COVID-19 Vaccine (inactivated, adjuvanted) Valneva: Periodic safety update report assessment

28th February 2022 to 27th August 2022

This document consists of:

1. The PRAC assessment report of the COVID-19 Vaccine (inactivated, adjuvanted) Valneva periodic safety update report (PSUR) covering the period 27th February 2022 to 27th August 2022, and;

2. The COVID-19 Vaccine (inactivated, adjuvanted) Valneva PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.

EMA/PRAC/104277/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00011001/202208

Active substance(s): SARS-CoV-2 virus, strain Wuhan hCoV-19/Italy/INMI1-isl/2020, inactivated (Valneva)

Period covered by the PSUR: 27/02/2022 To: 27/08/2022

Centrally authorised Medicinal product(s): For presentations: See Annex A	Marketing Authorisation Holder
COVID-19 Vaccine (inactivated, adjuvanted) Valneva	Valneva Austria GmbH

Status of this report and steps taken for the assessment

Current step	Description	Planned date	Actual Date
☐	Start of procedure:	17 November 2022	17 November 2022
☐	PRAC Rapporteur's preliminary assessment report (AR)	16 January 2023	16 January 2023
☐	MS/PRAC members and MAH comments	15 February 2023	15 February 2023
☐	PRAC Rapporteur's updated assessment report following comments	02 March 2023	02 March 2023
☒	PRAC recommendation	16 March 2023	16 March 2023

Procedure resources	
PRAC Rapporteur	Name: Gabriele Maurer Email:
Contact person - PRAC Rapporteur	Name Email:
Assessor – PRAC Rapporteur	Name Email:
EMA Procedure Lead	Name Tel: Email:
EMA Procedure Assistant	Name Tel: Email:

Table of contents

1. Background information on the procedure 4

2. Assessment conclusions and actions 4

3. Recommendations 4

4. Issues to be addressed in the next PSUR or as a post-authorisation measure (PAM) 4

5. PSUR frequency 4

1. Background information on the procedure

This is the assessment of the PSUR submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for SARS-CoV-2 virus, strain Wuhan hCoV-19/Italy/INMI1-isl/2020, inactivated (Valneva).

2. Assessment conclusions and actions

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) Valneva is a purified, inactivated, and adjuvanted whole virus SARS-CoV-2 (Wuhan strain hCoV-19/Italy/INMI1-isl/2020) vaccine grown on Vero cells. One dose of 0.5 mL contains 33 antigen units of inactivated virus and is injected intramuscularly twice at an interval of four weeks.

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) Valneva's international birth date is 28 February 2022, when emergency use authorisation was granted in the Kingdom of Bahrain. In the European Union (EU), on 24 June 2022, the vaccine received a marketing authorisation for the active and primary immunisation of individuals between 18 and 50 years of age to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The MAH quantifies the number of individuals who received the vaccine within the five ongoing studies at 3,969. Post-authorisation, it estimates that 200,000 doses were distributed in the Kingdom of Bahrain and 362,400 doses in the European Union (EU). How many doses were administered is not specified.

The MAH states not having received any ICSRs. No new safety-relevant aspects arose during the reporting interval. The safety concerns therefore remain unchanged. New data on efficacy in the approved indication are also not available.

In conclusion, no alterations with regard to the benefit-risk profile can be derived from the data in the present PSUR.

3. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing SARS-CoV-2 virus, strain wuhan hCoV-19/Italy/INMI1-isl/2020, inactivated (Valneva) remains unchanged and therefore recommends the maintenance of the marketing authorisation.

4. Issues to be addressed in the next PSUR or as a post-authorisation measure (PAM) [1]

Not applicable.

5. PSUR frequency

☒No changes to the PSUR frequency

The current **6**-monthly frequency for the submission of PSURs should remain unchanged.

[1] The submission of PAMs for CAPs must be done in eCTD format via the eSubmission Gateway/Web Client, and will be considered delivered to all National Competent Authorities representatives, alternates and scientific experts. PAMs must not be submitted to the PSUR Repository.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This first periodic safety update report (PSUR) for Coronavirus disease 2019 (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) covers the period from 28 February 2022 to 27 August 2022. The vaccine's international birth date (IBD), as well as its European Union (EU) reference date (EURD), is 28 February 2022, when COVID-19 vaccine (inactivated, adjuvanted, adsorbed) was first authorised for emergency use in the Kingdom of Bahrain.

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is a purified, inactivated, and adjuvanted whole severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine grown on Vero cells (African green monkey cells). It induces SARS-CoV-2 neutralising antibodies, as well as cellular immune responses (Th1) directed against the spike and other surface proteins. However, no data on induction of humoral immune responses directed against SARS-CoV-2 antigens other than spike protein are available in humans.

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is indicated for the active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 to 50 years of age. The vaccine is supplied in a multi-dose vial containing 10 doses of 0.5 mL suspension for injection. A dose consisting of 33 antigen units of inactivated SARS-CoV-2 is administered intramuscularly twice at an interval of 28 days.

1.2. Worldwide marketing authorisation status

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) was first authorised in the Kingdom of Bahrain on 28 February 2022, it was authorised in the EU on 24 June 2022. Besides, approval has been granted in the United Arab Emirates (12 May 2022, emergency use authorisation) and in the United Kingdom (13 April 2022, conditional marketing authorisation). The vaccine is marketed in the Kingdom of Bahrain and in the EU.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

The MAH states that during the reporting interval, no actions were taken for safety reasons.

1.3.2. Changes to reference safety information

The reference safety information in effect is the summary of product characteristics (SmPC) dated 25 July 2022. During the reporting interval, an update related to a shelf life extension of three months was made, but no safety related changes.

Rapporteur assessment comment: The MAH neither provides new safety information nor recommends new risk minimisation measures.

1.3.3. Estimated exposure and use patterns

Clinical trial exposure. According to the MAH, a total of 3,969 adults received COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in five ongoing clinical trials – one phase 1/2 trial (VLA2001-201, n = 153), one phase 2 trial (COV BOOST, n = 440), one phase 2/3 trial (VLA2001-307, n = 53), and two phase 3 trials (VLA2001-301, n = 3,017, and VLA2001-304, n = 306). With the exception of study VLA2001-307, for which data are not yet presented, the studies included 2,147 male, 1,764 female, and 5 diverse adult participants. In addition, the vaccine was administered to 10 male and 11 female adolescents (≥ 12 and < 18 years old).

Post-authorisation exposure. The MAH notes that a total of 562,400 COVID-19 vaccine (inactivated, adjuvanted, adsorbed) doses were distributed in the Kingdom of Bahrain (n = 200,000) and the EU (n = 362,400; Austria, n = 74,400; Denmark, n = 38,400; Germany, n = 249,600). Information on how many doses were administered is not available.

Rapporteur assessment comment:

Most people treated in clinical trials were white and between 18 and 55 years old. The report does not contain data on the post-authorisation use of the vaccine.

1.3.4. Data in summary tabulations

Serious adverse events from clinical trials. According to Table 15 (PSUR pp. 80-81), in studies VLA2001-201, VLA2001-301, and VLA2001-307, no serious adverse events were reported. In trial VLA2001-304, nine serious adverse events were recorded in a total of eight participants between 58 and 76 years of age with the following preferred terms: atrial fibrillation (two events), osteoarthritis, facial cellulitis, breast cancer, poorly differentiated adenocarcinoma oesophagus, parotitis, diverticulitis, and small bowel obstruction (one event each). In the COV-BOOST trial, two serious adverse events were listed with the preferred terms liver injury and myocardial infarction. Tables 16-20 (PSUR pp. 82-85), however, provide additional preferred terms of serious adverse reactions for studies VLA2001-201, VLA2001-301, VLA2001-304, and COV-BOOST.

Post-authorisation data. The MAH declares not having received any individual case safety reports (ICSRs).

Rapporteur assessment comment:

The data from Appendix 3 (PSUR pp. 80-81, Table 15, line listings of all serious adverse events from clinical trials, and PSUR pp. 82-85, Tables 16-20, summary tabulations of all serious adverse reactions from clinical trials) are partially inconsistent. It is not clear to the PRAC rapporteur how the number of serious adverse reactions can exceed the number of serious adverse events. Example from Table 18: Here, among others, pneumonia legionella, urosepsis and cerebrovascular accident (one reaction each) are documented, which are not mentioned in Table 15. The MAH is kindly requested to resolve these discrepancies.

Otherwise, as far as assessable, no new important safety information is identified.

1.3.5. Findings from clinical trials and other sources

Completed clinical trials. The MAH states that during the reporting interval of this PSUR, no trials were completed for COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

Ongoing clinical trials. The MAH states that in the five ongoing clinical trials, 3,969 participants

received at least one dose of COVID-19 vaccine (inactivated, adjuvanted, adsorbed). Cumulatively, 50 serious adverse events were reported, of which only one was considered possibly related to the vaccine. Cases of appendicitis (three participants), atrial fibrillation (two participants), osteoarthritis (two participants), and tibial fracture (two participants) were reported more than once. One patient experienced three episodes of atrial fibrillation, the first one two days after the first vaccination, the second one 18 days after the first vaccination, and the third one 47 days after the second vaccination. The reaction was classified as suspected unexpected serious adverse reaction (SUSAR) and possibly related to the administration of COVID-19 vaccine (inactivated, adjuvanted, adsorbed).
In contradiction to what has just been stated, the MAH mentions another two out of five serious adverse events in the standard dose group of the COV-BOOST study that were assessed by the investigator as possibly related to COVID-19 vaccine (inactivated, adjuvanted, adsorbed) (Munro APS et al. Lancet 2021;198(10318):2258-76, doi: 10.1016/S0140-6736(21)02717-3).
The MAH also refers to one pregnancy of a participant and one partner pregnancy in the VLA2001-201 study, as well as 39 pregnancies of study participants (29 in the VLA2001 group and 10 in the AZD1222 group) and 13 partner pregnancies (10 in the VLA2001 group and 3 in the AZD1222 group) in the VLA2001-301 study. Three participants in the VLA2001 group had a miscarriage, at least two of them in the first trimester. Eight women delivered a full-term healthy baby, and one woman had a premature birth with reduced infant growth. The MAH confirms that all pregnancies are followed up.

Long-term follow-up. According to the MAH, during the reporting interval, there were no long-term follow-up trials for COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

Other therapeutic use of medicinal product. The MAH states that during the reporting interval, COVID-19 vaccine (inactivated, adjuvanted, adsorbed) has not been investigated for any other therapeutic use(s).

New safety data related to fixed combination therapies. The MAH notes that no safety data related to combination therapies with COVID-19 vaccine (inactivated, adjuvanted, adsorbed) became available during the reporting interval.

Non-interventional studies. The MAH states that during the reporting interval, no non-interventional studies for COVID-19 vaccine (inactivated, adjuvanted, adsorbed) were initiated, conducted, completed, or reported.

Other clinical trial/study sources. The MAH notes that during the reporting interval, no other studies have been conducted with COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

Non-clinical data. According to the MAH, no non-clinical studies were initiated or ongoing involving COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in the reporting interval.

Literature. During the reporting interval of this PSUR, the MAH identified nine literature articles and briefly summarises them.

Lazarus et al. report on the safety and immunogenicity of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) and present results of the phase 1/2 trial VLA2001-201 (Lazarus R et al. J Infect 2022;85(3):306-17, doi: 10.1016/j.jinf.2022.06.009). Here, the most frequently reported solicited injection site and systemic reactions were injection site tenderness (89 of 153 participants, 58.2%) and headache (71 of 153 participants, 46.4%). As an adverse event of special interest (AESI) and therefore per protocol definition serious adverse event, one participant developed chilblains four days after the first vaccination.

Further, the MAH cites results of the interim analysis of the randomised phase 3 immunobridging trial VLA2001-301 (Lazarus R et al. Lancet Infect Dis 2022; in press, doi: 10.1016/S1473-3099(22)00502-3). Any adverse event was reported in 963 participants (92.6%) of the open-label VLA2001 group (n =

1,040; age 18–29 years), in 1,755 participants (88.8%) of the randomised VLA2001 group (n = 1,977; age ≥ 30 years), and in 976 participants (98.1%) of the ChAdOx1-S group (n = 995; age ≥ 30 years). In the safety population, up to day 43, serious adverse events were recorded in two (0.2%), six (0.3%) and three (0.3%) participants, respectively. Until the interim analysis cut-off date (14 October 2021), seven (0.7%), 14 (0.7%), and 10 (1.0%) participants experienced at least one unsolicited serious adverse event.

