Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

COVID-19 Vaccine Valneva suspension for injection

COVID-19 vaccine (inactivated, adjuvanted, adsorbed)

PL 43185/0002

Valneva Austria GmbH

LAY SUMMARY

COVID-19 Vaccine Valneva suspension for injection
COVID-19 vaccine (inactivated, adjuvanted, adsorbed)

This is a summary of the Public Assessment Report (PAR) for COVID-19 Vaccine Valneva. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using COVID-19 Vaccine Valneva, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

For ease of reading this product will be referred to as COVID-19 Vaccine Valneva throughout this lay summary.

What is COVID-19 Vaccine Valneva and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

COVID-19 Vaccine Valneva is a vaccine used to prevent COVID-19 caused by SARS-CoV-2.

How does COVID-19 Vaccine Valneva work?
COVID-19 Vaccine Valneva is a vaccine used to prevent COVID-19 caused by SARS-CoV-2 and is given to adults aged between 18 and 50 years.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that works against the virus so giving protection against COVID-19.

How is COVID-19 Vaccine Valneva used?
The pharmaceutical form of this medicine is suspension for injection and the route of administration is injection.

In individuals aged 18 – 50 years, COVID-19 Vaccine Valneva is administered intramuscularly as a course of 2 doses (0.5 mL each). It is recommended to administer the second dose at least 28 days after the first dose (see section 5.1).

The safety and immunogenicity of COVID-19 Vaccine Valneva in children and adolescents less than 18 years of age and in the elderly have not yet been established.

For further information on how COVID-19 Vaccine Valneva is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of COVID-19 Vaccine Valneva have been shown in studies?

COVID-19 Vaccine Valneva has been studied in healthy adults aged 30 years and older in an ongoing Phase III study to investigate the immunogenicity and safety of COVID-19 Vaccine Valneva compared to Vaxzevria, a vaccine that has been authorised based on large efficacy trials. Participants received either a 2-dose intramuscular immunisation with COVID-19 Vaccine Valneva or Vaxzevria (n=997) administered 28 days apart. The level of antibodies neutralising SARS-CoV-2 (Wuhan strain) was significantly higher after 2 doses of COVID-19 Vaccine Valneva than Vaxzevria. However, results indicated that a second dose of COVID-19 Vaccine Valneva was required to induce robust antibody levels in individuals with no SARS-CoV-2 neutralising antibodies at baseline and thereby provide protection against COVID-19.

Cellular immune response was investigated using two assays that measure the stimulation of T-cells by the spike, nucleocapsid and membrane proteins. The response against the spike protein tended to be lower for Covid-19 Vaccine Valneva compared to Vaxzevria. In contrast, a response against the nucleocapsid and membrane proteins was apparent for COVID-19 Vaccine Valneva, which was not observed for Vaxzevria as the latter is a purely spike protein vaccine.

What are the possible side effects of COVID-19 Vaccine Valneva?
For the full list of all side effects reported with this vaccine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with COVID-19 Vaccine Valneva, which have affected more than 30% of participants in clinical trials are injection site pain, tiredness, muscular pain and headache.

Why was COVID-19 Vaccine Valneva approved?
Based on the results of the immune response raised by COVID-19 Vaccine Valneva, it was concluded that COVID-19 Vaccine Valneva is effective in the prevention of COVID-19 caused by SARS-CoV-2. Furthermore, the side effects observed with use of this vaccine are considered to be typical for this type of vaccine. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this vaccine can be approved for use.

COVID-19 Vaccine Valneva has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of COVID-19 Vaccine Valneva?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for COVID-19 Vaccine Valneva. The RMP details the important risks of COVID-19 Vaccine Valneva, how these risks can be minimised, any uncertainties about COVID-19 Vaccine

Valneva (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for COVID-19 Vaccine Valneva:

Important identified risks	None
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD); failure to receive both vaccines; anaphylaxis
Missing information	Use in pregnancy and while breast feeding, in immunocompromised patients; in patients with autoimmune or inflammatory disorders, in frail patients with unstable health conditions and comorbidities e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD); use in adults >50 years of age and in children and adolescents <18 years of age; Long-term safety data; Interaction with other vaccines

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of COVID-19 Vaccine Valneva are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

A RMP and a summary of the pharmacovigilance system have been provided with this application and is satisfactory.

Other information about COVID-19 Vaccine Valneva

A Marketing Authorisation for COVID-19 Vaccine Valneva was granted in the United Kingdom (UK) on 13 April 2022.

The full PAR for COVID-19 Vaccine Valneva follows this summary.

This summary was last updated in June 2022.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for COVID-19 Vaccine Valneva (PL 43185/0002) could be approved.

The product is approved for the following indication: COVID-19 Vaccine Valneva is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in adults from 18 to 50 years of age.

Name of the active substance is COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

COVID-19 Vaccine Valneva is a purified, inactivated, and adjuvanted whole virus SARS-CoV-2 vaccine. Two adjuvants are added to increase the magnitude of vaccine-mediated immune responses. Following administration, the spike protein of SARS-CoV-2 as well as other viral surface antigens stimulate both neutralising and other functional binding antibodies, as well as cellular immune responses (Th1) directed against the spike and other surface proteins, which may contribute to protection against COVID-19.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

COVID-19 Vaccine Valneva VLA2001 has been authorised as a Conditional Marketing Authorisations (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for, COVID-19 Vaccine Valneva VLA2001. The CMA for COVID-19 Vaccine Valneva VLA2001, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-100196-PIP01-21.

At the time of the submission of the application the PIP was not yet completed as some measures were deferred

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 7 April 2022 as COVID-19 products are of major public interest.

A national marketing authorisation was granted in the United Kingdom (UK) on 13 April 2022.

II QUALITY ASPECTS

II.1 Introduction

This product consists of a white to off-white suspension for injection presented in a multi-dose vial. One vial contains 10 doses of 0.5 mL. One dose (0.5. mL) contains not less than 25 Antigen Units (AU) of inactivated SARS-CoV-2 adjuvanted with cytosine phospho-guanine (CpG) 1018 in combination with aluminium hydroxide.

In addition to SARS-CoV-2 virus (inactivated, adjuvanted, adsorbed), this product also contains the excipients: Dulbecco's phosphate buffer saline (DPBS) consisting of sodium chloride, sodium phosphate dibasic anhydrous, potassium phosphate mono anhydrous (E340), potassium chloride (E508) and water for injections; and recombinant human albumin (rHA) containing sodium, octanoate, polysorbate 80, and water for injections.

The finished product is packaged in a multi-dose vial (type I glass) with a stopper (flurotec-coated bromobutyl) and a flip-off plastic cap with aluminium seal containing 5 mL suspension for injection (10 doses of each 0.5 mL). Each vial contains 10 doses of 0.5 mL and the pack size is 10 multidose vials

Satisfactory specifications and have been provided for all packaging components. All primary packaging complies with the current regulations.

II.2 ACTIVE SUBSTANCE

rINN: None

Structure

The active substance of the SARS-CoV-2 vaccine (inactivated, adsorbed) is a purified inactivated virus, strain SARS-CoV-2 propagated in vero cells, inactivated with beta-propiolactone and purified.

SARS-CoV-2 is 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. Each viral transcript has a 5′-cap structure and a 3′ poly(A) tail.

SARS-CoV-2 virus, beta propiolactone inactivated is not the subject of a European Pharmacopoeia monograph.

Manufacture of the drug substance

Details of the sites of manufacture, testing and release have been provided and GMP certificates or a QP declaration have been provided for all relevant manufacturing sites, testing sites and QP release site. The manufacturer has provided details of the responsibilities of each facility involved in manufacture and testing including responsibilities performed by contract laboratories.

Description of manufacturing process and process controls
Vero cells are used as a substrate for the propagation of SARS-Cov-2 virus. After virus inoculation (infection of cells with the virus using production inoculum) and propagation, the viral harvest is treated, filtered, concentrated and inactivated with beta-propiolactone. Purification is performed by chromatography and the purified inactivated virus (PIV) diluted in drug substance buffer. The drug substance (DS) is further processed to final bulk vaccine. Critical process parameters and in-process controls with specifications are defined and are acceptable.

The DS batch size has been provided and is acceptable.

Control of materials
The raw and starting materials used in the manufacturing process of the active substance have been described and specifications provided. Starting materials consist of the master cell bank (MCB)/working cell bank (WCB) for production of viral inoculum, the serum-free MCB/WCB for production of the drug substance and the viral seed bank. The only raw material of animal origin is foetal bovine serum (FBS) which is obtained from BSE-free regions and is certified and traceable.

