Background to the recommendations for use of the Valneva VLA2001 vaccine against COVID-19

Background document to the WHO Interim recommendations for use of the Valneva vaccine VLA2001 against COVID-19

18 August 2022

World Health Organization

Note. This background document was developed to inform the initial recommendation-making process. It will not be updated on a regular basis. The latest Grade and ETR tables can be obtained here: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Valneva-VLA2001-annexes

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Background

This background document was prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines to inform the discussions of SAGE for Valneva vaccine (VLA2001) at its meeting on 11 August 2022, which resulted in the issuance of the interim recommendations *(1)* and evidence to recommendation tables (annexes) *(2)*. These are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Covid-19 Working Group webpage.

This document refers to the COVID-19 Valneva vaccine (VLA2001) developed by Valneva. It is based on the Valneva core non-clinical and clinical data for regulatory evaluation.

Context

The COVID-19 Valneva (VLA2001) vaccine is a highly purified, inactivated, and adjuvanted whole virus SARS-CoV-2 vaccine. The whole-virion inactivated vaccine is adsorbed to alum with a toll-like receptor 9 agonist (cytosine phosphor-guanine: CpG 1018) adjuvant *(3, 4)*. The two adjuvants increase the magnitude of vaccine-mediated cellular immune response without compromising safety. Following administration, the spike protein of SARS-CoV-2, and other viral surface antigens, stimulate both neutralizing and other functional binding antibodies, as well as cellular immune responses (Th1) directed against the spike and other surface proteins, all of which are thought to contribute to protection against COVID-19. Inactivated vaccines cannot replicate, therefore cannot infect individuals *(5)*.

The vaccine is developed by Valneva's research and development teams in France and Austria with the marketing authorization holder, Valneva Austria GmbH. As of 11 August 2022, the vaccine has received conditional marketing authorization from the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom of Great Britain and Northern Ireland (the United Kingdom) for use in adults aged 18–50 years; standard marketing authorization from the European Medicines Agency for use in adults aged 18–50 years; emergency use authorization from the National Health Regulatory Authority (NHRA) of the Kingdom of Bahrain, and that of the United Arab Emirates. The vaccine dossier is currently being reviewed by the national regulatory agency of Malaysia; submissions have been initiated for emergency use listing (EUL) by WHO as well as with the regulatory authorities of Argentina and Thailand (from data on file). In the subsequent text, the vaccine will be referred to as VLA2001.

Characteristics of COVID-19 vaccine VLA2001

Composition

The vaccine is provided as multidose vials containing 10 doses per vial (0.5 ml per dose). One dose (0.5 ml) contains 33 antigen units (AUs) of inactivated SARS-CoV-2. VLA2001 is composed of highly purified whole virus SARS-CoV-2 antigen (Wuhan strain hCoV-19/Italy/INMI1-isl/2020),[1] inactivated[2] and adjuvanted with CpG 1018,[3] in combination with aluminium hydroxide.[4]

The other excipients are the Dulbecco's Phosphate Buffer Saline (DPBS) (containing 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). VLA2001 contains potassium <1 mmol (39 mg) per 0.5 ml dose, and sodium <1 mmol (23 mg) per 0.5 ml dose; that is, the vaccine is essentially potassium- and sodium- "free" *(5, 6)*.

Dosing regimen

VLA2001 is administered intramuscularly as a course of two injections (0.5 ml per dose). The second dose is recommended to be administered at least 28 days after the first dose *(5)*.

Stability and shelf-life

The unopened multidose vial should be stored and transported at a temperature of 2–8 °C. The vials should be stored in the original packaging to protect from light. A shelf-life of 12 months is proposed for unopened vials.

The chemical and physical in-use stability of the vaccine has been demonstrated for 6 hours in-vial when stored at room temperature. The multidose vial should be discarded if the vaccine is not used within this time. Once opened and after first dose withdrawal, the multidose vial should be marked with discarding date and time. The vaccine should not be frozen *(5)*.

Drug product description

The vaccine is a white to off-white suspension with a pH of 7.5±0.5 *(5)*.

Developmental and reproductive toxicity

The developmental and reproductive toxicity (DART) study was performed prenatally and postnatally in female Han Wistar rats; the vaccine was administered by intramuscular injection twice (at 21 and 7 days) prior to mating, and on day 6 of gestation (*unpublished*, from data on file). Results showed that it did not affect reproductive parameters, delivery or fetal development (*(5)* and from data on file).

[1] Produced on Vero cell (African green monkey cells).
[2] Inactivated with beta-propiolactone.
[3] 1 mg CpG 1018 (cytosine phospho-guanine) adjuvant/0.5 ml dose.
[4] Adsorbed on aluminium hydroxide (0.5 mg Al^{3+})/0.5 ml dose.

Preclinical studies

Immunogenicity and efficacy

The immunogenicity of VLA2001 was evaluated in female BALB/c-strain mice and in nonhuman primates (cynomolgus macaques monkeys). The female BALB/c-strain mice were vaccinated twice (on days 0 and 21) subcutaneously with one dose of 100 µl VLA2001 vaccine. They were dosed in three groups: i) one group received a placebo (buffer with alum adjuvant only, or buffer with alum and CpG 1018); ii) the second group received VLA2001, with alum adjuvant only, in three different dose levels (0.3 AUs, 1.2 AUs, 3.0 AUs); and iii) the third group received VLA2001 with both alum and CpG 1018 adjuvants in three dose levels (0.3 AUs, 1.2 AUs, 3.0 AUs). Blood samples were collected. Immune responses were measured by ELISA (enzyme-linked immunosorbent assay) for total IgG and by PRNT (plaque reduction neutralization test) for antibody neutralization titres. The results showed consistently that the third group induced higher IgG titres than the alum-only formulation and also showed neutralization titres close to those present in serum from human convalescent patients of COVID-19. It was also observed that the addition of CpG 1018 led to a significant shift of the immune response towards a Th1 response, whereas VLA2001 formulated with alum only induced a Th2-skewed immune response (from data on file).

Groups of eight nonhuman primates (cynomolgus macaques monkeys) were vaccinated twice with placebo, or a medium dose (7 AUs), or high dose (35 AUs) of VLA2001 on days 0 and 21. They were subsequently challenged on day 47 or day 49 with 105 plaque forming units of SARS-CoV-2 through simultaneous intranasal and intratracheal infection. The levels of antibodies developed were then determined by ELISA. Significant antibodies were elicited after the first vaccination for both medium and high doses; the second vaccination boosted the magnitude of the response with no significant difference in levels of antibodies observed between the two doses. The sera were also used to assess virus-neutralizing responses using a cytopathic-effect based microneutralization assay. Compared to the control animals, the results showed that two vaccinations were required to induce a significantly neutralizing response and that the high dose formulation elicited a significantly stronger neutralizing response than the medium dose (p=0.0119). Peripheral blood mononuclear cells (PBMCs) were isolated from each animal 14 days after the second vaccination and analysed by IFN ELISpot; the cytokines IFN, TNF, and IL-2 were considered representative of a Th1 response, and IL-13 of a Th2 response. The results showed that cells expressing IFN, TNF, or IL-2 were abundant, while cells expressing IL-13 were practically undetectable; therefore, as consistent with mice, the nonhuman primate response to VLA2001 vaccination was heavily Th1-biased. Additionally, the immune response induced by vaccination seemed to prevent viral replication in the upper respiratory tract, measured with subgenomic viral RNA as a surrogate (several of the control animals showed signs of viral replication, i.e. presence of viral RNA, but none of the vaccinated animals of any dose had detectable viral RNA at any time point (from data on file)).

Toxicity

A repeat dose toxicity study of VLA2001 was performed in Han-Wistar rats with three intramuscular administrations (on days 1, 15 and 29) at two-week intervals which showed that the vaccine was well tolerated *(6, 7)*. The changes observed included transient loss of body weight; 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. These were considered physiological or immunological responses to the vaccine (*(5)* and from data on file). Therefore the non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity *(5)*.

Passive transfer

The pooled sera from participants in the phase 1/2 trial of VLA2001 (NCT04671017; ISRCTN 82411169) were passively transferred to Syrian golden hamsters in a study performed by the UK Health Security Agency (formerly known as Public Health England). The hamsters were challenged intranasally one day after serum transfer with SARS-CoV-2, while the negative human serum acted as the control. The animals that received the highest dose of passively transferred antibodies (50% neutralizing dose of 1699) were significantly protected against weight loss, while the others were protected against weight loss to an extent that approximately correlated with the dose of transferred neutralizing antibodies. A trend of protection against clinical signs of distress was also noted (from data on file).

Clinical studies

The pivotal data relating to safety, immunogenicity, and efficacy of VLA2001 are derived from the following studies *(8-10)*:

- **NCT04671017; ISRCTN 82411169**. This is a multicentre, dose-finding phase 1/2 study of people aged 18–55 years conducted in two parts. The first part was an open-label, dose-escalation; thereafter, it was double-blinded with participants randomized in a ratio of 1:1:1 to receive a low (3 AUs), medium (7 AUs), or high (35 AUs) vaccine dose *(4)*. The study was extended to investigate the tolerability, safety and immunogenicity of VLA2001 as a booster vaccination (equivalent to a phase 3 study dose), administered 7–8 months after the second dose of the primary vaccination series. All study participants in the booster phase will be followed up for safety and immunogenicity up to 6 months after receiving their booster vaccination.
- **NCT04864561; ISRCTN 79815558**.
    - VLA2001-301 COV-COMPARE. This is a multicentre, randomized, observer-blind, active-controlled, superiority phase 3 study to compare the immunogenicity of VLA2001 vaccine (33 AUs) against ChAdOx1-S [recombinant] vaccine (ChAdOx1-S). People aged ≥30 years were randomized in a 2:1 ratio to receive two intramuscular, recommended doses of either VLA2001 or ChAdOx1-S. People aged 18–29 years participated in the study in a non-randomized, open-label fashion to receive VLA2001. For both vaccines, the two doses were administered 28 days apart, on days 1 and 29. The study is ongoing, with completion expected in March 2023; preliminary results are available *(11)*.
    - VLA2001-301a. In this part of the trial, adolescents (aged 12–17 years) will be randomized in a 1:1 ratio to receive two intramuscular doses of either VLA2001 or placebo. Participants receiving VLA2001 will be administered a booster vaccination with VLA2001 at day 208; those in the placebo group will receive a two-dose primary vaccination with VLA2001 at day 208 and the second vaccination 28 days later. For safety reasons, the first 16 adolescents will be enrolled in an open label, non-randomized manner. The study has been initiated, with sentinel subjects vaccinated in the United Kingdom. It is now open for full randomization and will be expanded to Mexico, with expected completion in March 2023. Preliminary results are expected at the end of 2022.)
- **NCT04956224.** VLA2001-304. This is a phase 3, open label, multicentre, single arm study to assess the safety, tolerability and immunogenicity of VLA2001 in volunteers aged ≥56 years of age in New Zealand. The study is active; results are expected in the third quarter of 2022.

- **ISRCTN 73765130**:[5] This is a multicentre, randomized, controlled, phase 2 trial of a third dose booster vaccination against COVID-19, for people aged >30 years (COV-BOOST) *(12)*.
- **NCT05298644**. VLA2001-321. This is a randomized, double-blinded, active-controlled study to evaluate the safety, tolerability and immunogenicity of VLA2001 in children aged 2–12 years. The study is planned to be conducted in Latin America (with applications in Columbia, Guatemala and Hounduras), and due to be initiated in the third quarter of 2022.
- **EudraCT 2022-000035-23**. VLA2001-307. This is a multicentre, open-label, single-arm clinical study to investigate the safety, tolerability, and immunogenicity of a VLA2001 booster vaccination in adults aged ≥18 years. The study is planned to be conducted in the Netherlands; topline results are expected in the third quarter of 2022 (*press release (13)*).