Munro et al examined the safety and immunogenicity of different COVID-19 vaccines given as a third (booster) dose after two doses of ChAdOx1 nCov-19 or BNT162b2 (Munro APS et al. Lancet 2021;198(10318):2258-76, doi: 10.1016/S0140-6736(21)02717-3). They found that "all study vaccines boosted antibody and neutralising responses after ChAdOx1 nCov-19/ChAdOx1 nCov-19 initial course and all except one [namely COVID-19 vaccine (inactivated, adjuvanted, adsorbed)] after BNT162b2/BNT162b2, with no safety concerns."

The remaining six articles focus on other inactivated whole-virus COVID-19 vaccines and their immunogenicity, safety, efficacy, and use in special populations (children and adolescents with underlying medical conditions, individuals infected with human immunodeficiency virus).

Other periodic reports. The MAH refers to its monthly submitted summary safety reports (SSRs). During the reporting interval, this was SSR number 1, with the data lock point 31 July 2022.

Rapporteur assessment comment:

The information on serious adverse events should be coherent (also see the comment on section 1.3.4). The MAH is therefore kindly invited to revise this section with regard to the number and the assessment of serious adverse events.

The follow-up of pregnancies in participants of clinical trials is endorsed.

1.3.6. Lack of efficacy in controlled clinical trials

The MAH states that no new safety data emerged that indicated a lack of efficacy with COVID-19 vaccine (inactivated, adjuvanted, adsorbed) from clinical trials and from the review of published literature.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Important identified risks	No important risks have been identified.
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding Use in immunocompromised patient Use in patients with autoimmune or inflammatory disorders Use in frail patients with unstable health conditions and comorbidities, e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD) Long-term safety data Interaction with other vaccines

Table 1: Summary of safety concerns, EU risk management plan dated 21 June 2022 (PSUR p. 36, Table 12).

2.2. Signal evaluation

The MAH did not receive any new data relating to the above risks or missing information. It states that during the reporting interval, no signals were identified that warranted an update to the product safety specification for COVID-19 vaccine (inactivated, adjuvanted, adsorbed). Also, no signals were closed.

Rapporteur assessment comment: No new data on potential risks or missing information is presented, no signals have been raised.

2.3. Evaluation of risks and safety topics under monitoring

The MAH notes that health authorities requested an evaluation of the safety topics hypersensitivity, angioedema, autoimmune disorders, cardiomyopathy, peripheral neuropathy, and menstrual disorders involving COVID-19 vaccine (inactivated, adjuvanted, adsorbed). Besides, the MAH mentions fatal reports and the experience in special patient populations as additional safety topics under monitoring. As no ICSRs were received, these safety topics could not be further evaluated.

Further, the MAH queried its global vaccine safety database for AESIs including those considered for adjuvant CpG1018. However, it did not identify any ICSRs with MedDRA preferred terms related to these AESIs.

Rapporteur assessment comment: In consideration of the unchanged data situation and the lack of new information, no further action is considered warranted at this stage.

2.4. Characterisation of risks

The MAH refers to the presentation of important potential risks and missing information in the EU risk management plan approved on 21 June 2022. It notes that during the reporting interval, there were no additional risk minimisation measures in place for COVID-19 vaccine (inactivated, adjuvanted, adsorbed), and confirms that the effectiveness of routine risk minimisation measures will be monitored through the routine pharmacovigilance activities.

Rapporteur assessment comment: The safety concerns remain unchanged.

3. Benefit evaluation

The MAH briefly summarises the results of the ongoing study VLA2001-301. In the first interim analysis, immunogenicity of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) was at least similar to the comparator AZD1222. COVID-19 vaccine (inactivated, adjuvanted, adsorbed) demonstrated non-inferiority in terms of seroconversion rates at day 43 and induced broad T-cell responses with antigen-specific interferon-gamma producing T-cells. In the randomised participants ≥ 30 years of age, COVID-19 cases occurred at a similar frequency and time after vaccination in the VLA2001 and AZD1222 groups. After the second vaccine dose, 7.0% of the participants in the VLA2001 group tested COVID-19 positive,

with a median of 63.0 days after the second vaccination. In the AZD1222 group, 6.0% of the participants tested positive, with a median of 76.5 days after the second vaccination. The MAH notes that in the group of participants aged 18-29 years and treated with VLA2001, a higher number of COVID-19 cases was observed (8.4% of participants after the second vaccine dose, median 65.0 days from the second vaccination). All COVID-19 cases were assessed as mild or moderate by the investigator, none as severe. The MAH did not identify new safety information that could have an impact on the efficacy and effectiveness of COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

Rapporteur assessment comment:
There are no new data on efficacy that alters previous assessments, and which are described in the approved product information.

4. Benefit-risk balance

The present PSUR does not contain any new safety-relevant information. The benefit-risk profile of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) for the approved indication therefore remains positive.

5. Rapporteur request for supplementary information

1. The data from Appendix 3 (PSUR pp. 80-81, Table 15, line listings of all serious adverse events from clinical trials, and PSUR pp. 82-85, Tables 16-20, summary tabulations of all serious adverse reactions from clinical trials) are partially inconsistent, as is the description of serious adverse events in PSUR section 1.3.5. The MAH is therefore kindly asked for a clear and comprehensible presentation of serious adverse events observed in clinical studies (see comments in the respective sections).

6. MAH response to Request for supplementary information

We assume the Rapporteur refers to PSUR section 7.2 Ongoing clinical trials:

"Cumulatively, in Valneva's VLA2001 clinical program, 50 serious adverse events have been reported in participants who received VLA2001: 1 in study VLA2001-201, 32 in study VLA2001-301, and 17 in study VLA2001-304. The majority of these serious adverse events were mild to moderate in intensity, and only 1 was considered possibly related to VLA2001." "With the exception of 1 case of "atrial fibrillation", all serious adverse events are considered not "related" or "unlikely related" to the study vaccine.

The only serious adverse events that was "possibly related" to the study vaccine was a case of "atrial fibrillation" reported in study VLA2001-304."

→ Section 7.2. summarizes all SAE from start of clinical program, therefore differs from data shown in Table 15, which shows SAE only for the reporting period (28-Feb-2022 to 27-Aug-2022).

→ In table 15, we show SAE only for the reporting period. Please refer to tables 16-20 for summary tabulations of SAE from Clinical Trials since start of the clinical program.

→ Tables 16-20 were supposed to show "Cumulative Summary Tabulations of All Serious Adverse Reactions from Clinical Trials", instead we have shown Serious Adverse Events. We apologize for the misconception. Under the definition of "Serious Adverse Reactions = SAE considered at least

as possibly related to the medicinal product." we have only 1 Serious Adverse Reaction (=SUSAR; atrial fibrillation), see Table 21 below.

→ Please find on the following pages corrected tables for Appendix 3: Line Listings and Cumulative summary tabulations of all Serious Adverse Events from Clinical Trials. All data shown in the following tables are cumulative data since start of the clinical program until data cut (27-Aug-2022)

Table 16 Cumulative Summary Tabulation of All Serious Adverse Events from Clinical Trial VLA2001-201.

System Organ Class Preferred Term	VLA2001
Trial VLA2001-201	
Injury, poisoning and procedural complications	**1**
Chilblains	1

Table 17 Cumulative Summary Tabulation of All Serious Adverse Events from Clinical Trial VLA2001-301.

System Organ Class Preferred Term	Blinded Drug	Unknown
Trial VLA2001-301 – Adult Trial		
Infections and infestations	**2**	**9**
Anal abscess	0	1
Anorectal infection	0	1
Appendicitis	1	2
Appendicitis perforated	0	1
Encephalitis viral	0	1
Mesenteric abscess	1	0
Post-acute COVID-19 syndrome	0	1
Subcutanous abscess	0	1
Viral infection	0	1
Blood and lymphatic system disorders	**0**	**1**
Lymphadenitis	0	1
Nervous system disorders	**0**	**6**
Cauda equina syndrome	0	1
Headache	0	1
Nerve compression	0	1
Seizure	0	1
Subarachnoid haemorrhage	0	1
Thunderclap headache	0	1
Cardiac disorders	**0**	**1**
Tachycardia	0	1
Gastrointestinal disorders	**0**	**5**
Inflammatory bowel disease	0	1
Intestinal obstruction	0	1
Irritable bowel syndrome	0	1
Large intestine polyp	0	1
Pancreatitis	0	1
Musculoskeletal and connective tissue disorders	**0**	**2**
Intervertebral disc protrusion	0	1
Osteoarthritis	0	1
Pregnancy, puerperium and perinatal conditions	**0**	**4**
Abortion spontaneous	0	1
Foetal death	0	1
Foetal growth restriction	0	1
Premature delivery	0	1
Injury, poisoning and procedural complications	**0**	**2**
Post-procedural hemorrhage	0	1
Tibia fracture	0	1
Trial VLA2001-301 – Adolescent Trial		
No SAEs reported	--	--
TOTAL in 301 Study	**32**	

Table 18 Cumulative Summary Tabulation of All Serious Adverse Events from Clinical Trial- VLA2001-304.

Trial VLA2001-304	
(uncoded)	7
Breast Cancer (uncoded)	1
Diverticulitis (uncoded)	1
Facial Cellulitis (uncoded)	1
Parotitis (uncoded)	1
Poorly differentiated adenocarcinoma oesophagus (uncoded)	1
Small bowel obstruction (uncoded)	1
Atrial fibrillation (uncoded)	1
Nervous system disorders	3
Cerebrovascular accident	1
Hemiplegic migraine	1
Transient ischaemic attack	1
Infections and infestations	2
Pneumonia legionella	1
Urosepsis	1
Cardiac disorders	1
Atrial fibrillation	1
Gastrointestinal disorders	1
Inguinal hernia	1
Injury, poisoning and procedural complications	1
Tibia fracture	1
Musculoskeletal and connective tissue disorders	1
Osteoarthritis	1
Renal and urinary disorders	1
Ureterolithiasis	1
TOTAL in 304 Study	17

Table 19 Cumulative Summary Tabulation of All Serious Adverse Events from Clinical Trial- VLA2001-307.

Trial VLA2001-307	
No SAEs reported	--

Table 20 Cumulative Summary Tabulation of Serious Adverse Events in the COV-BOOST Trial

System Organ Class Preferred Term	VLA2001	Half VLA 2001
COV-BOOST		
Hepatobiliary disorders	1	0
Liver injury	1	0
Cardiac disorders	2	0
Myocardial infarction	1	0
Sinus node dysfunction	1	0
Gastrointestinal disorders	0	1
Oesophageal squamous cell carcinoma	0	1
Reproductive system and breast disorders	1	0
Breast cancer	1	0
Renal and urinary disorders	1	0
Pyelocaliectasis	1	0
TOTAL	5	1

Cumulative Summary Tabulations of All Serious Adverse Reactions from Clinical Trials for the entire clinical program until cut-off date 27-Aug-2022

Table 21: Serious Adverse Reactions from Valneva-Sponsored Clinical Trials

Participant No.	Age and Sex	Treatment Group	Dose	Date of Onset	End Date	PT	Outcome
[redacted]	Male, 61years	VLA2001	Post 1st dose	12-Sep-2021	13-Sep-2021	Atrial fibrillation	Recovered/ resolved
Comment: Reported as serious adverse event Sep 2022; Considered possibly related and classified as Suspected Unexpected Serious Adverse Reaction in June 2022.							

Table 22: Serious Adverse Reactions from the COV-BOOST Trial

Study arm	Site	Days to onset from boost	MedDRA Preferred Term	MedDRA System Order Class	Severity	Serious adverse event type	Causality assessment
VLA	University Hospital Southampton NHS FT	28	Liver injury	Hepatobiliary disorders	Grade4	An important medical event	Possible
	Leeds Teaching Hospitals NHS Trust	19	Myocardial infarction	Cardiac disorders	Grade3	Hospitalisation	Possible

Rapporteur assessment comment:

It would be helpful if information on the time periods covered could be found in the headings or labels of the respective tables. Table 15 (PSUR pp. 80-81) is titled "Line Listings of all Serious Adverse Events from Clinical Trials" without any reference to the fact that only the reporting interval of the present PSUR is covered. In contrast, the captions of Tables 16-20 contain the word "cumulative". The MAH is kindly asked to label the data in subsequent reports as clearly and unambiguously as possible in order to avoid misunderstandings and follow-up questions.

The headings of Tables 16-20 have now been revised to reflect serious adverse events and not serious adverse reactions from clinical trials. The coding and numbers remained unchanged.

Issue resolved.

7. Comments from Member States

No comments were received from member states.