Controls of critical steps and intermediates
Details of all in-process controls and acceptance criteria for the drug substance manufacturing process have been provided. All test methods have been suitably validated and adequate control has been demonstrated.

Process validation and/or evaluation
A process performance qualification (process validation) on several full-scale production runs has been completed to demonstrate consistency in the process for manufacture of SARS-CoV-2 drug substance.

Manufacturing process development
The manufacturing process of the SARS-CoV-2 vaccine candidate is based on the upstream and downstream principles of the manufacturing process for commercial vaccine production of Valneva's approved Japanese Encephalitis Virus (JEV).

The development for small-scale manufacture for phase 1/2 of the SARS-CoV-2 manufacturing process is described, which is essentially determination and optimization of cell culture, harvest, viral inactivation and purification. The changes made to the manufacturing process from phase I/II to phase III material have been described and justified. the main change being an increase in scale. The company have performed a comparability exercise for phase 3 to commercial supply which indicated that the process adjustment did not affect the quality, potency and safety of the SARS-CoV-2 vaccine. This is acceptable.

Characterisation
Material has been characterised from batches of phase I/II, phase III and commercial material using various techniques. A comparability exercise has been performed for material used in the phase III trial and commercial scale material. This is acceptable.

Control of drug substance
An appropriate specification is provided for the active substance. Drug substance release specifications have been provided for a range of quality attributes, including general properties (for example appearance and pH) identity, purity, potency, quantity and safety.

The manufacturer has provided adequate justification for specification acceptance criteria, based on manufacturing process capability, efficacy and safety considerations.

Validation of analytical procedure
Analytical methods are suitably validated according to current scientific and regulatory requirements.

Batch analyses
Batch analysis data are provided and comply with the proposed specifications.

Reference standard
Reference materials used during the release testing of the drug substance have been provided and are acceptable.

Container closure system
No drug substance container closure system is presented as no hold time is applied to the drug substance, which is formulated immediately following sterile filtration. This is acceptable. The container system used during processing has been adequately described and justified.

Stability
No drug substance stability information are presented as no hold time is applied to the drug substance, which is formulated immediately following sterile filtration. This is acceptable.

II.3 DRUG PRODUCT

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European monographs, the United States Pharmacopeia (USP), or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided. Manufacture of the drug product consists of the aseptic formulation of the final bulk vaccine, aseptic filling of the final lot into decadose vials followed by visual inspection, labelling and packaging.

The manufacturing process is described in sufficient detail, including a good summary of the changes between the clinical phase I/II and clinical phase III process.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. The controls of critical steps and intermediates have been suitably described and the methods have been shown to be suitable as well as the parameters tested.

Finished product specification
The finished product specifications at release and shelf-life are suitable. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container closure system
The container closure system has been well described and complies with the relevant quality standards of the Ph. Eur.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 12 months for the unopened multidose vial can be accepted, with the storage conditions '12 months when stored in a refrigerator (2°C to 8°C)'.

After first opening the multidose vial, a shelf-life of 6 hours applies with the storage conditions 'Do not freeze'.

Chemical and physical in-use stability of the vaccine has been demonstrated for 6 hours in vial when stored at room temperature. After this time, the vial must be discarded.

The Covid-19 Vaccine (inactivated, adjuvanted) Valneva does not contain any preservatives. Aseptic technique should be used to withdraw doses from the multi-dose vial. From a microbiological point of view, after first dose withdrawal the vaccine should be used as soon as practically possible and within 6 hours.

Once opened and after first dose withdrawal the multi-dose vial should be marked with discarding date and time.

The unopened multi-dose vial should be stored in a refrigerator at 2°C to 8°C. Do not freeze and store vials in the original package in order to protect from light.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
The following non-clinical studies were submitted with this application:

Type of study (experiment)	Species / strain / sex	Tested substance	Dose / route
Immunogenicity (Exp4743)	Mouse BALB/c female	VLA2001 with alum (17 µg Al3+) and VLA2001 with alum (50 µg) + CpG 1018 (10 µg)	3.0 AU, 1.2 AU and 0.3 AU per mouse, 100 µL s.c.

Immunogenicity (Exp4756)	Mouse BALB/c female	VLA2001 with alum (17 µg Al3+) and VLA2001 with alum (17 µg Al3+) + CpG 1018 (10 µg)	35 AU, 11 AU and 3.0 AU per mouse, 100 µL s.c.
Immunogenicity and protection (VAC2025)	Mauritian cynomolgus macaques (Macaca fascicularis)	VLA2001 with alum + CpG 1018	35 AU/0.5 mL and 7 AU/0.5 mL i.m., 0.5 mL, right thigh.
GLP Repeat dose toxicity (No. 514449)	Rat Han Wistar	VLA2001 with alum + CpG 1018, mixed cage side	28 AU/0.4 mL
GLP Reproductive toxicology study (No. 491250)	Rat Han Wistar	VLA2001 with alum and CpG 1018	26.4 AU/0.4 mL

All safety studies were conducted in accordance with current Good Laboratory Practice (GLP).

III.2 Pharmacology

In Study 4743 mice were immunised with different formulations of the experimental vaccine: VLA2001-CoV19 USP#4 (180 AU/ml) (formulated with alum (17 µg Al^{3+}/dose) (3 groups) or with alum (17 µg Al^{3+}/dose) and CpG 1018 (10 µg/dose) (another 3 groups): mice were given antigen doses of 0.3, 1.2 or 3.0 AU (antigen units). Mice in control groups were given the same amount of adjuvants (one received both adjuvants and the other received only alum) and excipients as contained in VLA2001-CoV19 USP#4.

Sera taken on days 28 and 35 were analysed and endpoint titres were determined with a cut-off set to 3-fold the blank. The immune responses in mice for different doses and adjuvant formulations were assessed with an IgG ELISA. Plates were coated with either the S1 part or the receptor binding domain (RBD) of the spike glycoprotein or with the nucleocapsid protein.

An increase in titres was observed for sera taken on Day 35 for both the spike glycoprotein and nucleoprotein as compared to Day 28. A significant increase in the titres against the S1 and RBD parts of the spike glycoprotein were obtained for VLA2001-CoV19 USP#4 formulated with alum and CpG 1018 as compared to vaccine formulated with alum alone. Further, a significant increase in the titres against the S1 and RBD parts of the spike glycoprotein was obtained for VLA2001 formulated with aluminium hydroxide and CpG 1018 as compared to vaccine formulated with aluminium hydroxide alone. No dose response against the N protein was seen in the presence of alum and CpG 1018, but in the presence of alum a weaker immune response was seen at the lowest dose. For all 3 doses of VLA2001-CoV19 USP#4, an increased immune response as determined by ELISA was seen for VLA2001-CoV19 USP#4 when formulated with CpG 1018 and alum as compared to alum alone, indicating a possible dose sparing effect for the addition CpG 1018.

In Study 4756 mice were dosed with VLA2001 formulated with alum or with alum and CpG 1018, using higher doses of the inactivated SARS-CoV-2 virus. These higher doses of antigen were the same as those used in the initial clinical trial and were 3, 11 and 35 AU; doses of adjuvants were the same as used in the first experiment in mice (17 µg Al^{3+} and 10 µg CpG 1018/dose).

An increase in immunogenicity was observed for vaccine in the presence of alum and CpG 1018 as compared to alum only. Immunogenicity data were very similar across the S1 and RBD subunits of spike glycoprotein and the pre-fusion stabilised trimeric spike protein. For these 3 coating antigens, VLA2001 formulated with alum and CpG 1018 showed increased immunogenicity as compared to VLA2001 formulated with alum only. No clear dose response against N-protein was observed.

With regard to IgG subclass immune responses, the addition of CpG 1018 to VLA2001 induced a Th1-skewed immune response in mice (more IgG2a), whereas with alum only the responses was Th2-skewed (more IgG1).

Neutralising capacity of the mouse antibodies was tested in the pseudovirus-based assay. When serial dilutions of mouse immune serum pools taken from day 35 were incubated with pseudovirus, the serum pool from mice given 35 AU with alum and CpG 1018 generated the strongest neutralising titres (NT50 value of 246). VLA2001 formulated with alum alone at the same antigen dose (35 AU) generated a NT50 of 52. Thus, the high dose of VLA2001 at 35 AU formulated with alum and CpG 1018 generated an immune response with approximately a 5-fold higher neutralising titre than the VLA2001 formulated only with alum, which is an increase in the same range as seen for the immune response measured by ELISA against the spike protein.