Immunogenicity studies in humans

Phase 1/2 immunogenicity findings

For phase 1 (NCT04671017; ISRCTN 82411169), 15 participants were enrolled in an open-label, dose-escalation study to receive one of three dose concentrations (low: 3 AUs, *n*=5; medium: 7 AUs, *n*=5; or high: 35 AUs, *n*=5) of VLA2001, administered intramuscularly. The participants were then vaccinated again three weeks later with the same dose concentrations. The phase 2 double-blinded randomized stage was initiated with 153 participants, after safety data from phase 1 had been collected (up to 3 days after the last high dose vaccination) and reviewed, and the independent data safety monitoring committee had observed no signals that required stopping the trial. The primary immunogenicity outcome was the geometric mean titre (GMT) for SARS-CoV-2 neutralizing antibodies at day 36. Secondary immunogenicity outcomes included GMT of spike protein binding and neutralizing antibodies at all time points. T-cell responses (spot forming units (SFUs) per 2 x 10^5 PBMC) were included as exploratory outcomes *(4)*.

The mean age of participants was 33.5 years (range 18–55 years); 46% were female; 94% were white (Caucasian) (see Table 1). There were no cases of hepatitis A, hepatitis C or HIV at the time of screening, at baseline. In the SARS-CoV-2 neutralizing MNA_{50} assay, the highest median GMTs recorded to date were reached on day 36 in all dose groups, in a dose-dependent manner. The seroconversion rates of neutralizing antibodies by day 36 were 90% (95% confidence interval (CI): 78–97) in the high-dose group; 74% (95% CI: 59–85) in the medium-dose group; and 51% (95% CI: 37–65) in the low-dose group. The results of SARS-CoV-2 neutralizing antibody titres ND_{40} and ND_{50} over time are presented in Table 2 and Table 3 respectively; the proportion of participants with seroconversion in terms of ND_{50} at days 36 and 106 are presented in Table 4 *(4)*.

A similar dose-dependent response, with a peak response at day 36, was observed in anti-spike-IgG GMT measured by ELISA, (see Table 5) *(4)*. The results of IgG antibody titres against SARS-CoV-2-S protein (ELISA) at days 1, 36 and 106 for the per protocol (PP) population are provided in Table 6 *(4)*.

Table 1. Baseline characteristics from the phase 1/2 study (NCT04671017; ISRCTN 82411169)*

Characteristics	Dose *n* (%)			
	Low dose (*N*=51)	Medium dose (*N*=51)	High dose (*N*=51)	Overall (*N*=153)
Age at the time of informed consent (years)				

[5] This study was sponsored by the University Hospital Southampton, and the NHS Foundation Trust, of the United Kingdom of Great Britain and Northern Ireland, and not by the company.

Characteristics	Dose *n* (%)			
	Low dose (*N*=51)	Medium dose (*N*=51)	High dose (*N*=51)	Overall (*N*=153)
Median	31	33	29	32
Min, Max	21, 53	21, 55	18, 54	18, 55
Sex, *n* (%)				
Male	27 (52·9)	34 (66·7)	22 (43·1)	83 (54·2)
Female	24 (47·1)	17 (33·3)	29 (56·9)	70 (45·8)
Diverse	0	0	0	0
Ethnicity, *n* (%)				
White	46 (90·2)	51 (100·0)	47 (92·2)	144 (94·1)
Asian	1 (2·0)	0	0	1 (0·7)
Mixed	0	0	4 (7·8)	4 (2·6)
Latino[a]	4 (7·8)	0	0	4 (2·6)
Body Mass Index at screening (kg/m^2)				
n	51	51	51	153
Mean (SD)	25 (3·0)	25 (2·2)	24 (3·1)	24·81 (2·8)
Median	24·7	24·9	24·5	24·8
Min, Max	19·6, 29·9	20·2, 29·2	18·1, 29·8	18·1, 29·9
COVID-19 test result at screening				
Positive	0	0	0	0
Negative	51 (100·0)	51 (100·0)	51 (100·0)	153 (100·0)

**Source*: Lazarus et al. 2022a *(4)*.

[a] "Latino" includes individuals who classified themselves as Latin, Latin American or Latino.

Table 2. SARS-CoV-2 neutralizing antibody titres (ND_{40}) at baseline prior to vaccination (day 1), 22 days after first vaccination (day 22), and 14 days after second vaccination (day 36), from the phase 1/2 study (NCT04671017; ISRCTN 82411169)*

Visit	Metric	Dose *n* (%)			
		Low dose (*N*=51)	Medium dose (*N*=51)	High dose (*N*=51)	Overall (*N*=153)
Day 1	*n*	51	49	50	150
	GMT (95% CI)	29·0 (29.0–29.0)	30·7 (28.5–33.6)	30·0 (28.8–31.2)	29·9 (29.1–30.7)
	Min, Max	29·0, 29·0	29·0, 232·0	29·0, 72·0	29·0, 232·0
	p-value	–	–	–	0.349
Day 22	*n*	50	48	48	146
	GMT (95% CI)	35·9 (32·3–39·9)	38·3 (31·9–46·1)	46·5 (38·8–55·7)	39·9 (36·5–43·8)
	Min, Max	29·0, 115·0	29·0, 640.0	29.0, 359·0	29·0, 640·0
	p-value	–	–	–	0.089
	n	51	48	50	149

Visit	Metric	Dose *n* (%)			
		Low dose (*N*=51)	Medium dose (*N*=51)	High dose (*N*=51)	Overall (*N*=153)
Day 36	GMT (95% CI)	161·1 (121·4–213·8)	222·3 (171·8–287·7)	530·4 (421·5–667·5)	266·6 (226·8–313·3)
	Min, Max	29·0, 2171·0	29·0, 1307·0	29·0, 2033·0	29·0, 2171·0
	p-value	–	–	–	<0·001

**Source*: *preprint, not peer-reviewed,* Lazarus et al. 2021 *(3).*

GMT: geometric mean titre; CI: confidence interval, values below limit of quantification (58) are set to 29.0; Max: maximum; Min: minimum; ND_{40}: 40% neutralizing dilution.

Table 3. SARS-CoV-2 neutralizing antibody titres (ND_{50}) over timepoints at days 1, 36 and 106 (per protocol population) from the phase 1/2 study (NCT04671017; ISRCTN 82411169)*

Metric	Low dose (*N*=50)	Medium dose (*N*=49)	High dose (*N*=45)	Overall (*N*=144)	Convalescent subjects (*N*=32)
Day 1					
n	50	49	45	144	–
GMT (95% CI)	31·0 (31·00–31·00)	32·8 (30·48–35·24)	31·5 (30·66–32·37)	31·8 (30·94–32·58)	–
Median	31·0	31·0	31·0	31·0	–
Min, Max	31·0, 31·0	31·0, 232·0	31·0, 64·0	31·0, 232·0	–
p-value: overall dose groups comparison[A]	–	–	–	0·366	–
Day 36					
n	50	49	45	144	32
GMT (95% CI)	168·7 (125·09–227·48)	218·9 (169·41–282·92)	545·6 (428·10–695·37)	266·0 (225·10–314·39)	526·9 (336·47–825·06)
Median	122·5	233·0	537·0	264·5	606·0
Min, Max	31·0, 3618·0	31·0, 1307·0	31·0, 2033·0	31·0, 3618·0	31·0, 6704·0
p-value: overall dose groups comparison [A]	–	–	–	<0·001	–
p-value: medium dose vs high dose [B]	–	–	–	<0·001	–
Day 106					
n	49	49	45	143	–
GMT (95% CI)	63·3 (50·42–79·48)	82·4 (64·26–105·63)	175·9 (136·02–227·56)	95·6 (82·23–111·08)	–
Median	31·0	77·0	211·0	89·0	–

Metric	Low dose (*N*=50)	Medium dose (*N*=49)	High dose (*N*=45)	Overall (*N*=144)	Convalescent subjects (*N*=32)
Min, Max	31·0, 1088·0	31·0, 1589·0	31·0, 1357·0	31·0, 1589·0	–
p-value: overall dose groups comparison [A]	–	–	–	<0·001	–
p-value: medium dose vs high dose [B]	–	–	–	0·001	–

**Source*: Lazarus et al. 2022a *(4)*.

CI: confidence interval; GMT: geometric mean titre; Max: maximum; Min: minimum; ND_{50}: 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 Dwass, Steel, Critchlow-Fligner (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).

Day 36: *p*-value: low dose vs medium dose: 0·358; *p*-value: low dose vs high dose: <0·001; *p*-value: low dose vs convalescent: 0·001; *p*-value: medium dose vs convalescent: 0·023; *p*-value: high dose vs convalescent: >0·999.

Day 106: *p*-value: low dose vs medium dose: 0·366; *p*-value: low dose vs high dose: <0·001.

Table 4. Proportion of participants with seroconversion in terms of neutralizing antibodies (ND_{50}) at days 36 and 106 (per protocol population) from the phase 1/2 study (NCT04671017; ISRCTN 82411169)*

Metric	Low dose (*N*=50)	Medium dose (*N*=49)	High dose (*N*=45)	Overall (*N*=144)
Day 36				
Participants with seroconversion (≥4-fold increase)				
n (%)	25 (50·0)	35 (71·4)	41 (91·.1)	101 (70·1)
95% CI [A]	0·36–0·64	0·57–0·83	0·79–0·98	0·62–0·77
p-value [B]	–	–	–	<0·001
p-value: low dose vs medium dose [C]	–	–	–	0·040
p-value: medium dose vs high dose [C]	–	–	–	0·038
p-value: low dose vs high dose [C]	–	–	–	<0·001
Participants with:				
≥2-fold increase, *n* (%)	43 (86·0)	44 (89·8)	44 (97·8)	131 (91·0)
≥10-fold increase, *n* (%)	13 (26·0)	17 (34·7)	34 (75·6)	64 (44·4)
≥20-fold increase, *n* (%)	8 (16·0)	8 (16·3)	21 (46·7)	37 (25·7)
Day 106				
Participants with seroconversion (≥4-fold increase)				
n (%)	11 (22·0)	14 (28·6)	27 (60·0)	52 (36·1)
95% CI [A]	0·12–0·36	0·17–0·43	0·44–0·74	0·28–0·45
p-value [B]	–	–	–	<0·001
p-value: low dose vs medium dose [C]	–	–	–	0·495
p-value: medium dose vs high dose [C]	–	–	–	0·007

Metric	Low dose (*N*=50)	Medium dose (*N*=49)	High dose (*N*=45)	Overall (*N*=144)
p-value: low dose vs high dose [C]	–	–	–	0·001
Participants with:				
≥2-fold increase, *n* (%)	22 (44·0)	29 (59·2)	38 (84·4)	89 (61·8)
≥10-fold increase, *n* (%)	4 (8·0)	5 (10·2)	15 (33·3)	24 (16·7)
≥20-fold increase, *n* (%)	2 (4·0)	1 (2·0)	4 (8·9)	7 (4·9)

**Source*: Lazarus et al. 2022a *(4)*.

CI: confidence interval; ND_{50}: 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 timepoints.

A: Exact 95% Clopper-Person CI for proportion.

B: Fisher-Freeman-Halton exact test for overall dose group differences.

C: Multiplicity adjusted *p*-values (using Hochberg method) for pairwise group differences from Fisher's exact test if the overall group difference was statistically significant (i.e. *p*-value for Fisher-Freeman-Halton exact test is ≤0·05).