PERIODIC SAFETY UPDATE REPORT

FOR

ACTIVE SUBSTANCE: COVID-19 vaccine (inactivated, adjuvanted, adsorbed)

ATC CODE: JO7BX03

MEDICINAL PRODUCTS COVERED:

Product Name	Country/Region	International non-proprietary name (INN)	Marketing authorisation numbers	Dates of authorisation	Marketing Authorisation Holder
COVID-19 Vaccine (inactivated, adjuvanted) Valneva	European Union	COVID-19 vaccine (inactivated, adjuvanted, adsorbed)	EU/1/21/1624/001	24-Jun-2022	Valneva Austria GmbH

AUTHORISATION PROCEDURE in the EU: Centralised

INTERNATIONAL BIRTH DATE (IBD): 28-Feb-2022

EUROPEAN UNION REFERENCE DATE (EURD): 28-Feb-2022

INTERVAL COVERED BY THIS REPORT: 28-Feb-2022 to 27-Aug-2022

Date of Report: 21-Oct-2022

OTHER INFORMATION: Not Applicable

MARKETING AUTHORISATION HOLDER'S NAME AND ADDRESS:

Valneva Austria GmbH
Campus Vienna Biocenter 3
1030 Vienna
Austria

NAME AND CONTACT DETAILS OF THE QPPV:

Zsuzsanna Unger,
Director Pharmacovigilance & QPPV

Valneva Austria GmbH
Campus Vienna Biocenter 3
1030 Vienna, Austria

Phone: [redacted]
E-mail: [redacted], QPPVOffice@valneva.com

Electronic signature approval signifies that the approver approves this document as acceptable, accurate, and complete.

DESCRIPTION	NAME / TITLE	SIGNATURE / DATE
APPROVED BY:	Zsuzsanna Unger, Director Pharmacovigilance & QPPV	[redacted]

EXECUTIVE SUMMARY

Introduction

This is the first Periodic Safety Update Report (PSUR) for COVID-19 vaccine (inactivated, adjuvanted, adsorbed) compiled for regulatory authorities which follows the International Conference on Harmonisation E2C Harmonized Tripartite Guideline Periodic Benefit-Risk Evaluation Report; EMA E2C guideline on periodic benefit-risk evaluation report; the EMA Module VII Guideline on Good Pharmacovigilance Practices – Periodic safety update report; and EMA Guideline on the Conduct of Pharmacovigilance for Vaccines for Pre- and Post-Exposure Prophylaxis Against Infectious Diseases. This report summarises the safety data received and processed by Valneva Austria GmbH (herein referred to as Valneva) from worldwide sources for the reporting interval covering 28-Feb-2022 to 27-Aug-2022.

The periodicity of this PSUR is based on the Emergency Use Authorisation in the Kingdom of Bahrain, which is consider to be the International Birth Date (IBD) of COVID-19 vaccine (inactivated, adjuvanted, adsorbed), which is 28-Feb-2022.

Medicinal Product

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is a purified, inactivated, and adjuvanted whole virus SARS-CoV-2 vaccine grown on Vero cells (African green monkey cells).

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) induces severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralising antibodies, as well as cellular immune responses (Th1) directed against the spike and other surface proteins, which may contribute to protection against Coronavirus Disease (COVID-19). Using this vaccine, the cellular immune response is thus not limited to the S-protein but also directed against other SARS-CoV-2 surface antigens. No data on induction of humoral immune responses directed against SARS-CoV-2 antigens other than S-protein are available in humans.

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

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is supplied in a multi-dose vial which contains 10 doses of 0.5 mL, 1 dose (0.5 mL) contains 33 Antigen Units (AU) of inactivated SARS-CoV-2 virus available in as suspension for injection (injection). The injection is white to off-white suspension (pH 7.5 ± 0.5) and is administered intramuscularly as a course of 2 doses of 0.5 mL each. The second dose should be administered 28 days after the first dose. The preferred site is the deltoid muscle of the upper arm (preferably the non-dominant arm).

Further details on the therapeutic class(es), mechanism of action, indications, pharmaceutical form(s), route(s) of administration and instructions for use are presented in the SmPC, effective date: 25-Jul-2022.

Worldwide Marketing Authorisation Status

The first Emergency Use Authorisation for COVID-19 vaccine (inactivated, adjuvanted, adsorbed) was granted in the Kingdom of Bahrain, which is considered to be the international birth date i.e. 28-Feb-2022. COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is currently authorised in 4 countries and marketed in 1 country (the Kingdom of Bahrain) and 1 region (European Union [EU]). Approval has been granted in the following countries: Kingdom of Bahrain (Emergency Use Authorisation), EU (Centralised), United Arab Emirates (Emergency Use Authorisation), and United Kingdom (Conditional Marketing Authorisation).

Update of Regulatory Authority or Marketing Authorisation Holder Actions Taken for Safety Reasons

During the reporting interval, there were no actions taken for safety reasons.

Changes to Reference Safety Information

The COVID-19 vaccine (inactivated, adjuvanted, adsorbed) Reference Safety Information in effect during the reporting interval was the Summary of Product Characteristics (SmPC), dated 25 Jul 2022.

During the reporting interval, an update related to a shelf life extension of 3 months was made. However, this change has no effect on safety.

Therefore, no safety related changes to the SmPC were made during the reporting interval.

Summary of Clinical Trials

During the reporting interval, there were 5 ongoing clinical trials with VLA2001, 1 Phase 1/2 trial (VLA2001-201), 1 Phase 2/3 trial (VLA2001-307), 2 Phase 3 trials (VLA2001-301 and VLA2001-304), and 1 Phase 2 trial (COV BOOST). Further details of the ongoing clinical trials are presented in Section 7.2.

During the reporting interval, there were no completed clinical trials.

Clinical Trial Exposure

Cumulatively, a total of 3.969 subjects received COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in 5 ongoing clinical trials.

Post-Authorisation Exposure

During the reporting interval, a total of 562.400 COVID-19 vaccine (inactivated, adjuvanted, adsorbed) doses were distributed in Kingdom of Bahrain and EU region.

Overview of Individual Case Safety Reports (ICSRs)

During the reporting interval and cumulatively, there were no ICSRs received.

Overview Summary of the Adverse Events of Special Interest (AESIs)

During this reporting interval and cumulatively, all ICSRs in the global Vaccine safety database were queried for AESIs. However, no ICSRs with MedDRA preferred terms related to the list of AESIs were identified (refer to Appendix 8).

Overview of Signals: New, Ongoing, or Closed

During the reporting interval, there were no signals identified that warranted an update to the product safety specification for COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

Summary Evaluation of Important Risks and New Information

During the reporting interval and cumulatively, no new information pertaining to important risks was identified.

Safety Topics for Routine monitoring

During this reporting interval and cumulatively, all ICSRs in the global Vaccine safety database were queried for the following safety topics:

- Fatal reports
- Experience in Special Patients Populations
- Hypersensitivity
- Angioedema
- Autoimmune disorders
- Cardiomyopathy
- Peripheral neuropathy
- Menstrual Disorders

Further evaluation of these safety topics were discussed in Section 15.2.2.

Overall Benefit-Risk Analysis Evaluation

The benefit of the COVID-19 Vaccine (inactivated, adjuvanted, adsorbed) Valneva have been seen in VLA2001-201 and VLA2001-301 clinical studies, which are summarised in section 17.1.

The risk associated with inactivated virus vaccines are considered low, further several inactivated whole virus vaccines have also shown excellent safety profile in the past. Additionally, the technological platform for developing inactivated vaccines has the advantage of rapidly scaling up production in pandemic situation using well-established infrastructure and methods.

The benefit-risk profile of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) which has been established across the clinical development program remains unchanged and positive from the date of first marketing authorisation. No new information has become available with regards to AESIs, serious AEs, fatal cases, new/ongoing/closed signals or safety concerns, both from cumulative and interval data.

Conclusion

In conclusion, the overall evaluation of the safety data from the use of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) during the reporting interval, and cumulatively, confirms the product's safety and tolerability.

The benefit-risk profile of COVID 19 Vaccine (inactivated, adjuvanted, adsorbed) remains positive and has not changed since its first marketing approval on 28-Feb-2022.

TABLE OF CONTENTS

Executive Summary **4**

Table of Contents **8**

List of Abbreviations **12**

1 Introduction **14**

2 Worldwide Marketing Authorisation Status **15**

3 Actions Taken in the Reporting Interval for Safety Reasons **15**

4 Changes to Reference Safety Information **15**

5 Estimated Exposure and use patterns **15**

5.1 Cumulative Subject Exposure in Clinical Trials 15

5.2 Interval and Cumulative Estimated Exposure Data from Post-Authorisation Experience 19

6 Data in Summary Tabulations **20**

6.1 Reference Information 20

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials 20

6.3 Cumulative and Interval Summary Tabulations from Post-Authorisation Data 20

7 Summaries of Significant Safety Findings from Clinical Trials During the Reporting Interval **20**

7.1 Completed Clinical Trials 20

7.2 Ongoing Clinical Trials 21

7.3 Long-Term Follow-Up 23

7.4 Other Therapeutic Use of Medicinal Product 23

7.5 New Safety Data Related to Fixed Combination Therapies 23

8 Findings from Non-Interventional Studies **23**

9 Information from Other Clinical Trials and Sources **23**

9.1 Other Clinical Trials 23

9.2 Vaccination Errors 23

10 Non-clinical data **23**

11 Literature **24**

12 Other Periodic Reports **28**

13 Lack of Efficacy in Controlled Clinical Trials **28**

14 Late-Breaking Information **28**

15 Overview of Signals: New, Ongoing, or Closed 28

15.1 Validated Signals During the Reporting Interval 28

15.2 Request for Evaluation of Safety Topic(s) from a Regulatory Authority(ies) 29

15.2.1 Adverse Events of Special Interest (AESI) and Observed to Expected (O/E) Analysis 29

15.2.2 Additional safety topics for monitoring 31

15.2.2.1 Fatal Reports 31

15.2.2.2 Experience in Special Patients Populations 32

15.2.2.3 Hypersensitivity 33

15.2.2.4 Angioedema 33

15.2.2.5 Autoimmune disorders 33

15.2.2.6 Cardiomyopathy 34

15.2.2.7 Peripheral neuropathy 34

15.2.2.8 Menstrual disorders 35

16 Signal and Risk Evaluation 35

16.1 Summary of Safety Concerns 35

16.2 Signal Evaluation 36

16.3 Evaluation of Risks and New Information 36

16.3.1 New Information on Important Potential Risks 37

16.3.1.1 Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) 37

16.3.2 New Information on Important Identified Risks 37

16.3.3 New Information on Other Potential Risks Not Categorised as Important: 37

16.3.4 New Information on Other Identified Risks Not Categorised as Important: 38

16.3.5 Update on Missing Information 38

16.3.5.1 Use in Pregnancy and While Breastfeeding 38

16.3.5.2 Use in Immunocompromised Patients 39

16.3.5.3 Use in patients with autoimmune or inflammatory disorders 39

16.3.5.4 Use in frail patients with unstable health conditions and comorbidities, e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD) 40

16.3.5.5 Long-Term Safety 41

16.3.5.6 Interaction with Other Vaccines 41

16.4 Characterisation of Risks 42

16.5 Effectiveness of Risk Minimisation (if applicable) 42

17 Benefit Evaluation....42

17.1 Important Baseline Efficacy/Effectiveness Information....42

17.2 Newly Identified Information on Efficacy/Effectiveness 45

17.3 Characterisation of Benefits....45

18 Integrated Benefit-Risk Analysis for Authorized Indications 45

18.1 Benefit-Risk Context-Medical Need and Important Alternatives....45

18.2 Benefit-Risk Analysis Evaluation....46

19 Conclusion 46

Appendix 1: COVID-19 vaccine (inactivated, adjuvanted, adsorbed) SmPC; Effective Date: 25-Jul-2022....48

Appendix 2: Worldwide Marketing Authorisation Status....78

Appendix 3: Line Listings and Cumulative Summary Tabulations of all Serious Adverse Events from Clinical Trials....80

Appendix 4: Cumulative and Interval Summary Tabulation of serious and non-serious PT from Post-Authorisation Data Sources....86

Appendix 5: Summary of Safety Signals New, Ongoing, or Closed During the Reporting Interval 87

Appendix 6: Listing of all Interventional Trials with the Primary Aim of Identifying, Characterising, or Quantifying a Safety Hazard or Confirming the Safety Profile of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) 88

Appendix 7: Listing of all MAH-Sponsored Non-Interventional Trials with the Primary Aim of Identifying, Characterising, or Quantifying a Safety Hazard or Confirming the Safety Profile of COVID-19 vaccine (inactivated, adjuvanted, adsorbed); or Measuring the Effectiveness of Risk Management Measures 95