Overall, the results from these two immunogenicity studies in mice show that VLA2001 induced antibodies against SARS-CoV-2 that were at least similar in magnitude as published data for other inactivated vaccines. The combination of alum + CpG 1018 showed a synergistic effect in mice, generating higher antibody titres than alum only formulations with a shift in the immune response towards Th1 (IgG2a) over Th2 (IgG1) observed by analysis of IgG subclasses.

In Study 514449 an intermittent repeat-dose (twice weekly [days 1, 15, 29]) intramuscular (IM) toxicity study, VLA2001 was highly immunogenic in the rat. After receiving a single-dose (28 AU/0.4 ml/dose) of the VLA2001, there were low but detectable antibody titres. Antibody titres increased significantly to a plateau following the 2nd immunisation. A 3rd immunisation did not further increase antibody titres.

In Study VAC 2025FR the immunogenicity and efficacy of VLA2001 adjuvanted with CpG 1018, against an experimental SARS-CoV-2 challenge was evaluated after two doses in cynomolgus monkeys.

24 male cynomolgus monkeys were included in this study and divided into 3 groups as described in the table below. Animals received either high dose (35 AU)) or medium dose (7 AU) VLA2001 vaccine adjuvanted with alum and CpG 1018 or buffer (DPBS) as control, at Days 0 and 21 by the IM route (0.5 mL), into the right thigh. All animals were exposed to 10(5) PFU SARS-CoV-2 by intranasal (0.25 mL per nostril) and intratracheal (4.5 ml into trachea) routes simultaneously on Days 47 (cohort 1) or 49 (cohort 2) post first immunisation.

Table 1: Experimental design of Study VAC2025

Groups	n	Immunogen	Route, Dose, Site	Immunization Schedule	Challenge, Route, Volume
Control	8	DPBS	IM, 0.5 ml, right thigh	2 Cohort (cohort 1 and cohort) immunizations at Days 0 and 21	SARS-CoV-2 intranasal (0.25 ml/nostril) +intratracheal (4.5 ml) at Week 7 post first immunization
Vaccinated High dose	8	VLA2001+ alum and CpG 1018	IM, 35 AU/ 0.5 ml, right thigh		
Vaccinated Medium dose	8	VLA2001+ alum and CpG 1018	IM, 7 AU/ 0.5 ml, right thigh		

CpG=cytosine phospho-guanine; DPBS=Dulbecco's phosphate-buffered saline; IM=intramuscular.

No changes in body weight were observed during the immunisation phase after dosing with VAL2001 and prior to the viral challenge. At the injection site, one monkey in the control group on day 22 was noted to have slight erythema which was not present on day 23. Vaccinated monkeys showed no oedema or erythema at the injection site.

In haematological parameters, transient monocytosis was seen in control monkey CGE022 (Control group) at day 28. Neutrophilia was observed for monkey CGC037 (given the lower dose of VLA2001) at day 14 and for control monkey CGC033 at day 35. Overall, there was no consistent effect of VLA2001 seen on haematological parameters.

Cellular responses were evaluated by IFN-γ ELISPOT assays and by intracellular cytokine staining. Analysis of T cell responses via these methods suggest an induction of a Th1-biased CD4+ T cell response following administration of VLA2001 vaccine.

No major changes were observed during the whole challenge phase for body weight and rectal temperature although transient temperature changes were noted. No differences were observed between vaccinated and unvaccinated groups in terms of clinical signs/behaviour of animals and haematological assessments.

Administration of VLA2001 vaccine reduced both the number of animals with detectable genomic and subgenomic viral RNA and the magnitude of these RNAs, suggesting that administration of the vaccine suppressed SARS-CoV-2 replication in the upper and lower respiratory compartments post challenge.

No differences in the presence of lung lesions were observed between the unvaccinated and vaccinated groups.

Assessment of the cytokine response showed that the vaccine reduced pro-inflammatory cytokine production, potentially by preventing viral infection.

At Day 7 post exposure, no statistical difference in IFN-γ production after peptide stimulation of PBMC was observed between the unvaccinated and vaccinated groups.

1 week after SARS-CoV-2 exposure, vaccinated monkeys showed CD154+ CD4+ T cells responses, but no CD137+ CD8+ T cells responses. At day 7 post exposure, an increase in N-specific IL-2- and TNF-α- producing CD4+ T cells was seen in both vaccinated groups compared to controls. An increase in S2-specific IL-2- and TNF-α- producing CD4+ T cells was seen as well. Only vaccination with the higher dose showed an increase in RBD-specific IL-2-producing cells, compared to controls. These increases indicate the induction of a Th1-biased immune response mainly mediated by IL-2 and TNF-α.

Analysis of T cell responses after SARS-CoV-2 exposure showed a Th1-biased CD4+ T cell response in vaccinated monkeys. The immune response to challenge in control monkeys was also Th1-biased.

For IgG responses, similar results were obtained targeting all three viral proteins: SARS-Cov-2 spike protein, SARS-Cov-2 nucleoprotein, and SARS-CoV-2 RBD. In controls, mean IgG concentrations were similar throughout the study and in both groups given VAL2001, mean IgG concentrations were similar to controls at baseline and on day 0. In monkeys given VAL2001, mean IgG concentrations increased from study days 14 to 28 and from study day 28 to day 7 post exposure, similar concentrations were seen in both groups. From day 14 post-exposure to the end of the study, there were higher IgG concentrations compared to controls in monkeys given VAL2001 with no difference between these two groups.

In general, neutralising antibody responses were lower than the lower limit of quantification (LLQ) at days 0 to 21 in all groups and increased between days 28 and 35 in the vaccinated groups.

Histological assessments found that vaccinated groups showed significantly less pulmonary lesions at days 7 and 15 than the non-vaccinated group.

In summary, VLA2001 at antigen doses of 7 and 35 AU adjuvanted with aluminium hydroxide and CpG 1018 elicited an anti SARS-CoV-2 IgG response against spike protein, nucleoprotein and the receptor binding domain of the spike protein, with no difference between the doses. This was a neutralising response against SARS-CoV-2 and for this neutralising response, there was a significant difference between the two doses of vaccines with a greater response with the higher dose. The company concluded that VLA2001 was safe with monkeys showing an immune response to vaccine that neutralised SARS-CoV-2 with a Th1-biased CD4+ T cell response against spike glycoprotein and against nucleocapsid. The vaccine reduced viral replication in the respiratory tract and reduced lung histopathology scores and prevented development of mild COVID-19 clinical signs in monkeys.

Safety pharmacology
Dedicated safety pharmacology studies were not conducted with VLA2001; such studies are not essential for vaccines.

Pharmacodynamic drug interactions
No specific pharmacodynamic studies to evaluate drug interactions have been conducted

III.3 Pharmacokinetics
No pharmacokinetic studies were performed which is acceptable.

III.4 Toxicology
No single-dose toxicity studies were performed which is acceptable.

Study 514449 was a repeat dose intramuscular toxicity study to determine the potential toxicity of VLA2001, and to evaluate the potential of reversibility for any of the findings.

VLA2001 was given by IM injection on three occasions at 2 weekly intervals (Days 1, 15, 29) to Han Wistar rats. The study involved 60 rats in total, that were divided in two groups (8 subgroups) as presented in the table below. Animals were given two IM injections into a hind limb (2 x 0.2 ml) on each dosing occasion.

Table 2: Repeat dose intramuscular toxicity study of VLA2001 – experimental design

Group Number	Treatment	Dose level (AU /dose)	Dose volume (ml)	Number of animals			
				Main study		Recovery	
				Male	Female	Male	Female
1	Control (0.9% (w/v) sodium chloride solution	0	0.4	10			
2	VLA2001+CpG1018	28	0.4	10	10	5	5
					10	5	5

The following parameters were evaluated in the study: mortality, clinical observations, body weights, food consumption, body temperature, ophthalmology, clinical pathology parameters (haematology, coagulation, clinical chemistry, and urinalysis), acute phase proteins (APP): α (1)-acid glycoprotein (AGP) and α-2 macroglobulin (A2M) analysis, immunogenicity analysis, organ weights and macroscopic and microscopic examinations.

Two deaths occurred (one in control group and one in vaccine group); each were reviewed in detail and were deemed not likely related to vaccine administration. There were no clinical signs of systemic toxicity considered related to vaccine administration however swelling at administration site was reported in four vaccine-treated animals.