Table 5. IgG antibody titres against SARS-COV-2 S-protein at baseline prior to vaccination (day 1), 22 days after first vaccination (day 22), and 14 days after second vaccination (day 36), from the phase 1/2 study (NCT04671017; ISRCTN 82411169)*

Visit	Metric	Dose *n* (%)			
		Low dose (*N*=51)	Medium dose (*N*=51)	High dose (*N*=51)	Overall (*N*=153)
Day 1	*n*	51	49	50	150
	GMT (95% CI)	25·6 (24·7–26·7)	26·4 (24·1–29·1)	25·0 (25·0–25·0)	25.7 (24·8–26·5)
	Min, Max	25·0, 87·2	25·0, 390·8	25·0, 25·0	25·0, 390·8
	p-value	–	–	–	0.604
Day 22	*n*	51	49	50	150
	GMT (95% CI)	27·1 (25·1–29·2)	31·9 (26·2–38·9)	30·0 (26·9–33·5)	29·6 (27·4–31·9)
	Min, Max	25·0, 99·7	25·0, 1348·6	25·0, 165·0	25·0, 1348·6
	p-value	–	–	–	0·293
Day 36	*n*	51	49	50	150
	GMT (95% CI)	325·1 (245·5–430·5)	691·6 (494·9–966·5)	2147·9 (1706·0–2704·2)	780·6 (643·9–946·4)
	Min, Max	25·0, 5566·1	25·0, 8637·6	116·8, 15419·5	25·0, 15419·5
	p-value	–	–	–	<0·001

**Source*: *pre-print, not peer-reviewed*, Lazarus et al. 2021 *(3)*

GMT: geometric mean titre; CI: confidence interval, values below limit of quantification (50.3) are set to 25.0; Max: maximum; Min: minimum.

Table 6. IgG antibody titres against SARS-CoV-2 S protein (ELISA) at days 1, 36 and 106 (per protocol population) from the phase 1/2 study (NCT04671017; ISRCTN 82411169)*

Metric	Low dose (*N*=50)	Medium dose (*N*=49)	High dose (*N*=45)	Overall (*N*=144)
Day 1				
n	50	49	45	144

Metric	Low dose (*N*=50)	Medium dose (*N*=49)	High dose (*N*=45)	Overall (*N*=144)
GMT (95% CI)	25·6 (24·6–26·7)	26·4 (24·1–29·1)	25·0 (25·0–25·0)	25·7 (24·8–26·6)
Median	25·0	25·0	25·0	25·0
Min, Max	25·0, 87·2	25·0, 390·8	25·0, 25·0	25·0, 390·8
p-value: overall dose groups comparison [A]	–	–	–	0·632
Day 36				
n	50	49	45	144
GMT (95% CI)	329·7 (247·8–438·7)	691·6 (494·9–966·5)	2116·0 (1642·6–2725·8)	758·4 (622·7–923·8)
Median	300·4	780·1	2087·7	778·4
Min, Max	25·0, 5566·1	25·0, 8637·6	116·8, 15419·5	25·0, 15419·5
p-value: overall dose groups comparison [A]	–	–	–	<0·001
p-value: low dose vs medium dose [B]	–	–	–	0·005
p-value: medium dose vs high dose [B]	–	–	–	<0·001
p-value: low dose vs high dose [B]	–	–	–	<0·001
Day 106				
n	49	49	45	143
GMT (95% CI)	111·4 (81·3–152·7)	201·5 (151·4–268·3)	524·8 (407·4–676·0)	222·3 (184·7–267·5)
Median	89·1	254·8	545·9	236·1
Min, Max	25·0, 5499·7	25·0, 2409·7	58·4, 6601·7	25·0, 6601·7
p-value: overall dose groups comparison [A]	–	–	–	<0·001
p-value: low dose vs medium dose [B]	–	–	–	0·016
p-value: medium dose vs high dose [B]	–	–	–	<0·001
p-value: low dose vs high dose [B]	–	–	–	<0·001

**Source*: Lazarus et al. 2022a *(4)*.

CI: confidence interval; DSCF: Dwass, Steel, Critchlow-Fligner; ELISA: enzyme-linked immunosorbent assay; gG: immunoglobulin gamma; GMT: geometric mean titre; Max: maximum; Min: minimum.

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).

Case definitions

Study immunogenicity and safety endpoints from the phase 3 study (NCT04864561; ISRCTN79815558) are described in Box 1 *(14)*.

Box 1. Primary and secondary immunogenicity and safety endpoints in the phase 3 study (NCT04864561; ISRCTN79815558)

Primary outcome measures

- Immune response measured after completion of a two-dose vaccination schedule, as determined by the geometric mean titre of SARS-CoV-2-specific neutralizing antibodies [time frame: day 43]
- Immune response measured after completion of a two-dose vaccination schedule, as determined by seroconversion (definded as 4-fold increase from baseline) of SARS-CoV-2-specific neutralizing antibodies [time frame: day 43]
- Frequency and severity of any adverse event [time frame: up to day 43 post-vaccination]

Secondary outcome measures (including safety outcomes)

- Proportion of participants with seroconversion [time frame: on day 8 (age ≥55 years only), day 29, day 43, day 71, day 208, and day 365]. Seroconversion is defined as ≥4-fold increase in SARS-CoV-2 neutralizing antibody titre and S-protein binding IgG levels between day 1 and post-vaccination timepoints.
- Immune response as determined by the geometric mean titre of SARS-CoV-2-specific neutralizing antibodies [time frame: on day 8 (age ≥55 years only), day 29, day 71, day 208 and day 365].
- Immune response as determined by the geometric mean titre of IgG antibodies to SARS-CoV-2 S-protein [time frame: on day 8 (age ≥55 years only), day 29, day 43, day 71, day 208 and day 365].
- Assessment of T-cell responses (Th1/Th2 polarization) from peripheral blood mononuclear cells in a subset of participants after in-vitro stimulation with SARS-CoV-2 antibodies using, e.g. ELISpot or intracellular cytokine staining [time frame: on day 1, day 8, day 29, day 43, day 71, day 208, and day 365].
- Frequency and severity of solicited injection site and systemic reactions [time frame: within 7 days after each/any vaccination]
- Frequency and severity of any adverse event [time frame: until month 12]
- Frequency and severity of any unsolicited adverse event [time frame: until day 43]
- Frequency and severity of any unsolicited vaccine-related adverse event [time frame: until day 43]
- Frequency and severity of any serious adverse event [time frame: until month 12]

Phase 3 immunogenicity findings

The phase 3 COV-COMPARE study (NCT04864561; ISRCTN79815558) is a randomized, observer-blind, active-controlled superiority study being conducted in the United Kingdom. In total, 2975 participants (aged ≥30 years) were randomized (2:1) to receive a two-dose intramuscular vaccination either with VLA2001 (*n*=1978) or ChAdOx1-S (*n*=997), to be administered 28 days apart. This trial is ongoing, with participants followed until day 365 (12 months after first vaccination), *(5, 6)* and *(11)*.

A primary statistical analysis was performed after all participants were vaccinated and had completed day 43. The data presented here represent the primary statistical analyses, including a mean safety follow-up of 151.4 days (standard deviation, 19.3 days). A second statistical analysis is planned when all participants have completed day 208; a final analysis is planned once the last participant has completed the study *(11)*.

The median age of the study was 34 years (range: 30–68 years) for VLA2001; and 35 years (range 30–71 years) for ChAdOx1-S; overall, less than 1% of the population studied was above 50 years of age. Both arms of the study included slightly more male (57%) than female (43%) participants; 93% were white (Caucasian). Most participants were seronegative for COVID-19 at screening using a rapid antibody test (95% in the VLA2001 arm and 97% in the ChAdOx1-S arm). The second vaccine dose was administered with a median interval of 29 days (range 23–64) after the first dose *(11)* (Table 7).

Table 7. Demographic characteristics (safety population) from the phase 3 study (NCT04864561; ISRCTN 79815558)*

Characteristics	VLA2001 Age <30 years (*N*=1040)	VLA2001 Age ≥30 years (*N*=1977)	ChAdOx1-S Age ≥30 years (*N*=995)
Age at the time of informed consent (years)			
n	1040	1977	995
Mean (SD)	24·4 (3·23)	35·4 (5·02)	35·6 (4·81)
Median	25·0	34·0	35·0
Min, Max	18, 29	30, 68	30, 71
Body Mass Index at screening (kg/m^2)			
n	1037	1975	993
Mean (SD)	25·44 (5·054)	27·25 (5·370)	27·43 (5·535)
Median	24·40	26·20	26·50
Min, Max	16, 49	16, 80	17, 58
Age group (years), *n* (%)			
18–29	1040	0	0
30–55	0	1958	990
>55	0	19	5
Sex, *n* (%)			
Male	555 (53·4)	1135 (57·4)	567 (57·0)
Female	483 (46·4)	839 (42·4)	427 (42·9)
Diverse	2 (0·2)	3 (0·2)	1 (0·1)
Ethnicity, *n* (%) [A]			
White	955 (91·8)	1844 (93·3)	927 (93·2)
Mixed	39 (3·8)	38 (1·9)	23 (2·3)
Asian	23 (2·2)	54 (2·7)	22 (2·2)
COVID-19 test result at screening			
Seropositive	52 (5·0)	108 (5·5)	32 (3·2)
Seronegative	988 (95·0)	1869 (94·5)	963 (96·8)

**Source*: *preprint, not peer-reviewed*, Lazarus et al. 2022b *(11)*.

Max: maximum; Min: minimum; SD: standard deviation.

Percentages are computed based on number of randomized participants.

A: Most frequently reported (≥2% incidence) ethnicities are included; *N*: (column headings) indicates the count of all participants who signed informed consent.

The immunogenicity (IMM) population included all vaccinated baseline seronegative participants of a subset of approximately 1200 participants (600 per group), which allowed for a statistical power of 90% to detect superiority in terms of the day 43 GMT ratio VLA2001/ChAdOx1-S (with an expected ratio of 1.3; a standard deviation of 0.6 (on a $\log_{10}$ scale); expected drop-out rate of 10%; and a two-sided significance level of 5%). Of the 1198 participants aged ≥30 years randomized into the IMM subset, 208 were excluded as they were identified as wild-type microneutralization assay (WT-MNA) seropositive at baseline. Therefore, 990

participants (23.7%) were analysed in the IMM age ≥30 years population, and 987 (23.6%) in the PP age ≥30 years population *(11)*. The results for the GMT of SARS-CoV-2 neutralizing antibodies at day 1 and day 43 in participants aged <30 years compared with those aged ≥30 years who were MNA baseline seropositive, are presented in Table 8 *(11)*.

Table 8. GMT of SARS-CoV-2 neutralizing antibodies at day 1 and day 43 in participants aged <30 years vs ≥30 years who were MNA baseline seropositive from the phase 3 study (NCT04864561; ISRCTN 79815558)*

Metric	VLA2001 Age <30 years (*N*=67)	VLA2001 Age ≥30 years (*N*=84)
Day 1		
n	67	84
GMT (95% CI) [B]	418·3 (340·9–513·2)	269·2 (226·4–320·0)
Median	440·0	279·0
Min, Max	67·0, 6884·0	62·0, 6738·0
Day 43		
n [A]	67	81
GMT (95% CI) [B]	2425·7 (2072·6–2839·0)	1478·6 (1245·6–1755·1)
Median	2400·0	1494·0
Min, Max	440·0–12800·0	85·0–12800·0

**Source*: Lazarus et al. 2022b *(11)*.

CI: confidence interval; GMT: geometric mean titre; Max: maximum; Min: minimum; MNA: microneutralization assay; *n*: number of participants with non-missing result.