Appendix 8: Search Strategy for AESI....96

Appendix 9: Search Strategy/Methodology for Safety Topics for Monitoring....101

Appendix 10: List of Sources of Information Used to Prepare the PSUR 103

List of Tables

Table 1: Summary of Estimated Cumulative Exposure in Adult Subjects up to and including August 27, 2022 15

Table 2: Estimated Cumulative Exposure in Adolescent Subjects by Gender 16

Table 3: Cumulative Participant Exposure to VLA2001 by Age and Gender - Trial VLA2001-201....16

Table 4: Cumulative Participant Exposure to VLA2001 by Race and Gender - Trial VLA2001-201....16

Table 5: Cumulative Participant Exposure to VLA2001 by Age and Gender - Trial VLA2001-301 17

Table 6: Cumulative Participant Exposure to VLA2001 by Race and Gender - Trial VLA2001-301 17

Table 7: Cumulative Participant Exposure to VLA2001 by Age and Gender - Trial VLA2001-304 18

Table 8: Cumulative Participant Exposure to VLA2001 by Race and Gender - Trial VLA2001-304 18

Table 9: Cumulative Subject Exposure to COVID-19 Vaccine (inactivated, adjuvanted adsorbed) in the COV-BOOST Trial by Age and Gender 18

Table 10: Interval Actual Exposure Data (Administered and Distributed) from Post-Authorisation Experience Presented by Region / Country 19

Table 11: Periodic SSRs submitted to Health Authorities 28

Table 12: Summary of Safety Concerns 36

Table 13: Positive reported COVID-19 cases after vaccination by treatment and age group and time of occurrence (safety population) (study VLA2001-301) 44

Table 14: Worldwide Marketing Authorisation Status 78

Table 15: Line Listings of all Serious Adverse Events from Clinical Trials 80

Table 16 Cumulative Summary Tabulation of All Serious Adverse Reactions from Clinical Trial-VLA2001-201. 82

Table 17 Cumulative Summary Tabulation of All Serious Adverse Reactions from Clinical Trial-VLA2001-301- Adult Trial. 82

Table 18 Cumulative Summary Tabulation of All Serious Adverse Reactions from Clinical Trial-VLA2001-304. 83

Table 19 Cumulative Summary Tabulation of All Serious Adverse Reactions from Clinical Trial-VLA2001-307. 84

Table 20 Cumulative Tabulations of Serious Adverse Events in the COV-BOOST Trial 85

Table 21: Ongoing Clinical Trials 88

Table 22: Search Strategy for AESI 96

Table 23: Search Strategy/Methodology for Safety Topics for Monitoring 101

LIST OF ABBREVIATIONS

Acronym	Abbreviation Definition
AESI	Adverse Event(s) of Special Interest
ACCESS	The vACCine COVID-19 monitoring readinESS Project
AU	Antigen Units
BC	Brighton Collaboration
ChAdOx1	Chimpanzee Adenovirus
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease
CTs	Clinical Trials
EMA	European Medicines Agency
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
GMRs	Geometric Mean Ratios
GMT	Geometric Mean Titre
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term(s)
HLT	High Level Term(s)
HNC	HIV-Negative Health Controls
IBD	International Birth Date
ICSR	Individual Case Safety Report(s)
IR	Incidence Rate
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Meningococcal Conjugate Vaccine
mL	Milliliter(s)
mRNA	Messenger Ribonucleic Acid
ND50	Fifty percent neutralising dilution
No.	Number
O/E	Observed to Expected
PSUR	Periodic Safety update report
PT	Preferred Term(s)
PLWH	People Living With HIV
RMP	Risk Management Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SmPC	Summary of Product Characteristics

Acronym	Abbreviation Definition
SMQ	Standardised MedDRA Query
SSR	Summary Safety Report
UK	United Kingdom
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
WWMA	Worldwide Marketing Authorisation

1 INTRODUCTION

This is the first periodic safety update report (PSUR) for Coronavirus Disease (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) compiled for regulatory authorities which follows the International Conference on Harmonisation E2C (R2) Harmonized Tripartite Guideline Periodic Benefit-Risk Evaluation Report ; European Medicines Agency (EMA) E2C guideline on periodic benefit-risk evaluation report; the EMA Module VII Guideline on Good Pharmacovigilance Practices – Periodic safety update report; and EMA Guideline on the Conduct of Pharmacovigilance for Vaccines for Pre- and Post-Exposure Prophylaxis Against Infectious Diseases. This PSUR summaries the safety data received and processed by Valneva Austria GmbH (herein referred to as Valneva) from worldwide sources for the reporting interval covering 28-Feb-2022 to 27-Aug-2022.

The periodicity of this PSUR is based on the Emergency Use Authorisation in the Kingdom of Bahrain, which is consider to be the International Birth Date (IBD) of COVID-19 vaccine (inactivated, adjuvanted, adsorbed), which is 28-Feb-2022.

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is a purified, inactivated, and adjuvanted whole virus SARS-CoV-2 vaccine grown on Vero cells (African green monkey cells).

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) induces severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralising antibodies, as well as cellular immune responses (Th1) directed against the spike and other surface proteins, which may contribute to protection against Coronavirus Disease (COVID-19). Using this vaccine, the cellular immune response is thus not limited to the S-protein but also directed against other SARS-CoV-2 surface antigens. No data on induction of humoral immune responses directed against SARS-CoV-2 antigens other than S-protein are available in humans.

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

Pharmacotherapeutic group: Viral vaccines, other viral vaccines.

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is supplied in a multi-dose vial which contains 10 doses of 0.5 mL, 1 dose (0.5 mL) contains 33 Antigen Units (AU) of inactivated SARS-CoV-2 virus available as suspension for injection (injection). The injection is white to off-white suspension (pH 7.5 ± 0.5) and is administered intramuscularly as a course of 2 doses of 0.5 mL each. The second dose should be administered 28 days after the first dose. The preferred site is the deltoid muscle of the upper arm (preferably the non-dominant arm).

Further details on the therapeutic class(es), mechanism of action, indications, pharmaceutical form(s), route(s) of administration and instructions for use are presented in the Summary of Product Characteristics (SmPC), effective date: 25-Jul-2022 (refer to Appendix 1).

2 WORLDWIDE MARKETING AUTHORISATION STATUS

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is currently authorised in various regions for the active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 to 50 years of age. The first Emergency Use Authorisation for COVID-19 vaccine (inactivated, adjuvanted, adsorbed) was granted in the Kingdom of Bahrain, which is considered to be the IBD i.e. 28-Feb-2022. COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is currently authorised in 4 countries/regions and marketed in 1 country ((the Kingdom of Bahrain) and 1 region (European Union [EU]). Approval has been granted in the following countries: Kingdom of Bahrain (Emergency Use Authorisation), EU (Centralised), United Arab Emirates (Emergency Use Authorisation), and United Kingdom (UK) (Conditional Marketing Authorisation).

Cumulative information on the market authorisation in all countries/regions, trade name(s), are presented in Appendix 2.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

During the reporting interval, there were no actions taken for safety reasons.

4 CHANGES TO REFERENCE SAFETY INFORMATION

The COVID-19 vaccine (inactivated, adjuvanted, adsorbed) Reference Safety Information in effect during the reporting interval was the Summary of Product Characteristics (SmPC), dated 25-Jul-2022.

During the reporting interval, an update related to a shelf life extension of 3 months was made. However, this change has no effect on safety.

Therefore, no safety related changes to the SmPC were made during the reporting interval.

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative Subject Exposure in Clinical Trials

A cumulative total number of 3.969 subjects were treated with VLA2001 in 5 ongoing clinical trials (CTs).

Table 1: Summary of Estimated Cumulative Exposure in Adult Subjects up to and including August 27, 2022

Study (Trial)	Treatment	Estimated Total Number of Participants Exposed (≥18 years of age)
VLA2001-201	VLA2001	153
VLA2001-301 (Adult Part)	VLA2001	3.017
VLA2001-304	VLA2001	306

Study (Trial)	Treatment	Estimated Total Number of Participants Exposed (≥18 years of age)
VLA2001-307	VLA2001	53
COV-BOOST	VLA2001	440
TOTAL	VLA2001	**3.969**

Table 2: Estimated Cumulative Exposure in Adolescent Subjects by Gender

Study	Treatment	Male	Female	Total Number of Participants Exposed (≥12 to < 18 years of age)
VLA2001-301 (Adolescent Part)	VLA2001	10	11	21

Trial VLA2001-201

Table 3: Cumulative Participant Exposure to VLA2001 by Age and Gender - Trial VLA2001-201

Age Range (years)	Number of Participants		
	Male	Female	Total
18-29	27	33	60
30-55	56	37	93
Total	**83**	**70**	**153**

Table 4: Cumulative Participant Exposure to VLA2001 by Race and Gender - Trial VLA2001-201

Race Group	Number of Participants		
	Male	Female	Total
White/White European	77	67	144
Mixed	3	1	4
Other	3	1	4
Asian	0	1	1
Total	**83**	**70**	**153**

Trial VLA2001-301

Table 5: Cumulative Participant Exposure to VLA2001 by Age and Gender - Trial VLA2001-301

Adult Trial				
Age Range (years)	**Number of Participants**			
	Male	**Female**	**Diverse**	**Total**
18-29	555	483	2	1.040
30-55	1.121	834	3	1.958
≥56	14	5	0	19
Total	**1.690**	**1.322**	**5**	**3.017**
Adolescent Trial				
Age Range (years)	**Number of Participants**			
	Male	**Female**	**Diverse**	**Total**
≥12 to < 18	10	11	0	21
Total	**10**	**11**	**0**	**21**

Table 6: Cumulative Participant Exposure to VLA2001 by Race and Gender - Trial VLA2001-301

Adult Trial				
Race Group	**Number of Participants**			
	Male	**Female**	**Diverse**	**Total**
White/White European	1.577	1,218	5	2.800
Mixed	32	45	0	77
Asian	47	30	0	77
Black	18	9	0	27
Other	9	10	0	19
Chinese	5	8	0	13
Hispanic	2	2	0	4
Total	**1.690**	**1.322**	**5**	**3.017**
Adolescent Trial				
	Number of Participants			
Race Group	**Male**	**Female**	**Diverse**	**Total**
White	9	10	0	19
Mixed	1	1	0	2
Total	**10**	**11**	**0**	**21**

Trial VLA2001-304

Table 7: Cumulative Participant Exposure to VLA2001 by Age and Gender - Trial VLA2001-304

Age Range (years)	Number of Participants		
	Male	Female	Total
≥56	146	160	306
Total	**146**	**160**	**306**

Table 8: Cumulative Participant Exposure to VLA2001 by Race and Gender - Trial VLA2001-304

Race Group	Number of Participants		
	Male	Female	Total
European	132	139	271
Maori	8	11	19
Other	4	6	10
Asian	1	4	5
Native Hawaiian or Other Pacific Islander	1	0	1
Total	**146**	**160**	**306**

Trial VLA2001-307

In study 307, 53 participants have received a VLA2001 booster dose up to and including 27-Aug-2022. Since recruiting has started only recently, and data have not been cleaned yet, no data for trial VLA2001-307 is presented here. However, no serious adverse events have been reported within the reporting period.

COV-BOOST Trial

Table 9: Cumulative Subject Exposure to COVID-19 Vaccine (inactivated, adjuvanted adsorbed) in the COV-BOOST Trial by Age and Gender

Characteristics	Prime with Oxford-AstraZeneca		Prime with Pfizer-BioNtech	
	VLA2001 n=109	Half-dose VLA2001 n=111	VLA2001 n=110	Half-dose VLA2001 n=110
Age (years)				
Mean (SD)	64.4 (15.3)	64.0 (14.9)	60.9 (18.1)	62.4 (16.7)
Median	71.8	71.0	61.2	62.0
<70 years, n (%)	51 (46.8)	51 (45.9)	63 (57.3)	61 (55.5)
≥70 years, n (%)	58 (53.2)	60 (54.1)	47 (42.7)	49 (44.5)
Gender				
Female	50 (45.9)	54 (48.6)	59 (53.6)	49 (44.5)

Characteristics	Prime with Oxford-AstraZeneca		Prime with Pfizer-BioNtech	
	VLA2001 n=109	Half-dose VLA2001 n=111	VLA2001 n=110	Half-dose VLA2001 n=110
Male	59 (54.1)	57 (51.4)	51 (46.4)	61 (55.5)
Ethnicity				
White	100 (91.7)	107 (96.4)	99 (90.0)	102 (92.7)
Black	2 (1.8)	1 (0.9)	2 (1.8)	0
Asian	5 (4.6)	2 (1.8)	7 (6.4)	6 (5.5)
Mixed	0	0	1 (0.9)	2 (1.8)
Other	1 (0.9)	0	1 (0.9)	0
Not given	1 (0.9)	0	0	0

5.2 Interval and Cumulative Estimated Exposure Data from Post-Authorisation Experience

During the reporting interval and cumulatively, a total of 562.400 COVID-19 vaccine (inactivated, adjuvanted, adsorbed) doses were distributed in Kingdom of Bahrain and EU region.