In vaccine-treated animals, a slight bodyweight loss was observed on days 2, 16 and 30 (following administration) compared to the control group. Vaccine-treated animals also had a lower food intake in the 4-day period after each vaccine administration, compared to the control group. Transitory higher body temperature was reported in VLA2001-treated animals 4h post-dose, when compared with controls and values recorded pre-dose and pre-treatment. The recovery was noted at 24 hours post-dose.

There were no ophthalmological findings in in VLA2001-treated animals. VLA2001 clinical pathology findings included differences in white blood cell numbers, lower platelet numbers, prolongation of activated partial thromboplastin time and higher fibrinogen, lower triglycerides, total protein, calcium and differences in plasma proteins (lower albumin and higher globulin), when compared with controls. There were also higher inflammatory proteins noted the day after dosing, when compared with controls. These effects had recovered or lessened at Day 51.

Plasma concentrations of α1-acid glycoprotein and α2-macroglobulin were higher in rats given VLA2001 than controls the day after injection, but then showed partial recovery by day 8 after the first dose then full recovery 3 weeks after the second dose. This was interpreted as an inflammatory response.

After receiving a single dose of the VLA2001 vaccine, there were low but detectable antibody titres. Antibody titres significantly increased and reached a plateau following the 2nd immunisation. The 3rd immunisation did not further increase antibody titres. No antibodies were detected in the control rats (not given VLA2001).

At macroscopic pathology on day 31, there was enlargement of the iliac lymph nodes in 1 of 15 female rats given VLA2001. On day 51, there was enlargement of the lumbar lymph nodes in 1 of 14 male rats given VLA2001. On both days 31 and 51, spleen and liver weights were raised in rats given VLA2001. A summary of the microscopic findings is given in the table below.

Table 3: Summary of microscopic findings

Organ/tissue	Day 31	Day 51
Administration site	Necrosis/inflammation of the myofiber (mild to moderate) was observed with higher incidence and severity than control sites (minimal)	Minimal to moderate necrosis/inflammation of the myofiber was still observed at the end of the recovery period. Moderate was the highest severity for this finding in both terminal euthanasia and recovery euthanasia. Necrosis/inflammation of the myofiber with moderate severity was noted with relatively lower incidences (range 1/5 to 3/4; 20-75%) in recovery euthanasia compared with terminal euthanasia (range 7/10 to 10/10; 70-100%), indicating partial recovery
Sciatic nerve	Minimal to mild inflammation of the sciatic nerve (6/20)	Minimal inflammation of the sciatic nerve in one female (1/5) and one male (1/4)
Femorotibial joint	Minimal inflammation (5/20) were observed in males and females administered VLA2001	Minimal inflammation of the femorotibial joint in one female (1/5) and one male (1/4)
Spleen	Minimal increased cellularity in the white pulp was observed in males and females (10/20) administered VLA2001	Minimal increased cellularity in the white pulp
Lymph nodes	Popliteal, iliac, inguinal lymph nodes of some animals of both sexes were found for minimal to mild increased cellularity of lymphoid and plasma cells was observed	Minimal to mild increased cellularity of lymphoid and/or plasma cells was reported in popliteal and lumbar lymph nodes, showing partial recovery

Genotoxicity
No genotoxicity studies were performed which is acceptable.

Carcinogenicity
No carcinogenicity studies were performed which is acceptable.

Reproductive and developmental toxicity
Study 491250 was carried out to determine the potential toxicity of VLA2001 when given before and after pregnancy via IM injection to rats during pre- and post-natal development. Females were assigned to one of two groups, a littering group who were followed to lactation day 21 (i.e. 21 days after the pups were born) and an embryofoetal developmental group who were followed to gestation day 21. Rats received VLA2001 at dose levels of 0 (control) and 26.4 AU/0.4 mL IM on day 1 (22 days prior to pairing), day 14 (14 days after the second dose/9 days prior to pairing), and gestation day 6.

There were no unscheduled deaths and no clinical signs of toxicity: all findings (e.g. fur loss, skin scab) were considered incidental. There were no effects of VAL2001 on pregnancy or ovarian and uterine parameters, and no differences in mean fetal or mean placental weights. No effects of VAL2001 were seen on delivery, gestation length or reproductive parameters. There were no pup deaths in the study and no effect of VAL2001 was seen on pup body weights or on markers of pup development. In the dams, on macroscopic pathology, there were no findings of toxicity and there were no effects of VAL2001 on fetal development.

VLA2001 was shown to be immunogenic with no booster response seen after the third dose. In the embryofoetal development phase, antibodies were detected in the fetuses, suggesting that SARS-CoV-2 specific antibodies are passed on to the fetuses. Antibody concentrations in the foetuses were ~10-fold lower than in dams. In the littering phase, slightly higher

antibody titres were seen in the pups, suggesting pups could take up SARS-CoV-2 specific antibodies in milk from their mothers.

Overall, VLA2001 appeared well tolerated by the dams and did not cause toxicity to development: no adverse effects were noted in the developing foetuses or the pups.

Local tolerance
No local tolerance studies were performed which is acceptable.

Other toxicity studies
No other toxicity studies have been done.

III.5 Ecotoxicity/Environmental Risk Assessment
A Environmental Risk Assessment has not been submitted with this application, which is acceptable. Inactivated SARS-CoV-2 virus is not a genetically modified organism. In line with regulatory guidance, applicable in the UK (EMEA/CHMP/SWP/4447/00 Corr 2 guideline on the Environment Risk Assessment (ERA) of medicinal products for human use, of 01 June 2006), vaccines are exempt from a requirement for an environmental risk assessment.

III.6 Discussion on the non-clinical aspects
The data provided are sufficient to characterise the profile of this vaccine for use to prevent Covid-19 disease on contact with SARS CoV-2 virus.

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The immunogenicity and safety data supporting this marketing authorisation have been generated by two ongoing studies, presented below. COVID-19 Vaccine Valneva is referred to as VLA2001 in this clinical review.

- Study VLA2001-201: Phase I/II dose finding trial in healthy individuals 18-55 years old to select the VLA2001 dose for further clinical trials
- Pivotal Study VLA2001-301: Phase III superiority trial on the immunogenicity and safety of VLA2001 in adults (≥ 18 years) compared to the already licensed vaccine AZD1222 (Vaxzevria)

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics
No pharmacokinetic data have been submitted for this application and none were required.

IV.3 Immunogenicity

Bioanalytical assays
The validation (or qualification) reports for each bioanalytical assay have been provided. These include the neutralising assay (live microneutralisation assay), binding anti-spike antibody assay (ELISA), IFN-γ ELISpot assay, and intracellular cytokine staining assay. Overall, the methods were considered acceptable and fit for purpose.

Study VLA2001-201
The Phase I dose-escalating trial tested 3 antigen doses (3, 7, 35 AU/dose). Both neutralising

and binding antibody levels remained very low in most subjects after the first injection and were only significantly elevated 2 weeks after the second injection at all doses tested with a clear dose-response relationship. A substantial decrease of these antibodies was observed after 12 weeks at all dose levels with a similar slope; at that point in time, the seroconversion (≥4-fold increase from baseline) rates were 22%, 29% and 60%, at the low, medium and high dose, respectively. Based on these data, the high dose was chosen given that reactogenicity was similar at all dose levels.

Phase III Study VLA2001-301

Method

The trial enrolled healthy subjects ≥ 18 years old or medically stable for 3 months prior to randomisation. Approximately, 3,000 participants, 30 years of age and older, were randomised in a 2:1 ratio to receive 2 intramuscular doses of either VLA2001 (n=2,000) or AZD1222 (n=1,000). This age restriction was considered necessary in view of the benefit/risk balance of AZD1222 in young adults and, therefore, an additional cohort of 1,000 participants enrolled subjects 18 to 29 years of age, who all received VLA2001.

Two vaccine injections were administered intramuscularly in the deltoid region of non-dominant arm, preferably 28 days apart.

The co-primary endpoints were the geometric mean titre (GMT) and the seroconversion (defined as 4-fold increase from baseline) of SARS-CoV-2-specific neutralising antibodies on Day 43 (two weeks after the second vaccination). The study was designed and powered to demonstrate superiority of the GMT elicited by VLA2001 as compared to AZD1222 using a margin of > 1-fold for the GMT ratio and non-inferiority of the seroconversion rate (SCR) elicited by VLA2001 as compared to AZD1222 using a non-inferiority margin of < 10% for the seroconversion rate difference.