A: Eligible is defined as having a sample available for analysis at day 43.

B: CI calculated using a two-sided t-test applied to $\log_{10}$ transformed data.

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 aged <30 years consists of all vaccinated participants aged <30 years who were seropositive at day 1 and have at least one evaluable antibody titre measurement after vaccination.

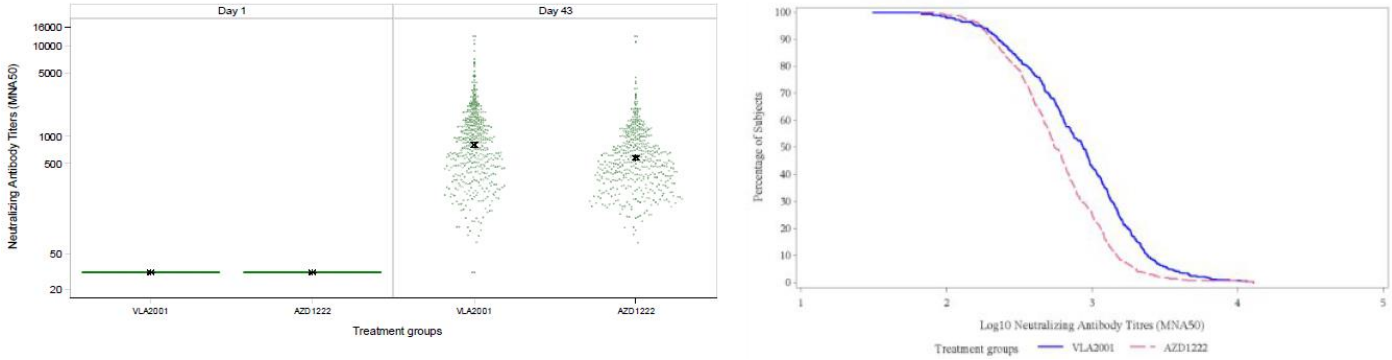
Samples from 990 participants (*n*=492: VLA2001; *n*=498: ChAdOx1-S) who were seronegative (with no neutralizing antibodies at baseline) were considered in the primary immunogenicity analysis. The co-primary immunogenicity endpoints were GMTs in the IMM population, and seroconversion rates (defined as a 4-fold increase from baseline) of SARS-CoV-2-specific neutralizing antibodies in the PP population, measured two weeks after the second dose (i.e. day 43). The objective of the trial was to demonstrate superiority of GMTs for VLA2001 compared to ChAdOx1-S and non-inferiority for seroconversion rates (with a margin of -10% for the difference) (Table 9) *(5)*. The mean age in the IMM population was 36.1 years for the VLA2001 group, and 35.8 years for the ChAdOx1-S group. Both groups included more male than female participants (55.3% vs. 44.3% in the VLA2001 group; 58.8% vs. 41.2% in the ChAdOx1-S group, respectively), with the majority in both treatment groups being white (Caucasian) (95.1% in the VLA2001 group; 93.6% in the ChAdOx1-S group) *(6)*.

On day 43, the GMT was 803.5 (95% CI: 748.5–862.6) among VLA2001 recipients aged ≥30 years; and 576.6 (95% CI: 543.6–611.7) among ChAdOx1-S recipients, which was statistically significant in favour of VLA2001 (p<0.0001, 1.39 [95% CI: 1.25–1.56] superiority) *(5, 6)* and *(11)*. In three participants aged >50 years who were included in the immunogenicity population, the neutralizing antibody GMT was 611.4 (95% CI: 158.9–2352.0). At day 43, the GMT for neutralizing antibodies was significantly higher in the VLA2001 group aged <30 years (1043.4 [95% CI: 926.6–1174.9]) compared to the VLA2001 ≥30-year age group.

For participants aged ≥30 years who were seropositive at baseline, on day 1, the GMT was 269.2 (95% CI: 226.4–320.0) with a range of 62–6738. By day 43, the neutralizing antibody GMT had increased to 1478.6 (95% CI: 1245.6–1755.1) *(11)*, (Fig 1).

Fig 1. Neutralizing antibodies in the phase 3 study (NCT04864561; ISRCTN 79815558)*‡

Panel A **Panel B**



*Source: Lazarus et al. 2022b *(11)*.

‡AZD1222: ChAdOx1-S vaccine.

Panel A: Plot of SARS-CoV-2 neutralizing antibodies (ND_{50}) over time by study group (immunogenicity population, IMM); MNA_{50}: 50% virus neutralization titre measured in a microneutralization assay; CI: confidence interval; ND_{50}: 50% neutralizing dilution. Day 1: VLA2001 (*n*=492), ChAdOx1-S (*n*=498); Day 43: VLA2001 (*n*=492), ChAdOx1-S (*n*=493).

Panel B: Reverse cumulative distribution function for SARS-CoV-2 neutralizing antibody titres (ND_{50}) for day 43 by treatment group (immunogenicity IMM population). Day 43: VLA2001 (*n*=492), ChAdOx1-S (*n*=493); ND_{50}: 50% neutralizing dilution.

Before the second vaccine dose (at day 29 after the first dose), GMTs measured in a subset of 235 samples were 68.6 (95% CI: 60.3–78.0) after VLA2001; and 225.7 (95% CI: 201.4–253.0) after ChAdOx1-S, with a GMT ratio of 0.30 (95% CI: 0.25–0.37). These results indicate that the second dose of VLA2001 was necessary to induce robust antibody levels in baseline negative participants and thereby provide protection against COVID-19 *(5, 6)*.

The GMTs and seroconversion rates of anti-spike binding IgG antibodies showed similar trends to neutralizing antibodies at days 29 and 43 *(5)*. At day 43, 98.0% of recipients of VLA2001, and 98.9% of ChAdOx1-S had seroconverted, as measured by ELISA for the IMM population; and 97.4% (VLA2001) vs 98.9% (ChAdOx1-S) in the PP population (difference: -0.015 [95% CI: -0.033–0.002]; *p*-value of 0.0911; non-inferiority: -3.3%) (*(5, 6)* and *(11)*) (Table 9, Table 10 and Table 11).

Table 9. SARS-CoV-2 neutralizing antibodies and seroconversion rates from the phase 3 study (NCT04864561; ISRCTN 79815558)*

Metric	VLA2001 (*N*=492) Age ≥30 years	ChAdOx1-S (*N*=498) Age ≥30 years	Comparison
ND_{50}			
Day 1			
n	492	498	–
GMT (95% CI)	31·0 (31·00–31·00)	31·0 (31·00–31·00)	–
GMT ratio (95% CI)	–	–	–
Median	31·0	31·0	–
Min, Max	31, 31	31, 31	–
p-value	–	–	–
Day 43			
n	492	493	–
GMT (95% CI)	803·5 (748·48–862·59)	576·6 (543·59–611·66)	–

Metric	VLA2001 (*N*=492) Age ≥30 years	ChAdOx1-S (*N*=498) Age ≥30 years	Comparison
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 at day 43			
n	456	449	–
SCR *n* (%)	444 (97·4)	444 (989)	–
95% CI	(0·954–0·986)	(0·974–0·996)	–
p-value	–	–	**0·0911**
Difference (95% CI)	–	–	**-0·015 (-0·033–0·002)**

**Source*: MHRA, 2022 *(5)* and EMA 2022 *(6)*.

GMT: geometric mean titre; GMT ratio: GMT VLA2001/GMT ChAdOx1-S; CI: confidence interval; SCR: seroconversion rate (defined as ≥4-fold increase in SARS-CoV-2-specific neutralizing antibody titre levels between day 1 and day 43); Difference: (VLA2001–ChAdOx1-S).

Statistically, a significantly higher GMT for S-protein binding antibodies at day 43 was observed for the cohort aged <30 years (3124.5 [95% CI: 2698.5–3617.8]) compared to the group aged ≥30 years (2385.0 [95% CI: 2159.5–2634.0]), with a GMT ratio of 1.3 (95% CI: 1.1–1.6) and associated *p*-value of 0.003. Thus, non-inferiority of the group aged <30 years in terms of GMT measured also by ELISA was confirmed (non-inferiority: margin value of 0.67), consistent with the phase 1/2 study *(11)*. A higher GMT of S-protein binding antibodies (IgG ELISA) was observed at day 43 in the VLA2001 group (GMT 2361.7 [95% CI: 2171.08–2569.11]) compared to the ChAdOx1-S group (GMT 2126.4 [95% CI: 1992.42–2269.45]) for the IMM population (see Table 10); the results were similar in the PP population. Numbers of participants with ≥2-fold, ≥10-fold, and ≥20-fold increases in S-protein binding antibody titre at day 43 were similar for both treatment groups, with nearly 100% for a ≥2-fold increase and 90% or more for a ≥10-fold and ≥20-fold increase *(6)*.

Table 10. IgG antibody titres against SARS-Cov-2 S-protein (ELISA) over time points (immunogenicity population) from the phase 3 study (NCT04864561; ISRCTN 79815558)*

Metric	VLA2001 (*N*=492) Age ≥30 years	ChAdOx1-S (*N*=498) Age ≥30 years	Overall (*N*=990)
Day 1			
n	489	496	–
GMT (95% CI) [A]	25·2 (25·0–25·4)	25·6 (25·2–26·0)	25·4 (25·2–25·6)
Median	25·0	25·0	–
Day 29			
n	484	489	–
GMT (95% CI) [A]	44·3 (41·3–47·5)	740·8 (680·9–806·0)	182·4 (166·4–200·1)
Median	25·0	716·2	–
Day 43			
n	492	493	–
GMT (95% CI) [A]	2361·7 (2171·1–2569·1)	2126·4 (1992·4–2269·5)	2240·9 (2124·8– 2363·3)

Metric	VLA2001 (*N*=492) Age ≥30 years	ChAdOx1-S (*N*=498) Age ≥30 years	Overall (*N*=990)
Median	2898·7	2112·4	–

Source: Lazarus et al. 2022b *(11)*.

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

A: CI calculated using $\log_{10}$ transformed.

Table 11. S-protein specific IgG antibodies seroconversion rate (per protocol population) from the phase 3 study (NCT04864561; ISRCTN 79815558)*

Metric	VLA2001 (*N*=489) Age ≥30 years	ChAdOx1-S (*N*=498) Age ≥30 years	Overall (*N*=987)
Day 29			
Participants with seroconversion (≥4-fold increase)			
n (%)	76 (15·5)	466 (93·6)	–
p-value [A]	–	–	<0·0001
Day 43			
Participants with seroconversion (≥4-fold increase)			
n	456	450	–
n (%)	447 (98·0)	445 (98·9)	–
p-value [A]	–	–	0·2914

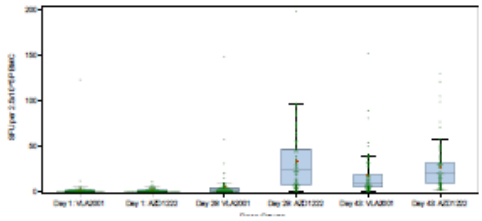
Source: Lazarus et al. 2022b *(11)*.

Seroconversion was defined as ≥4-fold increase in SARS-CoV-2 S-protein binding IgG levels between day 1 and post-vaccination sample collection time points.