Table 10: Interval Actual Exposure Data (Administered and Distributed) from Post-Authorisation Experience Presented by Region / Country

Region / Country	Total Doses Administered[a]	Total Doses Distributed[a]
	Interval	
Kingdom of Bahrain	Not available	200.000
EU		
Austria	Not available	74.400
Denmark	Not available	38.400
Germany	Not available	249.600
Total (EU Countries)	**Not available**	**362.400**
Total	**Not available**	**562.400**

[a] Data presented as recorded.
Abbreviations: Refer to Abbreviations Table

6 DATA IN SUMMARY TABULATIONS

6.1 Reference Information

The Medical Dictionary for Regulatory activities (MedDRA) version 25.0 was the coding dictionary utilised for the presentation of adverse events/adverse drug reactions. The summary tabulation report is organised by System Organ Class and Preferred Term (PT) in internationally agreed order which summarises each adverse event coincident with COVID-19 vaccine (inactivated, adjuvanted, adsorbed) rather than with each individual case safety report(s) (ICSR). The summary tabulation is generated from a dynamic global safety database which changes over time as ICSRs are updated and reflects the most current data available at the time that it was generated. As a single ICSR may contain both serious and nonserious and / or both listed and unlisted adverse events, an ICSR may be presented in more than 1 category under each source. Therefore, the sum of the total number of adverse events across sources may exceed the number of unique ICSRs that exist overall.

Follow-up attempts (defined as phone calls, letters, questionnaires) have been made by Valneva to request follow-up information and / or medical confirmation of the ICSRs. The data included within this report represent the most complete ICSR information available at the time of analysis.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative summary tabulation of serious adverse events from Company-sponsored interventional CTs is provided in Appendix 3.

6.3 Cumulative and Interval Summary Tabulations from Post-Authorisation Data

During the reporting interval and cumulatively, there were no ICSRs received. Therefore, a cumulative and interval summary tabulation of adverse drug reactions (serious and nonserious) i.e. Appendix 4 is not applicable.

7 SUMMARIES OF SIGNIFICANT SAFETY FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL

A list of any Marketing Authorisation Holder (MAH) sponsored post-marketing interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval are summarised in Appendix 6.

7.1 Completed Clinical Trials

During the reporting interval, there were no completed CTs for COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

7.2 Ongoing Clinical Trials

During the reporting interval, there were 5 ongoing CTs with VLA2001, 1 Phase 1/2 trial (VLA2001-201), 1 Phase 2/3 trial (VLA2001-307), 2 Phase 3 trials (VLA2001-301 and VLA2001-304), and 1 Phase 2 trial (COV-BOOST). Summary information for the trials can be found in Table 21 or Appendix 6.

A total of 4.985healthy or medically stable participants had been enrolled in VLA2001 trials as of the of the cut-off date for this report (27-Aug-2022), of which 3.969 participants have received at least 1 dose of VLA2001. In the COV-BOOST trial, 109 participants received VLA2001, and 111 participants received a half-dose of VLA2001 as a booster after 2 vaccinations of Oxford-AstraZeneca. In addition, 110 participants received VLA2001 and 110 participants received a half-dose of VLA2001 as a booster after 2 vaccinations of Pfizer-BioNtech.

Cumulatively, in Valneva's VLA2001 clinical program, 50 serious adverse events have been reported in participants who received VLA2001: 1 in study VLA2001-201, 32 in study VLA2001-301, and 17 in study VLA2001-304. The majority of these serious adverse events were mild to moderate in intensity, and only 1 was considered possibly related to VLA2001.

Only few serious adverse events were reported by more than 1 participant:

- Appendicitis, reported by 3 participants in study VLA2001-301
- Atrial fibrillation, reported by 2 participants in study VLA2001-304
- Osteoarthritis, reported by 1 participant in study VLA2001-301 and 1 participant in study VLA2001-304,
- Tibia fracture, reported by 1 participant in study VLA2001-301 and 1 participant in study VLA2001-304.

With the exception of 1 case of "atrial fibrillation", all serious adverse events are considered not "related" or "unlikely related" to the study vaccine.

The only serious adverse events that was "possibly related" to the study vaccine was a case of "atrial fibrillation" reported in study VLA2001-304. The participant had experienced 3 episodes of atrial fibrillation during the study, the first on 27-28-Aug-2021 (2 days after the 1st study vaccination), which was reported as adverse events. The second episode on 12-13-Sep-2021, led to overnight hospital admission and was therefore reported as serious adverse events but classified as unrelated. The participant received the 2nd study vaccination on 7-Oct-2021, and experienced worsening atrial fibrillation on 23-24-Nov-2021. This was reported to the study site only in June 2022, and the serious adverse events was then classified as suspected unexpected serious adverse reaction considering the repeated episodes.

As of the cut-off date for this PSUR and per the report in Munro *et al*, 2021 [1], 5 serious adverse events in the VLA2001 group (2 of which were considered possibly related to VLA2001 by the investigator) and 1 in the half dose VLA2001 group were reported in the COV-BOOST study.

Appendix 3: represents a cumulative list of serious adverse events organised by System Organ Class/PTs that have been reported during clinical trials of VLA2001, from study initiation up to the cut-off date of 27-Aug-2022, for this reporting interval.

One participant (Trial VLA2001 201) withdrew consent due to a non-serious adverse events not related to VLA2001 (COVID-19). Two participants in Trial VLA2001-301 withdrew consent due to non-serious adverse events (hypercalcaemia and worsening of anxiety) not related to VLA2001.

Cases with a Fatal Outcome

No participants died as the result of serious adverse events reported in clinical trials during the reporting interval.

Pregnancy and Lactation

In Trial VLA2001-201, there was 1 participant pregnancy and 1 partner pregnancy during the reporting period among participants who received VLA2001. Both participants continued with study visits. In Trial VLA2001-301, the total number of pregnancies reported up to 27-Aug-2022, is 52: 39 pregnancies were observed in study participants and 13 participants have reported a partner pregnancy. Of the pregnancies in participants, 29 occurred in the VLA2001 group and 10 in the AZD1222 group.

One woman in the VLA2001 group, 1st vaccination on 26-May-2021 and 2nd vaccination on 23-Jun-2021, positive pregnancy test on 21-Feb-2022, had a miscarriage at 8.5 weeks of gestation. Another woman in the VLA2001 group, 1st vaccination on 24-May-2021 and 2nd vaccination on 21-Jun-2021 had a positive pregnancy test on 07-Nov-2021 and a pregnancy loss in the first trimester, which resulted in foetal death. Another participant woman in the VLA2001 group had the 1st vaccination on 5-May-2021, the 2nd Vaccination on 02-Jun-2021, a positive pregnancy test on 12-Feb-2022, and a miscarriage on 18-Mar-2022.

A full-term healthy baby was born in 8 women who had received VLA2001, and 1 woman had a delivery of a premature infant with reduced growth, her 1st vaccination was on 16 May, the 2nd vaccination 12-Jun-2021, and her positive pregnancy test on 9-Oct-2021.

Two women who had received AZD1222 delivered a full-term healthy baby.

Of the partner pregnancies, 3 occurred in partners of participants in the AZD12222 group, and 10 in partners of participants in the VLA2001 group.

Out of the partners of pregnant women who had received 2 doses of VLA2001, 5 partners have delivered full-term healthy babies, 1 woman had a caesarean section and the other ones are being followed up. Out of the 3 partners of pregnant women who had received 2 doses of AZD1222, 2 have delivered a full-term healthy baby and the other 1 is being followed up.

All other pregnancies are either still ongoing or no outcome was yet reported; all of the pregnancies will be followed up.

7.3 Long-Term Follow-Up

During the reporting interval, there were no long-term follow-up CTs for COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

7.4 Other Therapeutic Use of Medicinal Product

During the reporting interval, COVID-19 vaccine (inactivated, adjuvanted, adsorbed) has not been investigated for any other therapeutic use(s).

7.5 New Safety Data Related to Fixed Combination Therapies

No safety data related to combination therapies with COVID-19 vaccine (inactivated, adjuvanted, adsorbed) became available during the reporting interval.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

During the reporting interval, no non-interventional studies for COVID-19 vaccine (inactivated, adjuvanted, adsorbed) were initiated, conducted, completed, or reported. Hence, Appendix 7: is not applicable.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other Clinical Trials

During the reporting interval, no other studies have been conducted with COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

9.2 Vaccination Errors

During the reporting interval and cumulatively, there were no ICSRs received. Hence, there was no data regarding vaccination error for COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

10 NON-CLINICAL DATA

During the reporting interval, no non-clinical studies were initiated or ongoing involving COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

11 LITERATURE

During the reporting interval, 9 literature articles were identified for discussion which are summarised below:

1. **Wong *et al* (2022)[2]** aimed to compare the incidence of various adverse events of special interest (AESIs) and all-cause mortality between CoronaVac (inactivated vaccine) and BNT162b2 (messenger ribonucleic acid [mRNA-based] vaccine). The approach included a retrospective, population-based cohort of individuals who had received at least 1 dose of BNT162b2 or CoronaVac from 23 February to 9 September 2021 in Hong Kong. Individuals were observed from the date of vaccination (first or second dose) until mortality, second dose vaccination (for first dose analysis), 21 days after vaccination. The results revealed that the most frequently reported AESI among CoronaVac and BNT162b2 recipients was thromboembolism (first dose: 431 and 290 per 100,000 person-years; second dose: 385 and 266 per 100,000 person-years). After the first dose, incidence rates (IRs) of overall AESIs (IR = 0.98, 95% confidence interval [CI] 0.89-1.08, p = 0.703) and mortality (IR = 0.96, 95% CI 0.63-1.48, p = 0.868) associated with CoronaVac were generally comparable to those for BNT162b2, except for Bell palsy (RR = 1.95, 95% CI 1.12-3.41, p = 0.018), anaphylaxis (IR = 0.34, 95% CI 0.14-0.79, p = 0.012), and sleeping disturbance or disorder (IR = 0.66, 95% CI 0.49-0.89, p = 0.006). After the second dose, IR of overall AESIs (IR = 0.97, 95% CI 0.87-1.08, p = 0.545) and mortality (IR = 0.85, 95% CI 0.51-1.40, p = 0.516) were comparable between CoronaVac and BNT162b2 recipients, with no significant differences observed for specific AESIs. The authors concluded that in this study, the incidences of AESIs (cumulative IRs of 0.06%-0.09%) and mortality following the first and second doses of CoronaVac and BNT162b2 vaccination were very low. The safety profiles of the vaccines were generally comparable, except for a significantly higher IRs of Bell palsy, but lower IRs of anaphylaxis and sleeping disturbance or disorder, following first dose CoronaVac versus BNT162b2 vaccination.

2. **Lazarus *et al* (2022)[3],** aimed to evaluate the safety and optimal dose of a novel inactivated whole-virus adjuvanted vaccine against SARS-CoV-2: VLA2001. The authors conducted an open-label, dose-escalation study followed by a double-blind randomised trial using low, medium and high doses of VLA2001 (1:1:1). The primary safety outcome was the frequency and severity of solicited local and systemic reactions within 7 days after vaccination. The primary immunogenicity outcome was the geometric mean titre (GMT) of neutralising antibodies against SARS-CoV-2 2 weeks after the second vaccination. The study is registered as NCT04671017. In this study 153 healthy adults aged 18–55 years were recruited in the UK. Overall, 81.7% of the participants reported a solicited adverse events, with injection site tenderness (58.2%) and headache (46.4%) being the most frequent. Only 2 participants reported a severe solicited event. All observed incidents were transient and non-life threatening in nature. Immunogenicity measured at 2 weeks after completion of the 2-dose priming schedule, showed significantly higher GMTs of SARS-CoV-2 neutralising antibody titres in the highest dose group (GMT 545.6; 95% CI: 428.1, 695.4) which were similar to a panel of convalescent sera (GMT 526.9; 95% CI: 336.5, 825.1). Seroconversion rates of neutralising antibodies were also significantly higher in the high-dose group (>90%) compared to the other dose groups. In the high dose group, antigen-specific interferon-γ expressing T-cells reactive against the S, M and N proteins were observed in 76, 36

and 49%, respectively. The authors concluded that VLA2001 was well tolerated in all tested dose groups, and no safety signal of concern was identified. The highest dose group showed statistically significantly stronger immunogenicity with similar tolerability and safety, and was selected for phase 3 clinical development.