Other immunogenicity endpoints included anti-spike binding IgG antibodies and T-cell responses measured in peripheral blood mononuclear cells (PBMC) after in vitro stimulation with SARS-CoV-2 antigens using ELISpot (IFNγ) or intracellular cytokine staining (IL-2, IL-4, IL-5, IL-13, TNFα, IFNγ).

Results

In total, 2,975 participants were randomised to receive either VLA2001 (n=1,978) or Vaxzevria (n=997). Median age was 34 and 35 years, respectively; overall, less than 1% of the population studied was older than 50 years. Both arms included slightly more male (57%) than female (43%) participants and 93% were White. The vast majority of participants were seronegative for COVID-19 at screening using a rapid antibody test (94.5% in the VLA2001 arm and 96.8% in the Vaxzevria arm). The second vaccine dose was administered with a median interval of 29 days (range 23 to 64) after the first dose.

Samples from 990 participants (n=492 VLA2001 and n=498 Vaxzevria) with no neutralising antibodies at baseline were considered in the primary immunogenicity analysis. The trial met its co-primary endpoints as shown in the table below.

Table 4: SARS-CoV-2 neutralising antibodies on Day 43 (immunogenicity population)

Parameter	VLA2001 (n=492)	Vaxzevria (n=498)	Comparison
GMT			
N	492	493	
GMT (95% CI)	803.5 (748.48, 862.59)	576.6 (543.59, 611.66)	
Median	867.0	553.0	
Min, Max	31, 12800	66, 12800	
GMT Ratio (95% CI)			**1.39 (1.25, 1.56)**
p-value			**<0.0001**
SCR			
N	456	449	
SCR n (%)	444 (97.4)	444 (98.9)	
95% CI	(0.954, 0.986)	(0.974, 0.996)	
Difference 95% CI			**-0.015 (-0.033, 0.002)**

Similar results were found in other analysis sets (per protocol and full immunogenicity set).

Importantly, before the second vaccine dose, i.e., 4 weeks after the first dose (Day 29), GMTs (95%CI) measured in a subset of 235 samples were 68.6 (60.3, 78.0) after VLA2001 and 225.7 (201.4, 253.0) after Vaxzevria, with a GMT ratio (95% CI) of 0.30 (0.25, 0.37). These results indicate that the second dose of VLA2001 is necessary to induce robust antibody levels in baseline negative participants and thereby provide protection against COVID-19.

The GMTs of anti-spike binding IgG antibodies showed similar trends to neutralising antibodies at Days 29 and 43 as shown in the table below.

Table 5: GMC (ELU/mL) of S-protein IgG (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

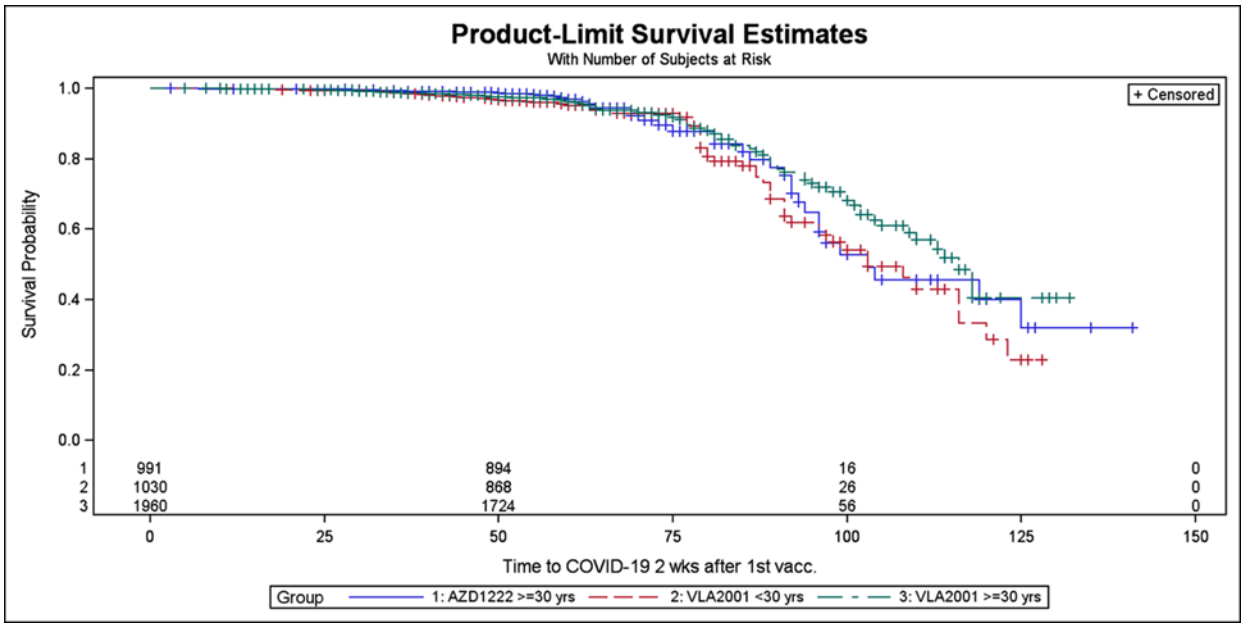
S-protein IgG concentration was determined in samples from a subset of the younger adult cohort < 30 years (N=210). GMC was significantly superior (30% higher) in the younger adult group (3724.1; 95%CI 2698.5, 6767.4) compared to the older adult group on Day 43.

A quantitative (SFU/2.5×10^5 PBMC) and qualitative evaluation (% of samples with SFU ≥ 6) of the IFNγ ELISpot was provided. The results showed a significantly higher response in subjects vaccinated with AZD1222 against the S-protein, especially the N-terminus (that includes the RBD), compared with those vaccinated with VLA2001. This response was already apparent after the first dose with AZD1222 (but not with VLA2001). In contrast, a weak response against the nucleocapsid protein was only detected with VLA2001. In addition, preliminary ICS data were provided suggesting that VLA2001 induces a Th1-skewed cellular response.

IV.4 Clinical efficacy

The number of COVID-19 cases was recorded during the study as an exploratory endpoint. Preliminary data showed no difference in the incidence of symptomatic COVID-19 cases in the informative part of the efficacy curves (approximately 2 months).

Figure 1: Kaplan-Meier curve for time to symptomatic COVID-19 onset 14 days after first vaccination