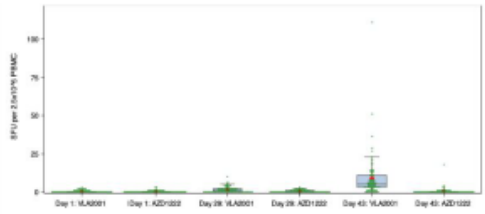
A: *p*-value or 2-sided CI is for the difference in proportions (VLA2001 – ChAdOx1-S) of participants with seroconversion at each particular visit.

Cellular immune response was investigated using an interferon gamma T-cell ELISpot® assay against the spike, nucleocapsid and membrane proteins. The response against the spike protein (SFU per 2.5 x 10^5 PBMC) tended to be lower for VLA2001 (median: 10; range: 0–152) compared to ChAdOx1-S (median: 20; range: 2–130); that is, 74.3% (55/74) of participants in the VLA2001 group and 86.5% (64/74) of participants in the ChAdOx1-S group had a T-cell response against peptide pools spanning the full-length S-protein detected on day 43, for the PBMC subset of the IMM population. In contrast, a response against the nucleocapsid and membrane proteins was apparent for VLA2001, with 45.9% (34/74) of participants showing responses to the N-protein, and 20.3% (15/74) to the M-protein, which did not exist for ChAdOx1-S participants (0/74 for the N-protein, and 1/74 for the M-protein), as assessed in the PBMC subset of the IMM population (*(5)*, *(6)* and *pre-print, not peer-reviewed (11)*), (Fig 2 and Table 12). For the cohort of 1042 participants aged 18–29 years who received VLA2001 in an open-label fashion, anti-spike IgG GMTs were higher in this group (3033 [95% CI: 2628–3500]) than in the group aged ≥30 years (2331 [95% CI: 2113–2573]) *(5)*.

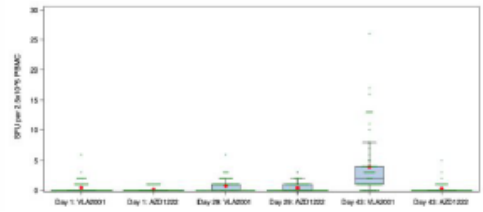
Fig 2. Boxplots for the cellular immune response in the phase 3 study (NCT04864561; ISRCTN 79815558)*‡



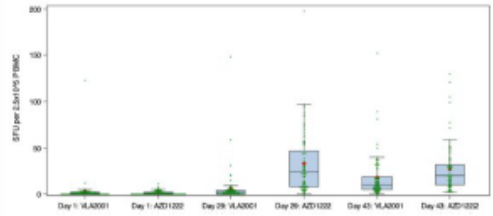
Panel A - Plot of Interferon Gamma Spot Forming Units per 2·5 × 10^5 PBMC by Dose Groups and Assessment Days for Spike Protein, Full Sequence.



Panel B - Plot of Interferon Gamma Spot Forming Units per 2·5 × 10^5 PBMC by Dose Groups and Assessment Days for Panel 3 Nucleocapsid Protein.



Panel C - Plot of Interferon Gamma Spot Forming Units per 2·5 × 10^5 PBMC by Dose Groups and Assessment Days for Panel 4 Membrane Protein.



Panel D - Plot of Interferon Gamma Spot Forming Units per 2·5 × 10^5 PBMC by Dose Groups and Assessment Days for Panel 14 Spike Protein Full Sequence.

*_Source_: Lazarus et al. 2022b *(11)*.

‡AZD1222: ChAdOx1-S vaccine.

Boxplots showing median, lower quartile and upper quartile; the horizontal line within each bar is the median and red + sign represents mean value for each group. Green scatter dots are the actual distribution of spot forming units (SFUs) per 2·5×10^5 peripheral blood mononuclear cells (PBMCs) within each group.

Table 12. Cellular immune response (reactogenicity against stimulation panel) – reactive percentages on day 1 and day 43 (immunogenicity population) from the phase 3 study (NCT04864561; ISRCTN 79815558)*

Metric	VLA2001 (*N*=492) Age ≥30 years	ChAdOx1-S (*N*=498) Age ≥30 years	Overall (*N*=990)
Spike protein N terminus			
Day 1			
n	77	79	156
Reactive	0	0	0
Day 43			

Metric	VLA2001 (*N*=492) Age ≥30 years	ChAdOx1-S (*N*=498) Age ≥30 years	Overall (*N*=990)
n	74	74	148
Reactive	38 (51·4)	58 (78·4)	96 (64·9)
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)
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)
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)
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)

Source: Lazarus et al. 2022b *(11)*.

Day 1: VLA2001 (*n*=77), ChAdOx1-S (*n*=79); Day 29: VLA2001 (*n*=73), ChAdOx1-S (*n*=75); Day 43: VLA2001 (*n*=71), ChAdOx1-S (*n*=70)

People with comorbidities

For people with obesity (BMI >30) within the IMM population, the ND_{50} GMT at day 43 was 689.3 (95% CI: 591.0–803.9) for the VLA2001 group (*n*=119), compared to 640.1 (95% CI: 565.3–724.8) for the ChAdOx1-S group (*n*=125), *p*-value of 0.534. The seroconversion rates for people with obesity from the PP population, were 94.4% (95% CI: 88.3–97.9) for the VLA2001 group and 99.1% (95% CI: 95.2–100.0) for the ChAdOx1-S group, *p*-value of 0.049 (from data on file). For people with risk factors, such as chronic obstructive pulmonary disease, cardiovascular risk, or diabetes, the subgroup sizes were small (Table 13).

Table 13. SARS-CoV-2 neutralizing antibodies and seroconversion rates for people with comorbidities from the phase 3 study (NCT04864561; ISRCTN 79815558)*

Metric	VLA2001 Age ≥30 years	ChAdOx1-S Age ≥30 years
People with obesity (BMI >30), day 43		
*n***	119	125
ND_{50} GMT (95% CI) IMM population	689·3 (591·0–803 ·9)	640·1 (565.3–724.8)
p-value	–	0·534
*n***	108	114
SCR (95% CI) PP population	94·4% (88·3–97 ·9)	99.1% (95·2–100·0)

p-value	–	0·049
People with cardiovascular risk		
*n***	7	1
ND_{50} GMT (95% CI) IMM population	720·5 (384·6–1349 ·5)	344·0 (NE–NE)
p-value	–	0·450
People with risk factors (COPD, cardiovascular risk or diabetes+), day 43		
*n***	8	1
ND_{50} GMT (95% CI) IMM population	785·0 (451.0–1 ·66 ·4)	344·0 (NE–NE)
p-value	–	0·379
*n***	8	1
SCR (95% CI) PP population	100% (63·1–100)	100% (2·5–100)
p-value	–	0·3785

**Source*: from data on file.

*n*** participants with eligible samples at day 43

+ there were no people with diabetes.

BMI: body mass index; GMT: geometric mean titre; CI: confidence interval; COPD: chronic obstructive pulmonary disease; IMM: immunogenicity; ND_{50}: 50% neutralizing dilution.; NE: not equal; PP: per protocol.

SCR: seroconversion rate (defined as ≥ 4-fold increase in SARS-CoV-2-specific neutralizing antibody titre levels between day 1 and day 43).

Immunogenicity for variants of concern

Studies are ongoing to evaluate the ability of VLA2001 to neutralize variants of the SARS-CoV-2 virus. Initial results are available from a study that considers serum antibodies induced by VLA2001 (from the phase 1/2 trial) against the Delta and Omicron variants of the SARS-CoV-2 virus. Sera from 30 participants were used in a pseudovirus assay to analyse neutralization of the ancestral SARS-CoV-2 virus as well as the Delta and Omicron variants; the pseudoviruses expressed the spike (S) protein for the three strains, with serial dilutions of individual serum samples for infecting target cells provided by the German Primate Center (Deutsches Primatenzentrum). Neutralization was calculated from the efficiency of reduction of infection at different serum dilutions compared to a no serum control *(15)*. All 30 samples (100%) presented neutralizing antibodies against the ancestral virus and Delta variant; 26 samples (87%) presented neutralizing antibodies against the Omicron variant with a mean fold reduction of neutralization relative to the ancestral virus of 2.7-fold for Delta and 16.7-fold for Omicron (*press release (16)*, and from data on file).

Efficacy studies

There are no data on vaccine efficacy from the phase 3 study conducted in the United Kingdom (NCT04864561; ISRCTN79815558). The results from the immunogenicity endpoints are available in the previous section.

Summary of results

The immunogenicity results from the phase 3 study (NCT04864561; ISRCTN79815558) are described in the previous section. There are no vaccine efficacy data available from this trial. WHO has acknowledged that data on immunogenicity may be used in certain situations as agreed under the auspices of the International Coalition of Medicines Regulatory Authorities (ICMRA), at a meeting in June 2020 which was co-chaired jointly by the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA).

Immunobridging

Immunobridging refers to "a situation where vaccine efficacy can be inferred by demonstrating a non-inferior immune response between an investigational vaccine and an authorized vaccine for which efficacy and/or effectiveness against a specific disease has been estimated". The ICMRA has noted that immunogenicity bridging studies may be needed if an assessment of effectiveness of next-generation COVID-19 vaccines in clinical endpoint efficacy studies are deemed no longer feasible. This is because given the increasing global coverage of COVID-19 vaccination, the conduct of placebo controlled clinical trials for next-generation vaccines becomes difficult to justify ethically. Regulators, including the members of the Access Consortium,[6] now take the position that the weight of evidence from studies with authorized COVID-19 vaccines is sufficient to support using neutralizing antibody titres as a primary endpoint in cross-platform immunobridging trials. Neutralizing antibody titres should be determined using WHO-certified reference standards *(17)*.

For active comparator superiority trials, WHO recommends that COVID-19 vaccine trials be designed as randomized, observer-blind, comparative immunogenicity superiority trials. The primary objective of such trials should be to demonstrate, at a specified time after the vaccination series, the superiority of an investigational candidate vaccine (in terms of GMT ratio of SARS-CoV-2-specific neutralization as a possible endpoint) compared to another COVID-19 vaccine *(17)*. The revised guidance for the considerations for evaluation of COVID-19 vaccines for the Emergency Use Listing (EUL) procedure now includes the criteria for immunobridging for new vaccines *(18)* and VLA2001 has been submitted for the EUL assessment through that revised process.

Exploratory analysis for evaluable COVID-19 cases

An exploratory analysis, conducted for the number of COVID-19 cases for the entire observation period (mean follow-up 151.4 days), showed no severe COVID-19 infection cases in any group. Among participants who received two doses of VLA2001, 87 (8.4%) cases of COVID-19 were reported in those aged 18–29 years, and 139 (7%) in those aged ≥30 years, compared with 60 (6%) cases of COVID-19 reported among participants who received two doses of ChAdOx1-S *(6)*.

No significant statistical difference was observed between the hazard ratios of PCR-confirmed COVID-19 cases from 14 days after the second vaccination between the groups aged ≥30 years (Table 14) *(11)*.

Table 14. Exploratory endpoint: hazard ratio analysis for evaluable COVID-19 cases from the phase 3 study (NCT04864561; ISRCTN 79815558)*

		VLA2001 Age <30 years	**VLA2001 Age ≥30 years**	**ChAdOx1-S Age ≥30 years**	**All participants**
Hazard ratio analysis for evaluable COVID-19 cases (14 days after second vaccination)					
	yes	69 (7·3)	88 (4·9)	42 (4·5)	199 (5·4)
	no	882 (92·7)	1706 (95·1)	899 (95·5)	3487 (94·6)
	Total	951	1794	941	3686
Maximum likelihood parameter estimates		**Probability > Chi-Square[a]**		**Hazard ratio [95% Wald CI]**	
Group: VLA2001 ≥30 yrs vs. ChAdOx1-S ≥30 yrs		**0·93**		**0·98 [0·68–1·42]**	

**Source*: Lazarus et al. 2022b *(11)*.

[a]Analysis of goodness of fit (maximum likelihood); likelihood ratio.