3. Lazarus *et al* (2022)[4], aimed to assess the safety and immunogenicity of primary vaccination with VLA2001 versus the chimpanzee adenovirus (ChAdOx1)-S adenoviral-vectored vaccine. In this immunobridging phase 3 trial (COV-COMPARE), participants aged 18 years and older who were medically stable were enrolled at 26 sites in the UK. In the double-blind, randomised, controlled arm of the trial, participants aged 30 years and older were randomly assigned (2:1) to receive 2 doses of VLA2001 (0·5 millilitres [mL]; with 33 AU per dose) or ChAdOx1-S (0·5 mL; with 2·5 × 108 infectious units per dose) on days 1 and 29. In another arm, participants aged 18–29 years received 2 doses of VLA2001 (same dose) open label on days 1 and 29. In this study, 4181 individuals were screened and 4017 enrolled, of whom 2975 (74%) were aged 30 years or older and randomly assigned to receive VLA2001 (n=1978) or ChAdOx1-S (n=997), and 1042 (26%) were aged 18–29 years (all received open-label VLA2001). Around 4012 participants received at least 1 dose of vaccine (1040 in the open-label VLA2001 group, 1977 in the randomised VLA2001 group, and 995 in the ChAdOx1-S group). The immunogenicity population comprised 492 participants in the randomised VLA2001 group and 498 in the ChAdOx1-S group. VLA2001 induced higher neutralising GMTs than did ChAdOx1-S (803·5 [95% CI 748·5–862·6] vs 576·6 [543·6–611·7]; GMT ratio 1·39 [95% CI 1·25–1·56]; p<0·0001), and non-inferior seroconversion rates (444 [97·4%] of 456 participants vs 444 [98·9%] of 449; difference –1·5% [95% CI –3·3 to 0·2]). Any adverse event was reported in 963 (92·6%) participants in the open-label VLA2001 group, 1755 (88·8%) in the randomised VLA2001 group, and 976 (98·1%) in the ChAdOx1-S group. Most adverse events reported were mild or moderate in severity. The authors concluded that VLA2001 has a favourable tolerability profile and met superiority criteria for neutralising antibodies and non-inferiority criterion for seroconversion rates compared with ChAdOx1-S.

4. Wang *et al* (2022)[5], in his review article gathered evidence regarding the safety, efficacy, and effectiveness of BBIBP-CorV an aluminium-hydroxide-adjuvanted, inactivated whole-virus vaccine, which has been widely distributed, with more than 400 million doses administered in more than 40 countries. It was highlighted that compared to vaccines on other platforms, such as mRNA vaccines, BBIBP-CorV shows less immunogenicity and durability in laboratory tests. Despite its lower level of efficacy and immunology, its real-world effectiveness in preventing people from severe diseases except infection still proved to be valuable. Complete vaccination with 2 doses is the essential requirement for the protective effect. A heterogeneous boosting dose of BBIBP might be an effective solution to reduce vaccine efficacy against emerging variants of concern in the future.

5. Zeng *et al* (2022)[6]. conducted a single centre study aimed to investigate the vaccine hesitancy reasons among the parents, and to monitor the adverse events of inactivated COVID-19 vaccines in children and teenagers with underlying medical conditions in China. Children with underlying medical conditions encountered at the Immunisation Advisory Clinic for COVID-19 vaccine counselling were enrolled. They were given immunisation recommendations and followed

up at 72 h and 28 d after immunisation to monitor the immunisation compliance after consultation and adverse events. A total of 324 children aged 3-17 years were included. The top 3 primary medical conditions for counselling were allergy (33.6%), neurological diseases (31.2%), and rheumatic diseases (8.3%). COVID-19 vaccination was promptly recommended for 242 (74.7%) children. Seventy-one (65.7%) children who had allergy issues were recommended to take the vaccination, which was significantly lower than that of other medical conditions ($p < 0.05$). The follow-up record showed that 180 children received 340 doses of inactivated COVID-19 vaccine after consultation. Overall, 39 (21.6%) children reported at least 1 adverse event within 28 d of either vaccination. No serious adverse reactions were observed. No difference in adverse effects between the first dose and the second dose of vaccination except fever. Parents' hesitancy in COVID-19 vaccination for children with underlying medical conditions was mainly due to safety concerns. It was concluded that both guidelines and healthcare providers remain cautious about recommending COVID-19 vaccines for children with underlying medical conditions due to the lack of published pre-and post-marketing safety surveillance data. The study also demonstrated the good safety of inactivated COVID-19 vaccines among children with underlying medical conditions.

6. **Zou *et al* (2022)[7],** planned a study with an aim to observe and compare the early immune response after COVID-19 vaccination in relation to human immunodeficiency virus (HIV) with 2 treatment arms i.e. people living with HIV (PLWH) and HIV-negative health controls (HNC). It was conducted between March to June 2021, 48 PLWH and 40 HNC, aged 18 to 59 years, were enrolled in the study in the Wuchang district of Wuhan city. All of them received inactivated COVID-19 vaccine (Sinopharm, WIBP-CorV, Wuhan Institute of Biological Products Co. Ltd) at day 0 and the second dose at day 28. The frequency of adverse reactions to the first and second dose was not different between PLWH (30% and 11%) vs. HNC (32% and 24%). Neutralising antibodies responses among PLWH peaked at day 70, while among HNC peaked at day 42. At day 42, the geometric mean concentration and seroconversion rate of neutralising antibodies among PLWH were 4.46 binding antibody units /mL (95% CI 3.18–5.87) and 26% (95% CI 14–41), which were lower than that among HNC [geometric mean concentration (18.28 BAU/mL, 95% CI 10.33–32.33), seroconversion rate (63%, 95% CI 44–79)] IgG responses among both PLWH and HNC peaked at day 70. At day 70, the geometric mean enzyme-linked immunosorbent assay (ELISA) units and seroconversion rate of IgG among PLWH were 0.193 ELISA units (endotoxin units)/mL (95% CI 0.119–0.313) and 51% (95% CI 34–69), which was lower than that among HNC (geometric mean ELISA units) (0.379 endotoxin /mL, 95% CI 0.224–0.653), seroconversion rate (86%, 95% CI 64–97)]. There were no serious adverse events. The authors concluded that early humoral immune response to the inactivated COVID-19 vaccine was weaker and delayed among PLWH population than that among HNC. This observation remained consistent regardless of a high CD4 count with effective antiretroviral therapy.

7. **Jin *et al* (2022)[8],** looked at the efficacy, safety and immunogenicity of CoronaVac, also known as the Sinovac inactivated SARS-CoV-2 vaccine, which has been widely implemented in combating the COVID-19 pandemic. The study summarised the results of CTs and real-world studies of CoronaVac in this review. The overall efficacy for the prevention of symptomatic COVID-19 (before the emergence of variants of concern) using 2 doses of 3 µg CoronaVac was

67.7% (95% CI, 35.9% to 83.7%). Effectiveness in preventing hospitalisations, ICU admissions, and deaths was more prominent than that in preventing COVID-19. A third dose inherited the effectiveness against non-variants of concern and increased effectiveness against severe COVID-19 outcomes caused by omicron variants compared to 2 doses. Most adverse reactions were mild. Few vaccine-related serious adverse reactions were reported. The authors concluded, 3-dose regimen significantly increased the seroconversion levels of neutralising antibodies against omicron as compared to 2-dose regimen.

8. Shwaky *et al* (2022)[9], evaluated the cutaneous reactions and their time of recovery after Sinopharm vaccination. It was a prospective multicentre study, the cases involved were over the age of 18. The data were anonymised. On the registry's vaccine section, we tracked vaccination dates, skin reactions, and recovery times. All respondents who reported only a cutaneous reaction to the first vaccination dose received a follow-up contact asking about a second vaccination dose cutaneous reaction. The study included 4560 cases. The mean age of all studied cases was 41.2 ± 6.1 years. There were dermatologic complications in 1190 patients (26.1%). There was induration at the injection site in 495 patients (10.9%), urticaria in 210 patients (4.6%), morbilliform eruption in 375 patients (8.2%), flare of skin site in 105 patients (2.3%), and angioedema in 105 patients (2.3%). The mean recovery days in all studied patients were 2.92 ± 0.94 days with a minimum recovery period of 2 days and a maximum of 7 days. The authors concluded that because Sinopharm's cutaneous reactions are frequently mild and self-limiting, vaccination should not be discouraged based on these findings. If the first vaccine dose creates a cutaneous reaction, there is no need to skip the second dose.

9. Munro *et al* (2021)[1] investigated the safety and immunogenicity of 7 different COVID-19 vaccines as a 3rd (booster) dose after 2 doses of ChAdOx1 nCov-19 or BNT162b2, in order to optimise selection of booster vaccines. It was a multicentre, randomised, controlled, phase 2 trial on participants from 18 sites across UK, aged older than 30 years with at least 70 days post 2 doses of ChAdOx1 nCov-19 or at least 84 days post 2 doses of BNT162b2 primary COVID-19 immunisation course and with no history of laboratory-confirmed SARS-CoV-2 infection. The participants were divided into 3 groups as follows: Group A who received NVX-CoV2373, a half dose of NVX-CoV2373 , ChAdOx1 nCov-19 , or quadrivalent meningococcal conjugate vaccine (MenACWY) control (1:1:1:1); Group B who received BNT162b2, VLA2001, a half dose of VLA2001, Ad26.COV2.S or MenACWY (1:1:1:1:1); Group C who received mRNA1273, CVnCov, a half dose of BNT162b2, or MenACWY (1:1:1:1). Participants and all investigatory staff were blinded to treatment allocation. Upon analysis, 3 vaccines showed increased reactogenicity: mRNA1273 after ChAdOx1 nCov-19 /ChAdOx1 nCov-19 or BNT162b2/BNT162b2; and ChAdOx1 nCov-19 and Ad26.COV2.S after BNT162b2/BNT162b2. For ChAdOx1 nCov-19 /ChAdOx1 nCov-19 -primed individuals, spike IgG geometric mean ratios (GMRs) between study vaccines and controls ranged from 1·8 (99% CI 1·5-2·3) in the half VLA2001group to 32·3 (24·8-42·0) in the mRNA1273group. GMRs for wild-type cellular responses compared with controls ranged from 1·1 (95% CI 0·7-1·6) for ChAdOx1 nCov-19 to 3·6 (2·4-5·5) for mRNA1273. For BNT162b2/BNT162b2-primed individuals, spike IgG GMRs ranged from 1·3 (99% CI 1·0-1·5) in the half VLA2001group to 11·5 (9·4-14·1) in the mRNA1273group. GMRs for wild-type cellular responses compared with controls ranged from

1·0 (95% CI 0·7-1·6) for half VLA2001to 4·7 (3·1-7·1) for mRNA1273. The results were similar between those aged 30-69 years and those aged 70 years and older. Fatigue and pain were the most common solicited local and systemic adverse events, experienced more in people aged 30-69 years than those aged 70 years or older. Serious adverse events were uncommon, and similar in active vaccine and control groups. Overall, it was concluded that, all study vaccines boosted antibody and neutralising responses after ChAdOx1 nCov-19 /ChAdOx1 nCov-19 initial course and all except 1 after BNT162b2/BNT162b2, with no safety concerns.

Review of published peer-reviewed scientific literature and available unpublished manuscripts did not identify any new and/or significant safety findings that would impact the overall benefit-risk balance of COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

12 OTHER PERIODIC REPORTS

Periodic reports as summary safety reports (SSR) submitted monthly to relevant health authorities by Valneva during the reporting interval are detailed in Table 11 below.

Table 11: Periodic SSRs submitted to Health Authorities

SSR No.	Reporting Interval	Data Lock Point	Regulatory Authority/IRB/EC
COVID-19 Vaccine (inactivated, adjuvanted) Valneva, SSR No. 1	24-Jun-2022 to 31-Jul-2022	31-Jul-2022	EMA

Abbreviations: Refer to Abbreviations Table

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

During the reporting interval and cumulatively, no new safety data emerged that indicated a lack of efficacy with COVID-19 vaccine (inactivated, adjuvanted, adsorbed) from interventional, non-interventional, retrospective CTs and from the review of published literature.