IV.5 Clinical safety

Local and systemic reactogenicity

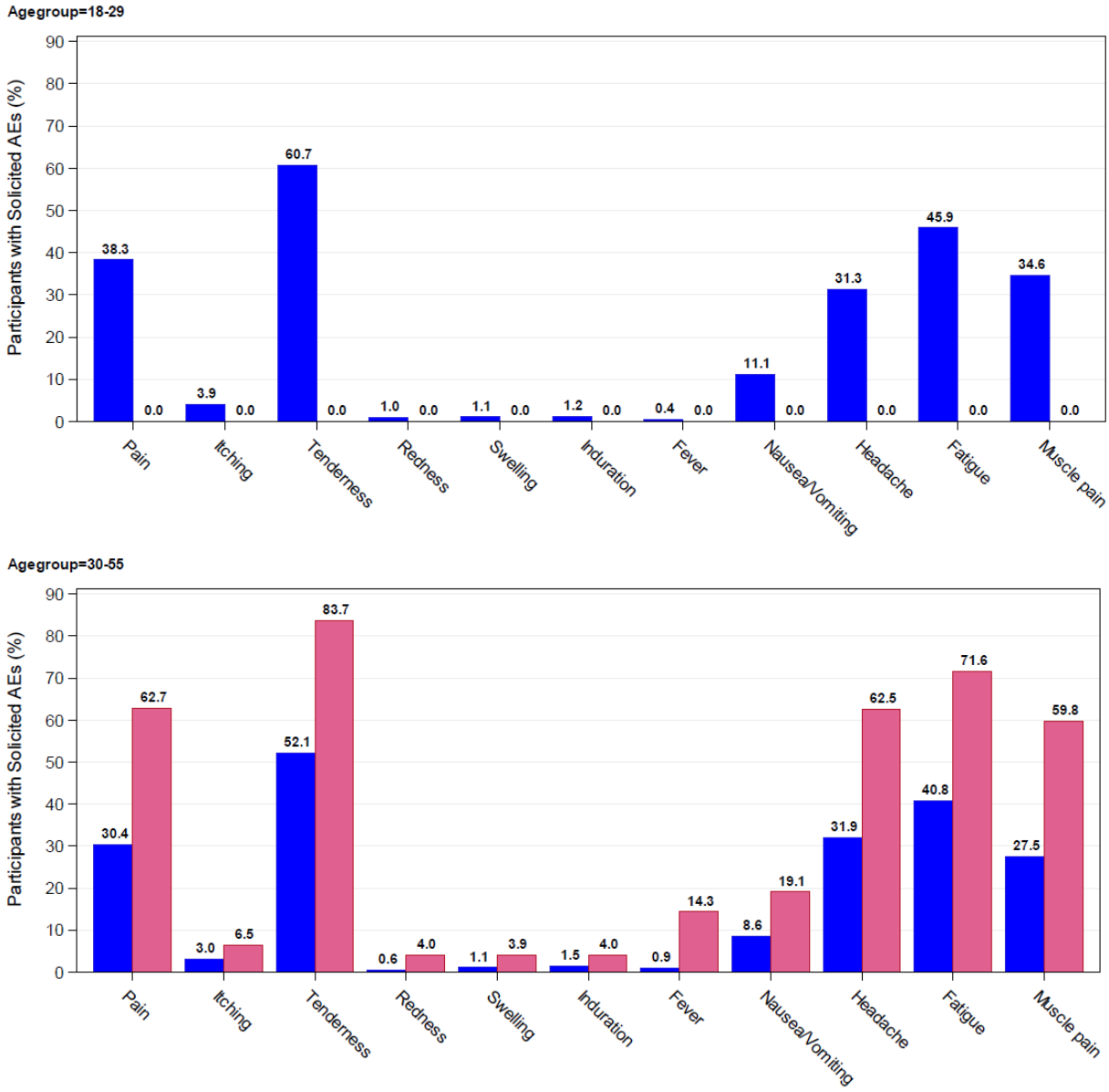
In study VLA2001-301, 3195/4012 participants (79.6%) reported at least one solicited injection site reaction within 7 days after any dose. The majority of participants (2831/4012; 88.6%) reported mild reactions, 355/4012 participants (11.1%) moderate reactions and only 9/4012 participants (0.3%) had severe reactions: 1 in the VLA2001 arm (pain) and 8 in the AZD1222 arm (redness, pain/tenderness, swelling, induration). The median duration was longer in the AZD1222 arm (2 days) than in the VLA2001 arm (1 day) in subjects ≥ 30 years; it was 2 days in the VLA2001 group 18-29 years.

Overall, 3093/4012 participants (77.1%) reported at least one solicited systemic reaction. The majority of participants (2119/3093; 68.5%) reported mild reactions, 904/3093 (29.2%) reported moderate reactions and only 70/3093 participants (2.3%) had severe reactions: 0.5%

and 1.0%, respectively, in the VLA2001 (age < 30 years) and VLA2001 (age ≥ 30 years) groups and 4.6% in the AZD1222 arm. Severe fever was reported in 7 subjects (0.4%) in the VLA2001 (age ≥ 30 years) arm and 10 subjects (1.0%) in the AZD1222 arm. The median duration of systemic reactions was 1 day in all groups.

The incidence of solicited local and systemic reactions is presented hereafter by injection for the various age groups:
. 18-29 years (N=1026 VLA200)
. 30-55 years (N=1930 VLA2001/984 AZD1222)
. > 55 years (N=19 VLA2001/5 AZD1222).

Figure 2: Solicited reactions after the first dose



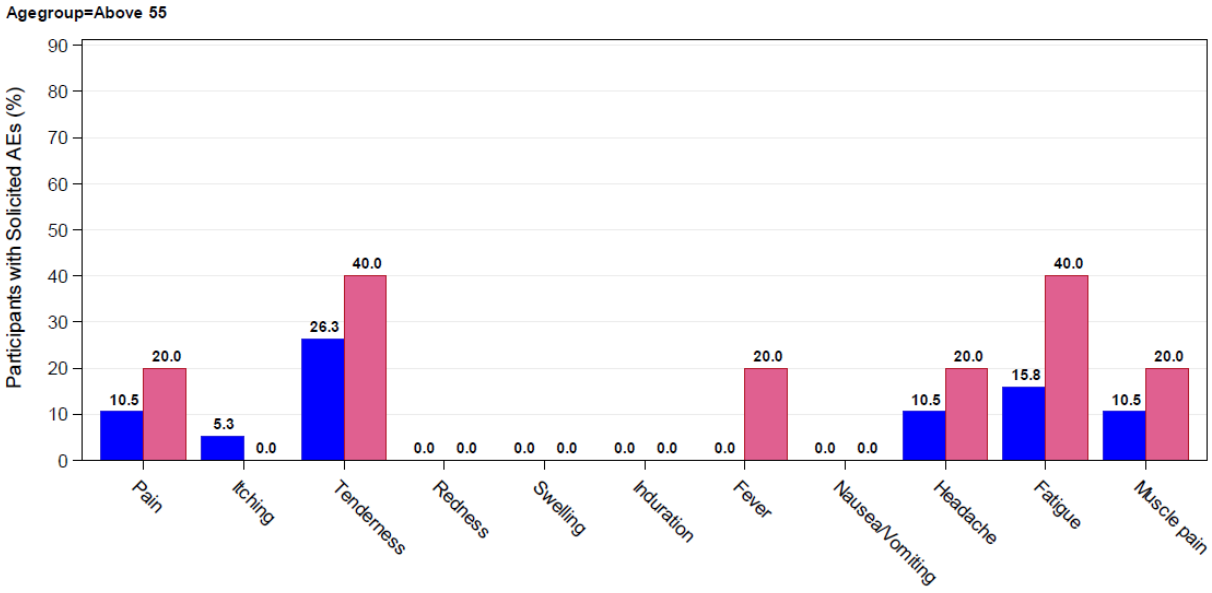
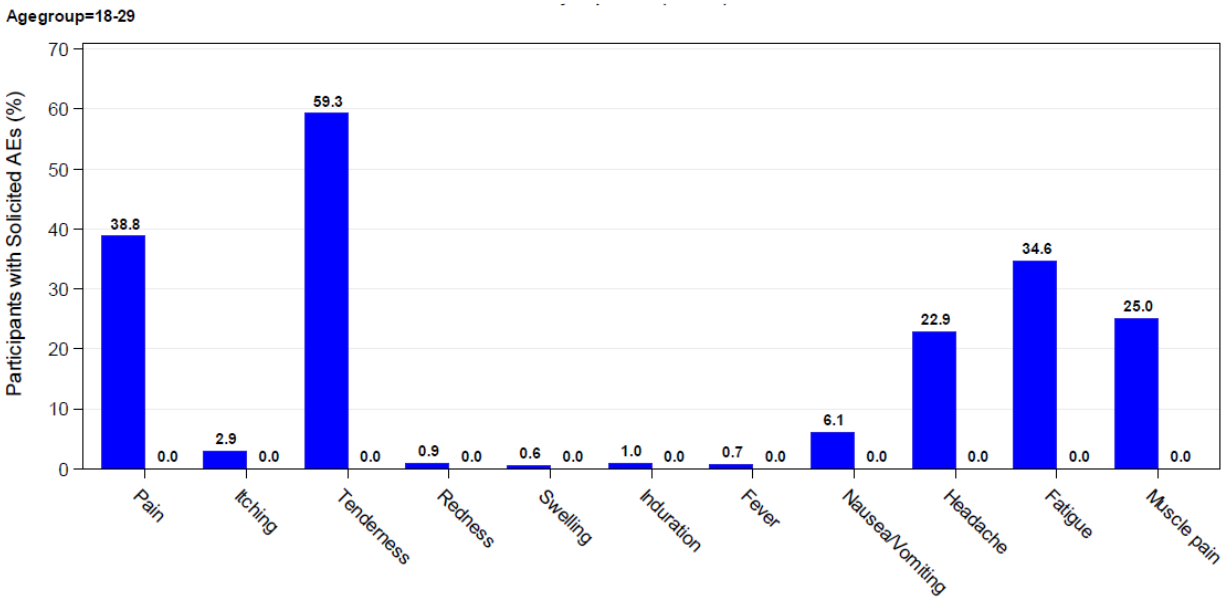
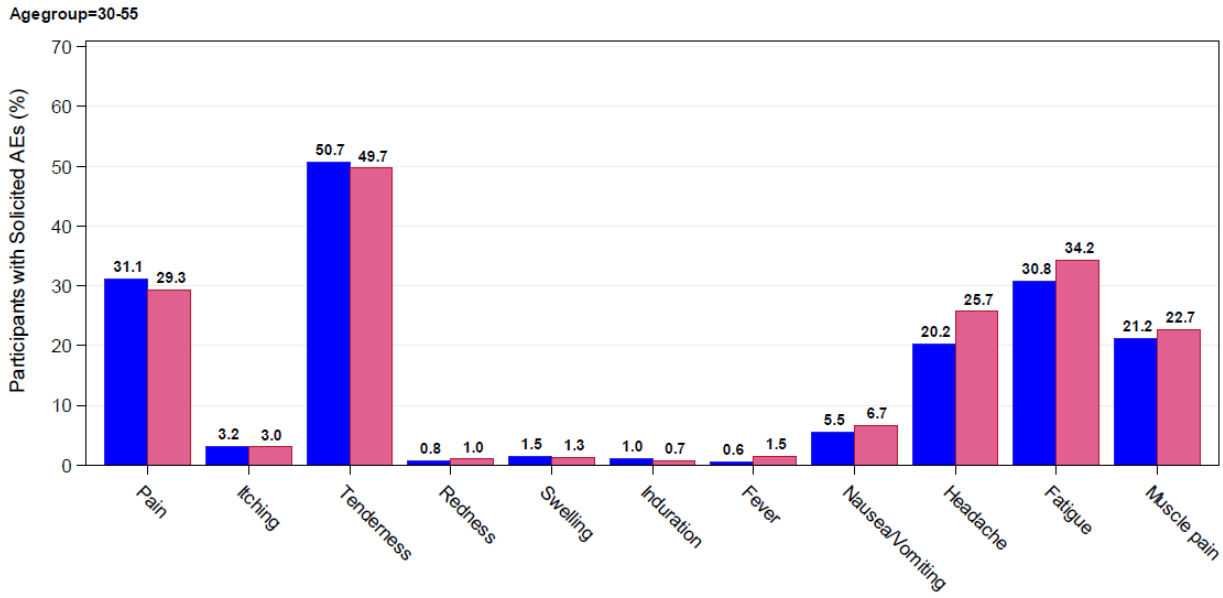
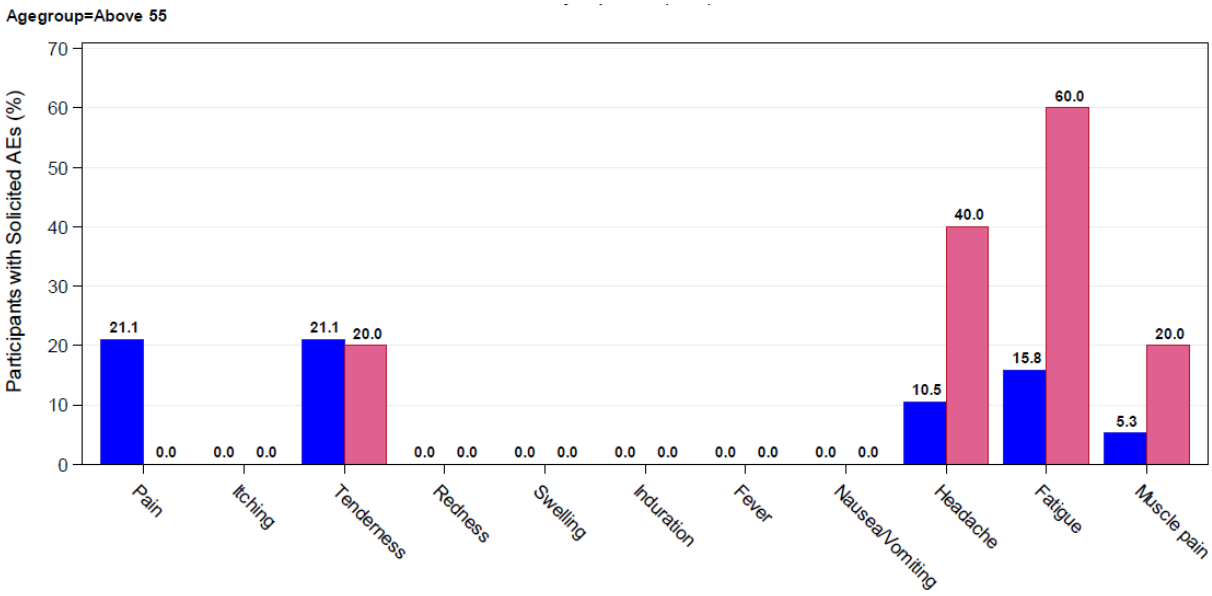


