years of age, did not reveal a new safety concern. There are however a few open questions. This is relevant, since off-label use cannot be excluded. The solicited adverse reactions were mostly mild or moderate in severity, transient and self-limited. The reactogenicity after vaccination with VLA2001 was milder in terms of frequency and severity compared to the authorised AZD1222, particularly after the first vaccination. Overall, the reactogenicity profile of VLA2001 can be considered as acceptable.

Long-term safety data has to be characterised further, and it is important to analyse the full safety follow-up of the ongoing trials, which is 12 months for study VLA2001-301. An extended safety follow-up was provided (in addition to the initial submission), which did not alter the safety profile of

VLA2001. The current dataset gives no indication of vaccine-enhanced disease, a potential concern that is addressed as a potential important risk in the RMP.

There are no data on use in pregnant women, but a protective effect is anticipated. The preclinical data from the DART study were reassuring. Considering that pregnancy as such is a risk factor for severe COVID-19, and that pregnant women may additionally belong to other risk groups, vaccination may be considered on a case by case basis. There are no data in breast-feeding women. A post-authorisation pregnancy registry is planned.

There are no safety data available for immunocompromised individuals, frail patients with co-morbidities, and patients with autoimmune or inflammatory disorders. The Applicant plans to gather safety data for these populations in a post-authorisation safety study (PASS). This study will also collect data on concomitant vaccination 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 VLA2001 for the sought indication "active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18-50 years of age" is positive.

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 COVID-19 Vaccine (inactivated, adjuvanted) Valneva 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 COVID-19 Vaccine (inactivated, adjuvanted) Valneva is favourable in the following indication(s):

"COVID-19 Vaccine (inactivated, adjuvanted) Valneva is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 to 50 years of age.

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 virus (inactivated) Wuhan strain hCoV-19/Italy/INMI1-isl/2020 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.