14 LATE-BREAKING INFORMATION

During the preparation of this report, there were no potentially important new safety and efficacy/effectiveness findings that arose for COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

15 OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

15.1 Validated Signals During the Reporting Interval

Valneva has an established signal management process including signal detection, validation, and evaluation. During the signal detection process, data sources are screened for new safety information related to COVID-19 vaccine (inactivated, adjuvanted, adsorbed) and any new potential signal is reviewed. Following initial review of the available data, a determination is made

on the basis of the nature and quality of the new information whether further investigation is warranted, at which point those safety topics that are referred for further investigation are considered "validated signals". Potential signal detection data sources include safety data from Valneva sponsored studies, spontaneous adverse events reports, published literature, and communications from external sources, including regulatory agencies. To supplement routine Pharmacovigilance surveillance, Valneva performs daily, weekly and monthly aggregate qualitative and quantitative signal detection review using the Global Safety Database Argus using a calculated disproportionality ratio(s).

During the reporting interval, there were no signals identified that warranted an update to the product safety specification for COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

During the reporting interval, no signals were closed.

15.2 Request for Evaluation of Safety Topic(s) from a Regulatory Authority(ies)

During the reporting interval, the Health Authorities requested an evaluation of following safety topics involving COVID-19 vaccine (inactivated, adjuvanted, adsorbed):

- Hypersensitivity
- Angioedema
- Autoimmune disorders
- Cardiomyopathy
- Peripheral neuropathy
- Menstrual Disorders

Further evaluation of these safety topics were discussed in Section 15.2.2.

15.2.1 Adverse Events of Special Interest (AESI) and Observed to Expected (O/E) Analysis

The global vaccine safety database was queried for AESI for the cumulative period up to 27-Aug-2022 according to prespecified search strategies (refer to [Table 22] or [Appendix 8] for search strategies).

Total List of AESI

- Acute disseminated encephalomyelitis
- Amniotic cavity infection
- Anaphylaxis
- Appendicitis
- Autoimmune thyroiditis
- Bell's palsy
- Cerebral venous sinus thrombosis
- Multiple sclerosis
- Multisystem inflammatory syndrome in children
- Myasthenia gravis
- Myocardial infarction
- Myocarditis, Pericarditis
- Narcolepsy
- Neonatal death

- Chronic fatigue syndrome
- Encephalitis, Encephalomyelitis
- Fetal growth restriction
- Fibromyalgia
- Foetal distress syndrome
- Generalized convulsions
- Gestational diabetes
- Guillain-Barre syndrome
- Hemorrhagic Stroke
- Herpes viral infections
- Immune-mediated/autoimmune disorders
- Ischemic stroke
- Kawasaki's disease
- Major congenital anomalies
- Maternal death
- Microcephaly
- Monoclonal gammopathy
- Optic neuritis
- Placenta praevia
- Postural orthostatic tachycardia syndrome
- Preeclampsia
- Preterm birth
- Renal failure neonatal
- Rheumatoid arthritis
- Spontaneous abortion
- Stillbirth
- Sudden death
- Thrombocytopenia
- Thrombosis with thrombocytopenia syndrome
- Tolosa-Hunt syndrome
- Transverse myelitis
- Uterine Rupture
- Vaccine-associated enhanced disease
- Venous thromboembolism

AESIs considered for adjuvants CpG1018

- Crohn's disease
- Ulcerative proctitis
- Psoriatic arthropathy
- Spondyloarthritis, including reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
- Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy)
- Tolosa Hunt syndrome
- Polyneuropathies associated with monoclonal gammopathy
- Narcolepsy
- Optic neuritis
- Transverse Myelitis
- Erythema nodosum
- Lichen planus
- Rosacea
- Sweet's syndrome
- Large vessels vasculitis including giant cell arteritis such as Takayasu's arteritis and temporal arteritis

- Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), Necrotizing vasculitis and antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis
- Idiopathic pulmonary fibrosis
- Raynaud's phenomenon
- Sarcoidosis
- Steven-Johnson syndrome
- Uveitis

During the reporting interval and cumulatively, no ICSRs with MedDRA PTs related to the following AESIs were identified. Hence, O/E analysis for these AESIs topics were not performed.

15.2.2 Additional safety topics for monitoring

During the reporting interval, the 8 additional safety topics for monitoring were considered which are discussed below:

- Fatal reports
- Experience in Special Patients Populations
- Hypersensitivity
- Angioedema
- Autoimmune disorders
- Cardiomyopathy
- Peripheral neuropathy
- Menstrual Disorders

15.2.2.1 Fatal Reports

Background

Fatal reports is a safety topic under surveillance due to insufficient information obtained from clinical studies.

Method of evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for fatal reports (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety topic could not be evaluated.

15.2.2.2 Experience in Special Patients Populations

15.2.2.2.1 Age group: Infants, Adolescents, Paediatrics

Background

As per the SmPC, the safety and immunogenicity COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in children and adolescents less than 18 years of age have not yet been established. No data are available.

Method of evaluation

A search was conducted in the global safety database for the interval and cumulative ICSRs in individuals less than 18 years of age (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety topic could not be evaluated.

15.2.2.2.2 Age group: Elderly

Background

Elderly age group is a safety topic under surveillance due to insufficient information obtained from clinical studies. However, as per the SmPC, the safety and immunogenicity of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in individuals ≥ 65 years of age have not yet been established. Very limited data are currently available on subjects over 50 years of age.

Method of evaluation

A search was conducted in the global safety database for the interval and cumulative ICSRs in individuals greater than 65 years of age i.e. the elderly age group category (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety topic could not be evaluated.

15.2.2.3 Hypersensitivity

Background

Hypersensitivity is a safety topic under surveillance due to insufficient information obtained from clinical studies. However, COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is contraindicated as per the SmPC, if there is hypersensitivity to the active substance or to any of the excipients listed, or yeast-derived residues (i.e. yeast deoxyribonucleic acid, yeast antigens and mannosylated recombinant human albumin) of the manufacturing process of the recombinant human albumin.

Method of evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for hypersensitivity (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety topic could not be evaluated.

15.2.2.4 Angioedema

Background

Angioedema is a safety topic under surveillance due to insufficient information obtained from clinical studies.

Method of evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for angioedema (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety topic could not be evaluated.

15.2.2.5 Autoimmune disorders

Background

Autoimmune disorders are a safety topic under surveillance due to insufficient information obtained from clinical studies.

Method of evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for autoimmune disorders (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety topic could not be evaluated.

15.2.2.6 Cardiomyopathy

Background

Cardiomyopathy is a safety topic under surveillance due to insufficient information obtained from clinical studies.

Method of evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for cardiomyopathy (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety topic could not be evaluated.

15.2.2.7 Peripheral neuropathy

Background

Peripheral neuropathy is a safety topic under surveillance due to insufficient information obtained from clinical studies.

Method of evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for peripheral neuropathy (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety topic could not be evaluated.

15.2.2.8 Menstrual disorders

Background

Menstrual Disorders is a safety topic under surveillance due to insufficient information obtained from clinical studies. However as per European public assessment report (EMA/627695/2022, Procedure no EMEA/H/C/006019/0000) dated 23-June-2022 adopted by the Committee for Medicinal Products for Human Use, stated that the incidence of menstrual disorders during study VLA2001-301 was similar to the comparator vaccine. There are recent publications suggesting that changes to the menstrual cycle do occur following vaccination, but they are small compared with natural variation and quickly reverse. Therefore, the Pharmacovigilance Risk Assessment Committee concluded that there is no evidence of a causal relationship of menstrual disorders with vaccines against COVID-19 but the MAH will monitor and report menstrual disorders as AESI in aggregate reporting.

Method of evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for menstrual disorders (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety topic could not be evaluated.

16 SIGNAL AND RISK EVALUATION

16.1 Summary of Safety Concerns

A summary of important safety concerns during the reporting interval are provided in Table 12. reflective of EU RMP v1.0, dated 21-Jun-2022.

Table 12: Summary of Safety Concerns

Risk Criteria	Description
Important identified risk(s)	• No important risks have been identified.
Important potential risks	• Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	• Use in pregnancy and while breast feeding • Use in immunocompromised patient • Use in patients with autoimmune or inflammatory disorders • Use in frail patients with unstable health conditions and comorbidities, e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD) • Long-term safety data • Interaction with other vaccines

Source: EU-RMP V1.0 dated 21-Jun-2022.

16.2 Signal Evaluation

During the reporting interval, there were no signals identified that warranted an update to the product safety specification for the COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

16.3 Evaluation of Risks and New Information

The following subsections are as follows:

- New information on important potential risks – Subsection 16.3.1
- New information on important identified risks – Subsection 16.3.2
- New information on other potential risks not categorised as important – Subsection 16.3.3.
- New information on other identified risks not categorised as important – Subsection 16.3.4.
- Update on important missing information – Subsection 16.3.5

16.3.1 New Information on Important Potential Risks

During the reporting interval, the following safety concern was considered as important potential risk:

- Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)

16.3.1.1 Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)

Background

VAED including VAERD was identified as an important potential risk in the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) EU RMP v1.0 dated 21-Jun-2022.

As per EU RMP, this safety concern is currently theoretical in relation to administration of COVID-19 vaccine (inactivated, adjuvanted, adsorbed). If VAED/VAERD were to occur in vaccinated individuals, it might manifest as a modified and/or more severe clinical presentation of SARS-CoV-2 viral infection upon subsequent natural infection.

Method of Evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the pre-specified search strategy for VAED including VAERD (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety concern could not be evaluated.

16.3.2 New Information on Important Identified Risks

During the reporting interval and cumulatively, there were no important identified risks associated with the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) as per EU RMP v1.0 dated 21-Jun-2022.

16.3.3 New Information on Other Potential Risks Not Categorised as Important:

During the reporting interval and cumulatively, there were no other potential risks not categorised as important associated with the COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

16.3.4 New Information on Other Identified Risks Not Categorised as Important:

During the reporting interval and cumulatively, there were no other identified risks not categorised as important associated with the COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

16.3.5 Update on Missing Information

During the reporting interval, the following 6 safety concerns were considered as missing information:

- Use in pregnancy and while breastfeeding.
- Use in immunocompromised patients.
- Use in patients with autoimmune or inflammatory disorders.
- Use in frail patients with unstable health conditions and comorbidities, e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD).
- Long-term safety data.
- Interaction with other vaccines.

Further evaluation regarding updates on missing information is discussed in the following sections.

16.3.5.1 Use in Pregnancy and While Breastfeeding

Background

The use in pregnancy and while breastfeeding was identified as missing information in the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) EU RMP v1.0 dated 21-Jun-2022.

As per the SmPC, the following information regarding Pregnancy and Breastfeeding is mentioned:

Pregnancy

There is no experience with use of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development.

Administration of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is excreted in human milk.

Method of Evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in pregnancy and while breastfeeding (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety concern could not be evaluated.

16.3.5.2 Use in Immunocompromised Patients

Background

The use in immunocompromised patients was identified as missing information in the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) EU RMP v1.0 dated 21-Jun-2022.

As per the SmPC, the efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) may be lower in immunosuppressed individuals.

Method of Evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in immunocompromised patients (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety concern could not be evaluated.

16.3.5.3 Use in patients with autoimmune or inflammatory disorders

Background

The use in patients with autoimmune or inflammatory disorders was identified as missing information in the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) EU RMP v1.0 dated 21-Jun-2022.

As per EU RMP, there is no information on the safety of the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in patients with autoimmune or inflammatory disorders. This is a theoretical concern that the vaccine may exacerbate their underlying disease.

Method of Evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in patients with autoimmune or inflammatory disorders (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety concern could not be evaluated.

16.3.5.4 Use in frail patients with unstable health conditions and comorbidities, e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD)

Background

The use in frail patients with comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) was identified as missing information in the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) EU RMP v1.0 dated 21-Jun-2022.

As per EU RMP, there is limited information on the safety of the vaccine in frail patients with co-morbidities who are potentially at higher risk of severe COVID-19. The COVID-19 vaccine (inactivated, adjuvanted, adsorbed) has been studied in individuals with stable chronic diseases (e.g. hypertension, obesity), however it has not been studied in frail individuals with severe co-morbidities that may compromise immune function due to the clinical condition or treatment of the clinical condition.

Method of Evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in frail patients with unstable health conditions and comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety concern could not be evaluated.

16.3.5.5 Long-Term Safety

Background

The long-term safety was identified as missing information in the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) EU RMP v1.0 dated 21-Jun-2022.