Figure 3: Solicited reactions after the second dose







Unsolicited adverse events

In study VLA2001-301, unsolicited AEs were evaluated at Day 43 and for the entire study (cut-off date: 11 Aug 2021). Overall, 1437/4012 participants (35.8%) reported an unsolicited AE over the entire study. Their incidence was similar among treatment arms: 35.2% in the VLA2001 (age <30) arm, 35.0% in the VLA2001 (age ≥30) arm, and 38.2% in the AZD1222 arm.

The most frequently reported AEs overall were oropharyngeal pain (4.1%), headache (3.4%), dizziness and diarrhoea (2.0%), cough (1.8%), and fatigue (1.7%). The incidence rate of these AEs was broadly similar across all arms, or slightly higher in the AZD1222 arm. These AEs are likely related to concurrent infections or reflecting vaccine reactogenicity.

Severe unsolicited AEs occurred in less than 1.5 % of the subjects in all vaccine arms.

Overall, 495/4012 participants (12.3%) reported at least one unsolicited AE that was considered vaccine-related. The most frequently events reported overall were oropharyngeal pain (50/4012 participants, 1.2%) and dizziness (39/4012, 1.0%). Most were reported until Day 43.

For the entire study, 18 of 4012 participants (0.4%) reported 22 SAEs but none was considered related to the vaccination:

- 2 participants (0.2%) in the VLA2001 (age 18-29 years) arm
- 10 participants (0.5%) in the VLA2001 (age ≥30 years) arm
- 6 participants (0.6%) in the AZD1222 arm.

Overall, 8/4012 participants (0.2%) reported an AESI:

- in 6 participants having received VLA2001: ageusia and/or anosmia (3), type 1 diabetes mellitus (1), alopecia areata and psoriasis (1), embolism (1); none was considered related to the vaccine;
- in 2 participants having received AZD1222: facial paralysis (mild, resolved) and pruritic rash (mild, resolving), both considered related to the vaccine.

A total of 3 subjects did not receive the second dose due to an AE, all in the VLA2001 arms, but only one was vaccine-related (generalised urticaria, which resolved within 2 days).

An updated safety analysis, corresponding to a median duration of follow-up of 126 days after the second dose is summarised in the table below. It did not reveal any new safety concern.

Table 6: Overall AE summary (cut-off date: 14 Oct 2021)

Characteristics	VLA2001 Age <30 years N=1040 n (%)	VLA2001 Age ≥30 years N=1977 n (%)	AZD1222 N=995 n (%)
Participants with any AE until Day 43	963 (92.6)	1755 (88.8)	976 (98.1)
Participants with any AE for entire study	974 (93.7)	1794 (90.7)	979 (98.4)
Participants with any treatment related AE until Day 43	955 (91.8)	1719 (86.9)	975 (98.0)
Participants with any treatment related AE for entire study	955 (91.8)	1723 (87.2)	976 (98.1)
Participants with any serious AE until Day 43	2 (0.2)	6 (0.3)	3 (0.3)
Participants with any serious AE for entire study	7 (0.7)	14 (0.7)	10 (1.0)
Participants with any medically attended AE until Day 43	78 (7.5)	138 (7.0)	72 (7.2)
Participants with any medically attended AE for entire study	134 (12.9)	244 (12.3)	118 (11.9)
Participants with any AESI until Day 43	2 (0.2)	1 (0.1)	2 (0.2)
Participants with any AESI for entire study	3 (0.3)	4 (0.2)	2 (0.2)

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance measures have been proposed:

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
A non-interventional post-authorisation safety study (PASS) of adverse events of special interest among recipients of the COVID-19 Vaccine Valneva in Europe. [Study countries: France, Germany, Italy, Austria – study countries will be adapted to the schedule of vaccine launch in Europe and will depend on immunization campaigns]	**Primary:** To estimate the incidence of adverse events of special interest (AESIs) that are medically attended following the administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the real-world immunisation setting **Secondary:** - For each AESI, to compare the observed incidence rate with the expected rate in the population - To quantify the association between COVID-19 Vaccine (inactivated, adjuvanted) Valneva and each AESI for which a risk window after vaccination can be defined, using estimates of relative risk - To describe the use of COVID-19 Vaccine (inactivated, adjuvanted) Valneva and the risk of AESIs in frail patients with comorbidities (e.g. chronic obstructive	• AESIs listed in the RMP and defined in ACCESS and SPEAC/Brighton Collaboration, and that have led to a medical visit or hospitalization • Incidence rate of each AESI and 95% confidence interval will be derived • Observed event rate to be compared with expected event rate as per ACCESS program guidelines • Where feasible, a self-controlled risk interval analysis or self-controlled case series analysis will be conducted to estimate the association between exposure and AESI occurrence	11,250 vaccinees expected to complete 18 months of follow-up, assuming 25% attrition rate for initial cohort of 15,000 vaccinees	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).

	pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders, use in patients with autoimmune or autoinflammatory disorders), in individuals aged > 55 years, as well as interaction with other vaccines.			
Pregnancy Registry of Women Exposed to COVID-19 Vaccine (inactivated, adjuvanted) Valneva immediately before or during Pregnancy as part of the C-VIPER Registry Consortium (Pregistry-sponsored) [Study countries: not stated]	• To estimate the risk of the most common obstetric outcomes, COVID-19 neonatal outcomes, and COVID-19, among pregnant women exposed to COVID-19 Vaccine 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 from the International Registry of Coronavirus Exposure in Pregnancy (IRCEP)	• Most common obstetric outcomes - pregnancy losses, placentation disorders, gestational diabetes, premature delivery • COVID-19 neonatal outcomes - congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission • COVID-19 • Pregnancy-related AESIs – pre-term labour, stillbirth, maternal or neonatal death, pre-eclampsia or eclampsia, haemorrhage, fetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low birth weight, neonatal renal failure, chorioamnionitis, major structural congenital malformations	• Women >/=18 years of age will be followed through the end of their pregnancy and until the infant reaches 12 months of age • A minimum of 500 women receiving the vaccine, including 200 exposed during the first trimester, will be recruited	• Total duration of the study will be 5 years. • Data on pregnancy, neonatal and infant outcomes will be included in the interim reports as soon as available. • The first two years will include, primarily, enrolment of pregnancies. the third and fourth years will involve follow-up of pregnancies and newborns; and, the final year, will be for data analyses and publications. • A final report will be prepared at the end of the study
Clinical Study VLA2001-201	To evaluate the tolerability, safety and immunogenicity of the inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 of a two-dose schedule in healthy adults aged 18 to 55 years.	Long-term safety data	• Interim CSR submitted as part of licensure application Q4 2021. • Interim CSR including follow-up to Month 6 planned to be submitted mid-2022.	-

This is acceptable.

IV.7 Discussion on the clinical aspects

Efficacy

An immunobridging approach has been accepted by the MHRA given the difficulties encountered by the Applicant to conduct an efficacy trial (against placebo or active vaccine). This approach means that vaccine efficacy is derived from an immunogenicity comparison with a vaccine that has been authorised on the basis of an efficacy trial. Although no immune correlate of protection has been established up to now, vaccine efficacy against symptomatic disease appears reasonably correlated across technology platforms to antibody levels achieved after immunisation, especially neutralising antibody levels. AZD1222 was the only licensed SARS-CoV-2 vaccine for which vaccine efficacy and immunogenicity were shown to increase as the dosing interval between the two primary doses increased, further supporting the assumption of a correlation between antibody levels and efficacy for this vaccine. Therefore, the MHRA agreed that superiority of neutralising antibody level (GMT) after 2 doses of VLA2001 compared to 2 doses of AZD1222 administered at a 4-week interval would reasonably predict a vaccine efficacy against symptomatic COVID-19 above the WHO standard threshold (50%).

Based on the data currently available, the comparison of the immunogenicity profile of VLA2001 to that of AZD1222 shows similarities and differences that reflect the different vaccine technology. The first dose of VLA2001 appears insufficient to induce a relevant immune response, and therefore, no protection can be assumed after the first dose of vaccine. This information is conveyed to the product information. In contrast, the antibody response after the second vaccine dose is robust in comparison with AZD1222, which supports a protective effect of VLA2001 against symptomatic infection after full immunisation.

Based on the IFNγ ELISpot data, the T-cell response appears lower with VLA2001 than with AZD1222; the impact of this finding regarding potential protection against severe disease is currently unknown. In contrast, T-cell data suggest an advantage in terms of the breadth of the immune response due to broader antigen composition although further data to support this assumption are currently very limited (e.g. cross-neutralisation of various VOCs).

The comparison of the immunogenicity profile of the two vaccines has been conducted in a population of subjects aged between 30 and 50 years (only 3 subjects were older than 50 years), which precludes an indication in subjects older than 50 years old at this point in time. Data in older subjects will be provided in the future.

Safety

A total of 3,068 subjects received at least one injection of VLA2001 at the recommended dosage in the clinical trials, which complies with the minimum regulatory requirements for vaccines.

Reactogenicity

Local tenderness and pain, fatigue, headache and muscle pain were the most frequent local reactions reported VLA2001 and their frequency decreased with age, as expected. The incidence of reactions was similar (or slightly higher) after the first dose compared to the second dose. There was essentially no severe local reaction and severe systemic reactions occurred in less than 1% of the subjects, mainly fatigue and fever. Overall, the reactogenicity profile of VLA2001 appears benign, with most reactions being mild and of short duration. It compares favourably with that of AZD1222.

Unsolicited events
With an average follow-up of 126 days after the second dose in study VLA2001-301, the number of participants with unsolicited adverse events was 1659/4092 (41.4%) and the difference amongst subjects ≥ 30 years between AZD1222 (44.5%) and VLA2001 (40.1%) was statistically significant (p=0.02). Most unsolicited AEs were likely related to concurrent infections or reflected vaccine reactogenicity. The incidence of SAEs was very low and similar across all treatment groups, 0.7% in the VLA2001 arms and 1.0% in the AZD1222 arm. None was considered related to vaccination. AESIs were reported in 9 cases overall (0.2%). None was considered related to VLA2001; they were mostly COVID-19 cases. A single subject did not receive a second dose of VLA2001 due to an adverse reaction (generalised urticaria), which resolved within 2 days. Overall, based on these data, there is no safety concern with VLA2001.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements. A user consultation study is required post-approval to be in accordance with legal requirements. This is one of the conditions of authorisation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of COVID-19 Vaccine Valneva to prevent COVID-19 caused by SARS-CoV-2 in adults from 18 to 50 years old.

Given the limitation of the current information, in particular the lack of data in older adults and an efficacy assumed on the basis of immunogenicity, COVID-19 Vaccine Valneva VLA2001 has been authorised with a Conditional Marketing Authorisation (CMA). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to fully demonstrate the ability of the sterile filters to retain bacteria for sterile filtration of drug substance and the diluted CpG 1018, the MAH should submit bacterial retention study reports for filters associated with the drug substance and CpG 1018.	Provided April 2022
It is a requirement to provide tumorigenicity tests results at 'end of production' for the working cell bank (WCB) used in manufacture. Although sufficient assurance of no tumourigenic potential has been provided, the tumourigenicity test remains outstanding for EOP WCB ICB/2020/007.	31 July 2022
As Study VLA2001-301 provides insufficient comparative immunogenicity data on COVID-19 Vaccine Valneva vs Vaxzevria in subjects above 50 years of age, additional immunogenicity data in older subjects should be provided, including in the elderly (> 65 years), which should allow for extrapolation of vaccine efficacy to this at-risk population.	30 September 2022
As vaccine effectiveness is derived from immunobridging and given that the immunogenicity profile of COVID-19 Vaccine Valneva differs from the comparator vaccine, the MAH should conduct effectiveness study(ies) to include all countries where the vaccine is used. A study protocol should be submitted.	TBD within 2 months of approval in each country

In order to further characterise the immunogenicity profile of COVID-19 Vaccine Valneva, the MAH should provide additional cross-neutralisation data of a panel of variants of concern in comparison with Vaxzevria.	30 June 2022
In order to evaluate antibody persistence, the MAH should submit the 6-month immunogenicity data of Study VLA2001-301.	31 October 2022
As the patient information leaflet approved at licence grant must comply with Regulation 260 (3) of the Human Medicines Regulations (Article 59.3 of the EU legislation), a user testing report should be submitted.	31 July 2022

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing have been provided.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**