Infections that occurred after the use of other non-study COVID-19 vaccinations (i.e. vaccines other than VLA2001 and ChAdOx1-S) are not considered. Only data to data cut date of 14 October 2021 are considered. Participants with infection or non-study COVID-19 vaccination earlier than two weeks after the second

[6] Access Consortium: Australia-Canada-Singapore-Switzerland-United Kingdom.

vaccination are not analysed. One participant from the VLA2001 ≥30 year age group with reported infection could not be included in this analysis, since the date of infection was not reported. Percentages are based on the number of non-missing observations (total).

Booster dose studies

Homologous vaccine booster

Preliminary results from a continuation of the existing clinical phase 1/2 trial were announced by Valneva in December 2021. In this trial, a third homologous booster dose of VLA2001 (high dose from the phase 1/2 trial and the same dose as the phase 3 COV-COMPARE trial) was administered 7–8 months after the second dose of the primary vaccination series. IgG antibody titres (spike protein-based) were measured at the time of the booster and at two weeks after the booster dose. Of the 153 participants (aged 18–55 years) of the original phase 1/2 study, 77 were given a booster vaccine, although only 45 of these[7] were included in the final analysis. The third booster dose of VLA2001 elicited an anamnestic response, with similar antibody levels observed regardless of whether participants had initially been vaccinated with a low, medium or high dose (GMT 9699.3 [95% CI: 8497.8–11070.7]). This indicates that the levels of antibodies against the ancestral virus increased by 42-fold to 106-fold, depending on the pre-boosting levels of antibodies (*press release (19)*).

Heterologous vaccine booster

EudraCT 2022-000035-23. VLA2001-307

This is an open-label, single-arm trial to investigate the safety, tolerability, and immunogenicity of VLA2001 as a booster vaccination administered 6–12 months after completion of the primary series vaccination with an mRNA COVID-19 vaccine, or 6–12 months after PCR confirmation of SARS-CoV-2 infection. The study will be conducted in the Netherlands and is expected to recruit about 150 participants who are generally healthy or with a stable medical condition. Early first preliminary results are expected in the third quarter of 2022 (*press release, (13)*).

COV-BOOST study (ISRCTN 73765130)[8] (12)

Participants enrolled for the COV-BOOST study were aged >30 years, and were at least 70 days post receipt of two doses of ChAdOx1nCov-19 (Oxford–AstraZeneca, ChAdOx1-S), or at least 84 days post receipt of two doses of BNT162b2 (Pfizer–BioNtech, BNT162b2) as their primary vaccination series, with no history of laboratory-confirmed SARS-CoV-2 infection. Across the 18 sites in the United Kingdom, participants were randomly assigned to one of three groups (A, B or C) to receive either an experimental vaccine or control. Group A received (in a 1:1:1:1 ratio), NVX-CoV2373 (Novavax, NVX-CoV2373), *or* a half dose of NVX-CoV2373, *or* ChAdOx1-S, *or* a quadrivalent meningococcal conjugate vaccine (MenACWY) control. Group B received (in a 1:1:1:1:1 ratio), BNT162b2, *or* VLA2001, *or* a half dose of VLA2001, *or* Ad26.COV2.S (Janssen, Ad26.COV2.S) *or* MenACWY. Group C received (in a 1:1:1:1 ratio), mRNA1273 (Moderna, mRNA1273), *or* CVnCov (CureVac, CVnCov), *or* a half dose of BNT162b2, *or* MenACWY.

[7] Of the remaining participants who were not included in the final analysis, 27 had also received another COVID-19 vaccine, and additionally 5 of the remaining participants experienced a COVID-19 infection during the study. These all were excluded from the final analysis.

[8] This study was sponsored by the University Hospital Southampton, and the NHS Foundation Trust, of the United Kingdom of Great Britain and Northern Ireland, and not by the company.

The median age of ChAdOx1-S/ChAdOx1-S-primed participants was 53 years (interquartile range (IQR): 44–61 years) in the younger age group, and 76 years (IQR: 73–78 years) in the older age group. In BNT162b2/BNT162b2-primed participants, the median age was 51 years (IQR: 41–59 years) and 78 years (IQR: 75–82 years). In the ChAdOx1-S/ChAdOx1-S-primed group, 676 (47%) participants were female, and 1380 (95%) were white (Caucasian); in the BNT162b2/BNT162b2-primed group, 770 (54%) of the participants were female, and (92%) were white (Caucasian) (Table 15) *(12)*.

Table 15. Baseline characteristics by third dose vaccine allocation and priming vaccine schedule, Group B (includes VLA2001) from the COV-BOOST study (ISRCTN 73765130)*

	Primary vaccine schedule with ChAdOx1-S/ChAdOx1-S					**Primary vaccine schedule with BNT162b2/BNT162b2**				
	Control (*n*=106)	**BNT162b2 (*n*=107)**	**VLA2001 (*n*=109)**	**VLA2001 half dose (*n*=111)**	**Ad26.COV2.S (*n*=108)**	**Control (*n*=109)**	**BNT162b2 (*n*=110)**	**VLA2001 (*n*=110)**	**VLA2001 half dose (*n*=110)**	**Ad26.COV2.S (*n*=106)**
Age, years										
Mean (SD)	66·0 (14·3)	65·1 (15·3)	64·4 (15·3)	64·0 (14·9)	65·0 (14·9)	62·9 (16·9)	62·6 (17·1)	60·9 (18·1)	62·4 (16·7)	62·0 (17·4)
Median (IQR)	72·6 (57·6–77·2)	71·4 (53·8–77·0)	71·8 (51·2–76·5)	71·0 (51·2–75·9)	71·9 (51·0–76·4)	63·5 (50·4–78·3)	64·2 (49·8–77·4)	61·2 (46·2–77·7)	62·0 (51·8–76·2)	61·6 (49·2–78·3)
Intervals between doses, days										
Intervals between first and second doses, days	68·5 (63·0–77·0)	73·0 (66·0–77·0)	70·0 (63·0–77·0)	72·0 (64·0–77·0)	74·5 (68·0–77·0)	64·0 (24·0–74·0)	65·0 (28·0–74·0)	64·5 (27·2–73·0)	63·5 (27·2–74·0)	62·0 (25·2–74·0)
Intervals between second and third doses, days	78·0 (75·0–84·0)	77·0 (73·0–84·8)	79·0 (73·0–85·0)	77·0 (73·0–84·0)	77·0 (72·0–83·0)	101·0 (89·0–147·0)	100·0 (91·0–135·0)	100·5 (91·0–146·8)	101·5 (90·2–141·5)	106·0 (91·0–143·8)
Age groups, years										
<70	48 (45·3%)	50 (46·7%)	51 (46·8%)	51 (45·9%)	50 (46·3%)	62 (56·9%)	60 (54·5%)	63 (57·3%)	61 (55·5%)	59 (55·7%)
≥70	58 (54·7%)	57 (53·3%)	58 (53·2%)	60 (54·1%)	58 (53·7%)	47 (43·1%)	50 (45·5%)	47 (42·7%)	49 (44·5%)	47 (44·3%)
Sex										
Female	53 (50·0%)	50 (46·7%)	50 (45·9%)	54 (48·6%)	48 (44·4%)	52 (47·7%)	61 (55·5%)	59 (53·6%)	49 (44·5%)	60 (56·6%)
Male	53 (50·0%)	57 (53·3%)	59 (54·1%)	57 (51·4%)	60 (55·6%)	57 (52·3%)	49 (44·5%)	51 (46·4%)	61 (55·5%)	46 (43·4%)
Occupation										

	Primary vaccine schedule with ChAdOx1-S/ChAdOx1-S					Primary vaccine schedule with BNT162b2/BNT162b2				
	Control (*n*=106)	**BNT162b2 (*n*=107)**	**VLA2001 (*n*=109)**	**VLA2001 half dose (*n*=111)**	**Ad26.COV2.S (*n*=108)**	**Control (*n*=109)**	**BNT162b2 (*n*=110)**	**VLA2001 (*n*=110)**	**VLA2001 half dose (*n*=110)**	**Ad26.COV2.S (*n*=106)**
Health worker	24 (22·6%)	28 (26·2%)	33 (30·3%)	32 (28·8%)	29 (26·9%)	54 (49·5%)	55 (50·0%)	51 (46·4%)	48 (43·6%)	55 (51·9%)
Other	82 (77·4%)	79 (73·8%)	76 (69·7%)	78 (70·3%)	79 (73·1%)	55 (50·5%)	55 (50·0%)	59 (53·6%)	62 (56·4%)	51 (48·1%)
Ethnicity										
White	103 (97·2%)	104 (97·2%)	100 (91·7%)	107 (96·4%)	100 (92·6%)	101 (92·7%)	105 (95·5%)	99 (90·0%)	102 (92·7%)	103 (97·2%)
Black	0	0	2 (1·8%)	1 (0·9%)	0	0	1 (0·9%)	2 (1·8%)	0	0
Asian	1 (0·9%)	3 (2·8%)	5 (4·6%)	2 (1·8%)	5 (4·6%)	4 (3·7%)	3 (2·7%)	7 (6·4%)	6 (5·5%)	2 (1·9%)
Mixed	1 (0·9%)	0	0	0	0	2 (1·8%)	0	1 (0·9%)	2 (1·8%)	1 (0·9%)
Other	1 (0·9%)	0	1 (0·9%)	0	2 (1·9%)	2 (1·8%)	1 (0·9%)	1 (0·9%)	0	0
Not provided	0	0	1 (0·9%)	0	1 (0·9%)	0	0	0	0	0
Comorbidities										
Cardiovascular	33 (31·4%)	39 (36·4%)	39 (35·8%)	30 (27·0%)	42 (38·9%)	25 (22·9%)	30 (27·3%)	29 (26·4%)	27 (24·5%)	30 (28·3%)
Respiratory	18 (17·1%)	10 (9·3%)	15 (13·8%)	14 (12·6%)	20 (18·5%)	10 (9·2%)	12 (10·9%)	16 (14·5%)	13 (11·8%)	17 (16·0%)
Diabetes	4 (3·8%)	7 (6·5%)	8 (7·3%)	6 (5·4%)	7 (6·5%)	5 (4·6%)	6 (5·5%)	5 (4·5%)	5 (4·5%)	4 (3·8%)

**Source*: Munro 2021 *(12)*.

Data are median (IQR) or *n* (%), unless otherwise stated. For 3 participants, data on occupation were missing; for 5 participants data on ethnicity were missing. These 8 participants were not included in this table. ChAdOx1-S: ChAdOx1nCoV-19 vaccine, Oxford–AstraZeneca. Control: quadrivalent meningococcal conjugate vaccine. BNT162b2: BNT162b2 vaccine, Pfizer–BioNTech. VLA2001: VLA2001 vaccine, Valneva. VLA2001 half: half dose of VLA2001 vaccine. Ad26.COV2.S: Ad26.COV2.S vaccine, Janssen. IQR: interquartile range. SD: standard deviation. Baseline characteristics for Group A and Group C are available from Munro 2021 *(12)*.