As per EU RMP, the long-term safety of the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is not available currently. However further safety data are being collected from ongoing clinical studies for up to 1 year following administration of dose 2 of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) and in parallel from post-authorisation / post-marketing studies.

Method of Evaluation

Long-term safety is evaluated by routine monitoring of post-authorisation safety studies (refer to Appendix 9).

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety concern could not be evaluated.

16.3.5.6 Interaction with Other Vaccines

Background

The interaction with other vaccines was identified as missing information in the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) EU RMP v1.0 dated 21-Jun-2022.

As per EU RMP, COVID-19 vaccine (inactivated, adjuvanted, adsorbed) will be used in individuals who also may receive other vaccines. Studies to determine the effect of co-administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva with other vaccines on efficacy and safety of either vaccine have not been performed.

Method of Evaluation

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for reports of interaction with other vaccines (refer to Appendix 9).

All the reports retrieved based on the search strategy were further filtered manually for vaccines from the non-company co-suspect field and concomitant drugs field for further review and assessment.

Conclusion

During the reporting interval and cumulatively, there were no ICSRs received. Hence, further assessment of this safety concern could not be evaluated.

16.4 Characterisation of Risks

Risk characterisation for important potential risks and missing information are discussed in EU RMP Part II, module SVII, based on latest version of EU RMP,v1.0 approved on 21-Jun-2022.

16.5 Effectiveness of Risk Minimisation (if applicable)

During the reporting interval, there were no additional risk minimisation measures in place for COVID-19 vaccine (inactivated, adjuvanted, adsorbed). The effectiveness of routine risk minimisation measures will be monitored through the routine pharmacovigilance activities. Any signals detected during the reporting interval will be evaluated and described in the PSUR (Section 15.1) including if a product label update is warranted.

17 BENEFIT EVALUATION

17.1 Important Baseline Efficacy/Effectiveness Information

The efficacy of VLA2001 study is assessed in the currently ongoing Phase 3 trial VLA2001-301 using an immune-bridging approach.

Study VLA2001-301 is a multicentre, randomised, observer-blind, active-controlled, stratified superiority study to compare the immunogenicity of VLA2001 to the already registered vaccine AZD1222 in terms of GMT of SARS-CoV-2-specific neutralising antibodies.

Furthermore, comparative immunogenicity results from trial VLA2001-301 are supported by immunogenicity results from study VLA2001-201, especially from the high dose group (33 AU/dose).

This section on efficacy gives a short summary of results relevant for efficacy evaluation of VLA2001 in study VLA2001-301. This includes immunogenicity results from the trial VLA2001-301 and discusses the relevance of those results for the evaluation of the efficacy of VLA2001. Furthermore, as an exploratory analysis, occurrence of COVID-19 cases was analysed, to evaluate the protective effect of vaccination.

Summary of results relevant for efficacy evaluation of VLA2001 in study VLA2001-301:

Please note, that due to the fact that study VLA2001-301 is still ongoing, this section contains results with different data cut off points.

Immunogenicity results

In the first interim analysis, study VLA2001-301, confirmed results of study VLA2001-201 that VLA2001 at the high dose (33 AU/dose), is highly immunogenic. This high immunogenicity was higher or similar at 2 weeks after the second vaccination (Day 43) compared to the immune response produced by the already licensed comparator COVID-19 vaccine AZD1222 for which efficacy has been proven.

Two weeks after the second vaccination in adults aged 30 years and above, VLA2001 demonstrated superiority against the already licensed COVID-19 vaccine AZD1222 in terms of GMT for fifty percent neutralising dilution (ND50) (GMT ratio=1.39, p<0.0001). The GMT of the VLA2001 group was 803.5 (95% CI: 748.5, 862.6) and in AZD1222 group 576.6 (95% CI: 543.6, 611.7) (immunogenicity population). Results in the per-protocol population were similar.

Furthermore, VLA2001 demonstrated non-inferiority in terms of seroconversion rates at Day 43. In the per-protocol population, 97.4% (95% CI: 0.954, 0.986) of participants in the VLA2001 group were seroconverted and 98.9% (95% CI: 0.974, 0.996) in the AZD1222 group confirming non-inferiority of seroconversion rates between the 2 treatment groups with a lower bound of the 95%CI for the difference between the 2 treatment groups of -3.3%. Results in the immunogenicity population were similar.

GMT- fold increases for neutralising antibodies (ND50) at Day 43 compared to baseline were 25.9 in the VLA2001 group and 18.6 in the AZD1222 group (p<0.0001) (immunogenicity population). Results in the per-protocol population were similar.

Similar to the neutralising antibodies, for the S-protein binding antibodies as measured by IgG ELISA a higher GMT at Day 43 was observed in the VLA2001 group (GMT 2,361.7) than in the AZD1222 group (GMT 2,126.4). At Day 43, 98.0% of participants in the VLA2001 group were seroconverted and 98.8% in the AZD1222 group.

VLA2001 induced broad T-cell responses with antigen-specific interferon-gamma producing T-cells against the S-protein in 74.3%, against N in 45.9% and against M in 20.3%. Of note, no T-cell response was induced by the licensed comparator AZD1222 against N- and M-protein which could be expected due to the type of active substance in AZD1222.

Occurrence of COVID-19 cases

The occurrence of COVID-19 cases was assessed in participants who received at least 1 vaccination (= safety population) as an exploratory efficacy endpoint. The data cut for the presented analysis is 14 October 2021.

COVID-19 cases occurred at a similar frequency and time after vaccination in the VLA2001 and AZD1222 group in the randomised participants 30 years and above (Table 13). The occurrence of COVID-19 cases in the VLA2001 group of participants aged 18-29 years was numerically higher.

All COVID-19 cases up to the data cut 14 October 2021 (entire study) were assessed as mild or moderate by the investigator and none of the COVID-19 cases were severe.[10]

Table 13: Positive reported COVID-19 cases after vaccination by treatment and age group and time of occurrence (safety population) (study VLA2001-301)

Treatment and age group / Statistics of COVID-19 cases	VLA2001 Age 18 to <30 years (N=1040) n (%)	VLA2001 Age 30 and above (N=1977) n (%)	AZD1222 Age 30 and above (N=995) n (%)	Overall (N=4,012) n (%)
Participants tested COVID-19 positive after 1st dose of vaccination	**2 (0.2)**	**7 (0.4)**	**2 (0.2)**	**11 (0.3)**
Days From 1st vaccination to COVID-19 positive test				
N	2	7	2	11
Mean (SD)	22.5 (6.36)	15.3 (11.58)	20.0 (2.83)	17.5 (9.04)
Median	22.5	16.0	20.00	18.0
Min, Max	18.0, 27.0	1.0, 28.0	18.0, 22.0	1.0, 28.0
Participants tested COVID-19 positive after 2nd dose of vaccination	**87 (8.4)**	**139 (7.0)**	**60 (6.0)**	**286 (7.1)**
Days from 2nd vaccination to COVID-19 positive test • All participants positive				
N	87	139	60	286
Mean (SD)	57.9 (30.19)	63.0 (34.09)	70.1 (31.89)	63.0 (32.66)
Median	65.0	63.0	76.5	66.0
Min, Max	3, 130	7, 126	15, 124	3, 130
Days from 2nd vaccination to COVID-19 positive test • Participants positive 14 or more days after 2nd dose	82 (7.9)	131 (6.6)	60 (6.0)	273 (6.8)
N	82	131	60	273
Mean (SD)	61.0 (28.35)	66.2 (32.47)	70.1 (31.89)	65.5 (31.22)
Median	66.0	69.0	76.5	67.0
Min, Max	15, 130	14, 126	15, 124	14, 130

safety population: received at least one dose of vaccine.
SD: standard deviation, Max: maximum, Min: minimum
Source: VLA2001-301, extended safety CSR addendum to the interim CSR, v1.0, 25 February 2022,

Overall, VLA2001 demonstrated statistical superiority in inducing neutralising antibodies and non-inferiority for seroconversion rates of neutralising antibodies compared to the already licensed comparator AZD1222.

A relationship between high immunogenicity and efficacy in preventing COVID-19 infection is known from the literature. Although antiviral T and B cell memory also contribute to the protection, strong evidence of a protective role for neutralising serum antibodies

exists.[11,12,13,14,15,16] Therefore, the immunogenic response by both vaccines may provide protection against COVID-19 to a similar degree. This assumption is based on factors which include 1.) the high immunogenicity of both vaccines, the already licensed COVID-19 vaccine AZD1222 and VLA2001, 2.) the low and similar frequency of COVID-19 cases in both treatment groups and 3.) the mild to moderate severity of all COVID-19 cases and the complete absence of severe COVID-19 cases during the trial until now. Suggesting that both vaccines prevent severe COVID-19 and hospitalisation.

In conclusion, VLA2001 shows a similar efficacy from the data available to date as the AZD1222, for which efficacy is already established. Additionally, VLA2001 being an inactivated whole-virus vaccine had advantage of eliciting immune response not only against the spike protein but also against other SARS-CoV-2 surface antigens compared to AZD1222 that only presents the S-protein as antigen to the immune system.

17.2 Newly Identified Information on Efficacy/Effectiveness

During the reporting interval, no new safety information that could have an impact on the efficacy and effectiveness of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) was identified.

17.3 Characterisation of Benefits

During the reporting interval, no new information on efficacy and effectiveness of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) became available, the characterisation of baseline benefits is presented in Section 17.1.

Evidence from interim analysis of 2 CTs VLA2001-201 and VLA2001-301 suggested that VLA2001 has very good immunogenicity and efficacy as described above in Section 17.1. Another benefit available from the study VLA2001-301, was the safety profile of VLA2001 which was found to be more favourable than the safety profile of the already licensed comparator COVID-19 vaccine AZD1222.

18 INTEGRATED BENEFIT-RISK ANALYSIS FOR AUTHORIZED INDICATIONS

18.1 Benefit-Risk Context-Medical Need and Important Alternatives

The disease COVID-19 was first detected in late 2019 and shortly afterwards, in March 2020, it was declared a global pandemic. This has caused high morbidity and mortality globally. Given the global impact of the pandemic there was an urgent need for safe and effective COVID-19 vaccines and therapeutic treatment. As per World Health Organisation, more than 609 million confirmed cases of COVID-19 and 6 million deaths have been reported globally since January 2020.[17]

Significant health risks are associated with COVID-19 infection, including a higher rate of mortality among patients with chronic medical conditions and weakened immune systems.

The management of COVID-19 cases has developed since the start of the pandemic, and includes supportive care, which may include fluid therapy, oxygen support, and supporting of other affected vital organs. Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone, targeted immunomodulatory agents, anticoagulants, antiviral therapy and monoclonal antibodies.

Despite unprecedented efforts to control the outbreak, the pandemic has been ongoing. initial observational studies following vaccine rollout suggested that vaccines may lead to protection against COVID-19 infection and also reduce transmission. Numerous SARS-CoV-2 vaccine candidates have been authorised for emergency use globally. These vaccine candidates include inactivated whole virus vaccine compositions, protein subunits, viral vectors, mRNA vaccines etc.

Of all the vaccine types available, the COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is the only alternative with inactivated whole virus compositions. As the vaccine is made of whole virus particles, it presents a wide range of native viral antigens. Hence, it is expected that the immune response elicited by COVID-19 vaccine (inactivated, adjuvanted, adsorbed) will not be limited to the S protein but also be directed against other SARS-CoV-2 antigen. [10,18,19,20,21]

It is noteworthy that COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is stable at 2°C to 8°C and is being manufactured by traditional well-established methods. It can prove to be an effective resolution for achieving vaccine equity worldwide even where vaccine manufacturing and cold chain technologies are not that established.

18.2 Benefit-Risk Analysis Evaluation

The benefit of the COVID-19 Vaccine (inactivated, adjuvanted, adsorbed) Valneva have been seen in VLA2001-201 and VLA2001-301 clinical studies, which are summarised in section 17.1.

The risk associated with inactivated virus vaccines are considered low and several inactivated whole virus vaccines, have been shown to have an excellent safety profile in the past.[22,23,24] The technological platform for developing inactivated vaccines has the advantage of rapidly scaling up production in pandemic situation using well-established infrastructure and methods.

The benefit-risk profile of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) which has been established across the clinical development program remains unchanged and positive from the date of first marketing authorisation. No new information has become available with regards to AESIs, serious AEs, fatal cases, new/ongoing/closed signals or safety concerns, both from cumulative and interval data.

19 CONCLUSION

In conclusion, the overall evaluation of safety data from the use of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) during the reporting interval, and cumulatively, confirms the product's safety and tolerability.