Immunogenicity:

For participants primed with ChAdOx1-S/ChAdOx1-S, all COVID-19 vaccines given as the third booster dose induced significantly higher anti-spike IgG at 28 days post boost, compared with their corresponding controls. The geometric mean ratio (GMR) values between the vaccines and controls ranged from 1.8 (99% CI: 1.5–2.3) in the half-dose VLA2001 group to 32.3 (99% CI: 24.8–42.0) in the mRNA1273 group. The GMRs for pseudotype virus neutralizing antibodies against wild-type were consistent with those of anti-spike IgG. All the study vaccines except ChAdOx1-S, VLA2001, and half VLA2001, given as the third dose, significantly induced cellular responses by T-cell ELISpot in ChAdOx1-S/ChAdOx1-S-primed participants. Overall, the response with VLA2001 was higher than the control and equivalent to ChAdOx1-S, but lower than all other options *(12)*.

For participants primed with BNT162b2/BNT162b2 as the primary schedule, significant GMRs were also observed in all study vaccine groups compared with controls for anti-spike IgG at 28 days post boost, ranging from 1.3 (99% CI: 1.0–1.5) in the half-dose VLA2001 group, to 11.5 (99% CI: 9.4–14.1) in the mRNA1273 group. However the upper limit of the 99% CI for VLA2001 and for the half-dose VLA2001 did not reach the pre-established minimum clinically important difference of 1.75. Again, for the BNT162b2/BNT162b2 participants, the GMRs for pseudotype virus neutralizing antibodies and anti-spike IgG antibodies were consistent. An increase in anti-spike IgG concentrations at day 7 compared with baseline was observed in all study vaccine groups, except VLA2001 and half-dose VLA2001. The study showed that the immunogenicity of homologous or heterologous third dose boosters with all tested vaccines was superior to the control, regardless of which vaccine had been received in the primary schedule. The exception to this was VLA2001, which did not achieve the predefined criteria for minimum clinically important difference following BNT162b2/BNT162b2 (i.e. the response with VLA2001 was marginally higher (B-cell) or equivalent (T-cell) to the control) *(12)*.

Safety:

Until the data lock on 19 August 2021, 1306 adverse events were reported from 912 participants; this included 20 adverse events of special interest (AESIs), after excluding SARS-CoV-2 infection in the 14 days immediately after the third dose, and serious adverse events (SAEs) among which 6 were deemed possibly related to the study vaccine. The AESIs included 2 participants (VLA2001, full dose) reporting ventricular extrasystoles (cardiac arrhythmia with premature contractions of the heart ventricles) and acute kidney injury, respectively. A total of 21 participants reported a PCR test result positive for SARS-CoV-2 with no hospitalization; of these, 8 cases (38%) were within the VLA2001 arms – 4 with full dose (18, 34, 52 and 66 days after the third booster dose) and 4 with half dose (17, 25, 28 and 37 days after the third booster dose); 5 cases (24%) occurred within the other vaccine arms (1 case (5%) each for ChAdOx1-S and Ad26.COV2.S, and 3 cases (14%) within the NVX-CoV2373 arms – 2 of which were in the half-dose group); the remaining 8 cases (38%) were in control arms.

There were 24 SAEs reported, including 4 suspected unexpected serious adverse reactions. Of these, 6 were in VLA2001 arms, 5 with the full dose: a grade 4 liver injury, 28 days onset from the booster and noted as possibly related to the the intervention; a grade 3 myocardial infarction requiring hospitalization, 19 days onset from the booster and noted as possibly related to the intervention; a grade 3 breast cancer case, 46 days onset from the booster and noted as unrelated; a grade 4 sinus node dysfunction requiring hospitalization, 15 days onset from the booster and noted as unlikely to be related; and a grade 3 pyelocaliectasis, 49 days onset from the booster and noted as unrelated. The 1 case with the half-dose VLA2001, was a grade 3 oesophageal squamous cell carcinoma, 0 days onset from the booster and noted as unrelated to the intervention. The profiles of any grade local and systemic reactions within 7 days after all vaccines were similar, with fatigue and headache being the most commonly reported systemic reactions, and pain being the most frequently reported local reaction. For the ChAdOx1-S/ChAdOx1-S-primed group, the frequencies of severe local and systemic reactions were less than 5% for all vaccine groups, the exception being severe fatigue which was reported in 12% of the 112 recipients of mRNA1273. For the BNT162b2/BNT162b2-primed group, rates were above 5% for the following reactions: malaise (6%) for each of the ChAdOx1-S (108 recipients), mRNA1273 (109 recipients), and CVnCov (104 recipients) boosted groups; and chills (6%) and fatigue (8%) for the 103 participants boosted with Ad26.COV2.S *(12)*.

Safety

Phase 1/2 safety findings

The primary safety outcome was frequency and severity of solicited adverse events (AEs) within 7 days of either the first or second vaccination. Secondary outcomes reported were the number and percentage of participants with unsolicited AEs, related AEs, AEs of special interest (AESIs) and serious AEs (SAEs) by severity up to day 36. No significant differences were seen in reactions between the first and second vaccine doses or the different dose concentrations. Overall, 67% of the vaccinees reported at least one solicited injection site reaction, with tenderness and pain at injection site being most commonly reported (Table 16); 69% reported at least one solicited systemic reaction, with headache, fatigue and muscle pain being most frequently reported (Table 17).

Unsolicited AEs, including laboratory abnormalities thought to be related to vaccination, were reported in 27 (18%) participants, with 24%, 14% and 16% reported in the low-, medium- and high-dose groups, respectively. Two cases of confirmed COVID-19 were reported: 1 mild case in the medium-dose group, 16 days after the first vaccination; and 1 case of moderate severity in the low-dose group, 4 days after the second vaccination. There was 1 AESI – a mild case of chilblains 4 days after the first vaccination; the participant tested negative for COVID-19 *(4)*.

Table 16. Injection site reactions 7 days after any vaccine by frequency and severity from the phase 1/2 study NCT04671017; ISRCTN 82411169)*

Adverse event/Severity	Dose n (%)			
	Low dose (*N*=51)	Medium dose (*N*=51)	High dose (*N*=51)	Overall (*N*=153)
Participants with at least one solicited injection site reaction	35 (68·6)	31 (60·8)	36 (70·6)	102 (66·7)
Mild (Grade 1)	32 (62·7)	27 (52·9)	32 (62·7)	91 (59·5)
Moderate (Grade 2)	3 (5·9)	4 (7·8)	4 (7·8)	11 (7·2)
Injection site tenderness	32 (62·7)	23 (45·1)	34 (66·7)	89 (58·2)
Mild (Grade 1)	30 (58·8)	20 (39·2)	33 (64·7)	83 (54·2)
Moderate (Grade 2)	2 (3·9)	3 (5·9)	1 (2·0)	6 (3·9)
Injection site pain	19 (37·3)	21 (41·2)	24 (47.1)	64 (41·8)
Mild (Grade 1)	17 (33·3)	20 (39·2)	21 (41·2)	58 (37·9)
Moderate (Grade 2)	2 (3·9)	1 (2·0)	3 (5·9)	6 (3·9)
Injection site itching	3 (5·9)	3 (5·9)	2 (3·9)	8 (5·2)
Mild (Grade 1)	3 (5·9)	3 (5·9)	2 (3·9)	8 (5·2)
Injection site swelling	1 (2·0)	0	1 (2·0)	2 (1·3)
Mild (Grade 1)	1 (2·0)	0	0	1 (0·7)
Moderate (Grade 2)	0	0	1 (2·0)	1 (0·7)

**Source*: *preprint, not peer-reviewed,* Lazarus et al. 2021 *(3)*; and Lazarus et al. 2022 *(4)*.

Table 17. Solicited adverse reactions 7 days after any vaccine by frequency and severity from the phase 1/2 study (NCT04671017; ISRCTN 82411169)*

Adverse event/Severity	Dose *n* (%)			
	Low dose (*N*=51)	Medium dose (*N*=51)	High dose (*N*=51)	Overall (*N*=153)
Participants with at least one solicited systemic reaction	37 (72·5)	32 (62·7)	37 (72·5)	106 (69·3)
Mild (Grade 1)	26 (51·0)	23 (45·1)	26 (51·0)	75 (49·0)
Moderate (Grade 2)	11 (21·6)	9 (17·6)	9 (17·6)	29 (19·0)
Severe (Grade 3)	0	0	2 (3·9)	2 (1·3)
Headache	28 (54·9)	17 (33·3)	26 (51·0)	71 (46·4)
Mild (Grade 1)	22 (43·1)	14 (27·5)	20 (39·2)	56 (36·6)
Moderate (Grade 2)	6 (11·8)	3 (5·9)	5 (9·8)	14 (9·2)
Severe (Grade 3)	0	0	1 (2·0)	1 (0·7)
Fatigue	23 (45·1)	15 (29·4)	22 (43·1)	60 (39·2)
Mild (Grade 1)	16 (31·4)	10 (19·6)	15 (29·4)	41 (26·8)
Moderate (Grade 2)	7 (13·7)	5 (9·8)	5 (9·8)	17 (11·1)
Severe (Grade 3)	0	0	2 (3·9)	2 (1·3)
Muscle Pain	18 (35·3)	15 (29·4)	17 (33·3)	50 (32·7)
Mild (Grade 1)	15 (29·4)	13 (25·5)	16 (31·4)	44 (28·8)
Moderate (Grade 2)	3 (5·9)	2 (3·9)	1 (2·0)	6 (3·9)
Nausea/Vomiting	5 (9·8)	7 (13·7)	6 (11·8)	18 (11·8)
Mild (Grade 1)	5 (9·8)	6 (11·8)	5 (9·8)	16 (10·5)
Moderate (Grade 2)	0	1 (2·0)	1 (2·0)	2 (1·3)
Fever/Body temperature (>38 °C)	2 (3·9)	0	0	2 (1·3)
Mild (Grade 1)	0	0	0	0
Moderate (Grade 2)	2 (3·9)	0	0	2 (1·3)

**Source*: Lazarus et al. 2022 *(4)*.

Phase 3 safety findings

In total, 3037 participants received VLA2001, and 995 received ChAdOx1-S. The incidence of any reported AEs until day 43, was 93% in the VLA2001 <30 year age group, 89% in the VLA2001 ≥30 year age group, and 98% in the ChAdOx1-S cohort; most AEs were reported as being mild *(11)* (Table 18). Significantly fewer participants in the VLA2001 age ≥30 cohort reported solicited AEs up to 7 days after the first vaccination, both with regards to local injection site reactions (73% VLA2001 vs 91% ChAdOx1-S; $p<0.0001$), (
Fig 3 Panel A) and systemic reactions (70% VLA2001 vs 91% ChAdOx1-S; $p<0.0001$), (
Fig 3, Panel B). Injection site tenderness and fatigue were the most frequently reported solicited reactions after the first vaccine dose *(11)*, (
Fig 3).

The most frequently reported adverse reactions were tenderness at injection site (>60%), pain (>40%), fatigue (>50%), headache (>30%), muscle pain (>30%), and nausea/vomiting (>10%). Most adverse reactions were mild and resolved within two days of

vaccination. The incidence and severity of adverse reactions were similar after the first and second doses and tended to decrease in relation with participants' age. VLA2001 appeared less reactogenic than ChAdOx1-S in participants aged ≥30 years following the second dose, with significantly more participants reporting solicited systemic reactions in the ChAdOx1-S group than in the VLA2001 ≥30 year age group after any vaccination (p<0.0001) (Table 19) or after the second vaccination (p=0.0369), (*(5)* and *(11)*). The most frequently reported adverse reactions from the study overall are provided in

Table *20 (5)*.

Incidence of unsolicited AEs with the VLA2001 vaccine was 29% in both the <30 year and ≥30 year age groups; with the ChAdOx1-S vaccine, incidence was 35% (the difference between the two vaccines in the ≥30 age groups was statistically significant (p=0.0003)) (*(11)*, Table 21). No solicited SAE was reported in any treatment group; 0.8% of participants reported an unsolicited SAE, although these were considered unrelated to the vaccination. The incidences of SAEs overall were similar across all treatment groups (0.7% in the VLA2001 groups and 1.0% in the ChAdOx1-S group) *(11)*.

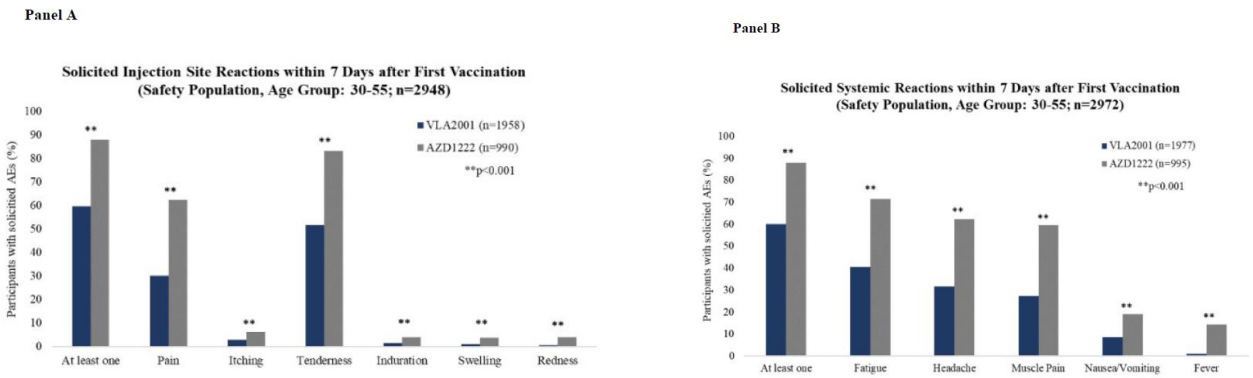
Table 18. Overall summary of adverse events until day 43 from the phase 3 study (NCT04864561; ISRCTN 79815558)*

Characteristics	VLA2001 Age <30 years (*N*=1040) *n* (%)	VLA2001 Age ≥30 years (*N*=1977) *n* (%)	ChAdOx1-S Age ≥30 years (*N*=995) *n* (%)
Participants with any AE until day 43	963 (92·6)	1755 (88·8)	976 (98·1)
Participants with any treatment related AE until day 43	955 (91·8)	1719 (86·9)	975 (98·0)
Participants with any SAE until day 43	2 (0·2)	6 (0·3)	3 (0·3)
Participants with any medically attended AE until day 43	78 (7·5)	138 (7·0)	72 (7·2)
Participants with any AESI until day 43	2 (0·2)	1 (0·1)	2 (0·2)

**Source*: Lazarus et al. 2022b *(11)*.

AE: adverse event; AESI: adverse event of special interest; SAE: serious adverse event.

Fig 3. Solicited injection site reactions within 7 days after the 1st vaccination from the phase 3 study (NCT04864561; ISRCTN 79815558)* ‡



**Source*: Lazarus et al. 2022b *(11)*.

***p*-value compares the VLA2001 (age ≥30 years) group with the ChAdOx1-S group.

‡ AZD1222: ChAdOx1-S vaccine.

Table 19. Solicited systemic reactions within 7 days after any vaccination from the phase 3 study (NCT04864561; ISRCTN 79815558)*

Solicited systemic reaction	VLA2001 Age <30 years (*N*=1040) *n* (%)	VLA2001 Age ≥30 years (*N*=1977) *n* (%)	ChAdOx1-S Age ≥30 years (*N*=995) *n* (%)	Overall (*N*=4012) *n* (%)
Participants with at least 1 solicited systemic reaction				
n (%)	800 (76·9)	1387 (70·2)	906 (91·1)	3093 (77·1)
95% CI [A]	(74·2–79·5)	(68·1–72·2)	(89·1–92·8)	(75·8–78·4)
p-value [B]				<0·0001
Fatigue				
n (%)	596 (57·3)	1012 (51·2)	767 (77·1)	2375 (59·2)
95% CI [A]	(54·2–60·3)	(49·0–53·4)	(74·4–79·7)	(57·7–60·7)
p-value [B]				<0·0001
Headache				
n (%)	422 (40·6)	787 (39·8)	674 (67·7)	1883 (46·9)
95% CI [A]	(37·6–43·6)	(37·6–42·0)	(64·7–70·6)	(45·4–48·5)
p-value [B]				<0·0001
Muscle pain				
n (%)	458 (44·0)	732 (37·0)	639 (64·2)	1829 (45·6)
95% CI [A]	(41·0–47·1)	(34·9–39·2)	(61·2–67·2)	(44·0–47·1)
p-value [B]				<0·0001
Nausea/Vomiting				
n (%)	154 (14·8)	231 (11·7)	227 (22·8)	612 (15·3)
95% CI [A]	(12·7–17·1)	(10·3–13·2)	(20·2–25·6)	(14·2–16·4)
p-value [B]				<0·0001
Fever/Body temperature				
n (%)	11 (1·1)	29 (1·5)	154 (15·5)	194 (4·8)
95% CI [A]	(0·5–1·9)	(1·0–2·1)	(13·3–17·9)	(4·2–5·6)
p-value [B]				<0·0001

**Source*: *preprint, not peer-reviewed*, Lazarus et al. 2022b *(11)*.

Table presents solicited systemic reactions from participant diary.

CI: confidence interval.

A: Exact 95% Clopper-Pearson CI for proportion.

B: *p*-value compares the VLA2001 (age ≥30) group with the ChAdOx1-S group.

Table 20. Adverse reactions reported from the phase 3 study (NCT04864561; ISRCTN 79815558)*

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy

MedDRA system organ class	Frequency	Adverse reactions
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness, lethargy Paraesthesia, dysgeusia, hypoaesthesia
Gastrointestinal disorders	Very common	Nausea, vomiting
	Uncommon	Diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis, rash
	Rare	Urticaria
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Uncommon	Pain in extremity, muscle spasms, arthralgia
General disorders and administration site conditions	Very common	Fatigue Injection site pain
	Common	Injection site pruritus, induration, swelling, erythema Pyrexia

**Source*: MHRA, 2022 *(5)*.

Adverse reactions reported are listed per MedDRA system organ class and according to the following frequency categories: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100); Rare (≥1/10 000 to < 1/1000); Very rare (<1/10 000); Not known (cannot be estimated from available data).

Table 21. Overall summary of unsolicited adverse events from the phase 3 study (NCT04864561; ISRCTN 79815558)*

	VLA2001 Age <30 years (*N*=1040)	VLA2001 Age ≥30 years (*N*=1977)	ChAdOx1-S Age ≥30 years (*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]	(26·1–31·7)	(26·6–30·7)	(32·1–38·1)	(28·9–31·4)
p-value [B]				0·0003
Participants with any unsolicited AE until interim analysis				
n (%)	423 (40·7)	793 (40·1)	443 (44·5)	1659 (41·4)
95% CI [A]	(37·7–43·7)	(37·9–42·3)	(41·4–47·7)	(39·8–42·9)
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]	(0·0–0·7)	(0·1–0·7)	(0·1–0·9)	(0·14–0·49)
p-value [B]				0·9926

	VLA2001 Age <30 years (*N*=1040)	VLA2001 Age ≥30 years (*N*=1977)	ChAdOx1-S Age ≥30 years (*N*=995)	Overall (*N*=4012)
Participants with any serious unsolicited AE until interim analysis				
n (%)	7 (0·7)	14 (0·7)	10 (1·0)	31 (0·8)
95% CI [A]	(0·3–1·4)	(0·4–1·2)	(0·5–1·8)	(0·5–1·1)
p-value [B]				0·3034
Participants with any AESI until day 43				
n (%)	2 (0·2)	1 (0·1)	2 (0·2)	5 (0·1)
95% CI [A]	(0·0–0·7)	(0·0–0·3)	(0·0–0·7)	(0·0–0·3)
p-value [B]				0·2230
Participants with any AESI until interim analysis				
n (%)	3 (0·3)	4 (0·2)	2 (0·2)	9 (0·2)
95% CI [A]	(0·1–0·8)	(0·1–0·5)	(0·0–0·7)	(0·1–0·4)
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]	(8·8–12·6)	(9·7–12·5)	(15·5–20·3)	(11·6–13·7)
p-value [B]				<0·0001
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]	(5·7–9·0)	(5·9–8·1)	(5·4–8·6)	(6·2–7·8)
p-value [B]				0·9277
Participants with any treatment related unsolicited AE until interim analysis				
n (%)	113 (10·9)	227 (11·5)	178 (17·9)	518 (12·9)
95% CI [A]	(9·0–12·9)	(10·1–13·0)	(15·6–20·4)	(11·9–14·0)
p-value [B]				<0·0001
Participants with any medically attended unsolicited AE until interim analysis				
n (%)	132 (12·7)	243 (12·3)	114 (11·5)	489 (12·2)
95% CI [A]	(10·7–14·9)	(10·9–13·8)	(9·5–13·6)	(11·2–13·2)
p-value [B]				0·5092

*Source: *preprint, not peer-reviewed*, Lazarus et al. 2022b *(11)*.

AE: adverse event; AESI: adverse event of special interest; CI: confidence interval.

A: Exact 95% Clopper-Pearson CI for proportion.

B: *p*-value tests difference in proportions between VLA2001 at age ⩾30 years, and ChAdOx1-S.

Special considerations

Pregnancy

Participants were excluded if they were pregnant or planned to become pregnant within 3 months of vaccine administration. Use of VLA2001 vaccine in pregnant women is limited. There were 47 pregnancies in 36 trial participants from the phase 3 study; further details and analyses will be available from the third quarter of of 2022. Animal studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development *(5)*. Aluminium containing adjuvants have been widely used in vaccines since the 1930s; however, CpG 1018 has only recently been developed. CpG 1018 consists of cytosine phosphoguanine (CpG) motifs, a synthetic form of DNA that mimics bacterial and viral genetic material; when included in a vaccine, the body's immune response is increased. CpG 1018 is used as an adjuvant in the Heplisav-B vaccine and in pre-licensure clinical trials; adverse events after vaccination with Heplisav-B were comparable to those observed after another licensed, non-adjuvanted hepatitis B vaccine *(20)*. A retrospective chart review comparing the identified 40 documented pregnancies in the HepB-CpG arm, with the identified 19 documented pregnancies in the HepB-alum arm, showed similar pregnancy safety outcomes for both arms and higher seroprotection rates for the HepB-CpG arm *(21)*. Based on previous experience with use of other inactivated vaccines used during pregnancy, WHO anticipates the effectiveness and safety of VLA2001 in pregnant women to be comparable to those observed for non-pregnant women in similar age groups.

Paediatric population

The safety and immunogenicity of VLA2001 vaccine in children and adolescents (aged <18 years) have not yet been established. No data are available. Two trials are currently underway for this age range: VLA2001-301a, for adolescents aged 12–17 years; and VLA2001-321, for children aged 2–12 years.

Immunosuppression

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy.

Breastfeeding

It is unknown whether the vaccine is excreted in human milk.

Safety related to vaccine interactions

There are no data on the use of the VLA2001 vaccine provided concomitantly with other vaccines.

Post licensure studies

There are no data available from post licensure studies for VLA2001 from the countries where the vaccine has received regulatory approval. The first set of vaccinations with VLA2001 in the Kingdom of Bahrain were initiated in May 2022 (from data on file).

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