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

28th August 2022 to 27th February 2023

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 28th August 2022 to 27th February 2023, 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/411013/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00011001/202302

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

Period covered by the PSUR: 28/08/2022 To: 27/02/2023

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:	1 June 2023	1 June 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	31 July 2023	31 July 2023
☐	MS/PRAC members and MAH comments	30 August 2023	30 August 2023
☐	PRAC Rapporteur's updated assessment report following comments	14 September 2023	08 September 2023
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	28 September 2023	28 September 2023

Procedure resources	
PRAC Rapporteur	Name: Gabriele Maurer [redacted]
Contact person – PRAC Rapporteur	
Assessor – PRAC Rapporteur	
EMA Procedure Lead	
EMA Procedure Assistant	

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1. Background information on the procedure

This is the assessment of PSUR(s) 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

The marketing authorisation holder (MAH) submitted the 2nd periodic safety update report (PSUR) for COVID-19 vaccine (inactivated, adjuvanted, adsorbed), covering the period from 28 August 2022 to 27 February 2023.

Coronavirus disease 2019 (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) is a purified, inactivated, and adjuvanted whole virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine grown on Vero cells (African green monkey cells). It 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 with 10 doses of 0.5 mL each. One dose (0.5 mL) contains 33 antigen units of inactivated SARS-CoV-2 virus as suspension for injection. The basic immunisation consists of two vaccine doses administered intramuscularly at an interval of 28 days.

The international birth date (IBD) of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is 28 February 2022, when it was first authorised for emergency use in the Kingdom of Bahrain. Approval has been granted also in the United Kingdom (13 April 2022), in the United Arab Emirates (12 May 2022), and in the European Union (EU, 24 June 2022). COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is marketed in the Kingdom of Bahrain and in the EU.

During the reporting interval, direct healthcare professional communication letters (DHPC) were distributed in Austria, Germany, Denmark and Bulgaria to inform about the extension of the shelf life of the vaccine.

The reference safety information in effect during the reporting interval were the EU summaries of product characteristics (SmPCs) dated 25 July 2022, 21 September 2022, 22 November 2022 and 17 February 2023. According to the MAH, no changes to the safety sections were made during the reporting interval.

The MAH states that a cumulative total of 4,094 subjects received COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in five ongoing clinical trials. Cumulatively, 1,171,700 vaccine doses were distributed in the Kingdom of Bahrain and in the EU, and of these, 2,109 were administered in Austria and 7,087 in Germany.

During the reporting interval and cumulatively, the MAH states having received spontaneously reported information on 31 adverse events, thereof three serious, in 12 patients. The MAH's review of the reports did not provide significant new information on the safety profile of COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

According to the MAH, no signals were identified that warranted an update to the product safety specification for COVID-19 vaccine (inactivated, adjuvanted, adsorbed). Also, no data are presented that may alter the assessment regarding the efficacy of the vaccine.

It can be concluded from the information in this PSUR that the benefit-risk profile of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) remains unchanged.

3. Recommendations

Based on the PRAC Rapporteur's 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(s).

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

The MAH should address the following issues in the next PSURs:

- In subsequent reports, the MAH is kindly asked to adhere to the common terminology on the one hand and the requirements of the GVP Module VII on the other.
- Inconsistencies in successive reports should be addressed and explained to avoid queries. If the preceding PSUR is used as a template, the information must be checked for accuracy and up-to-datedness. For more details, see the assessor's comments in the individual sections.
- The MAH is kindly asked to indicate its approach to literature search and the criteria used to select the articles discussed.
- The MAH is kindly requested to recheck the number of ICSRs in its database (see section 5).

5. PSUR frequency

☒ No changes to the PSUR frequency

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

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This second periodic safety update report (PSUR) for Coronavirus disease 2019 (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) covers the period from 28 August 2022 to 27 February 2023. 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.

The MAH does not propose any changes to the product information as part of the submission of this PSUR.

1.2. Worldwide marketing authorisation status

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) was first authorised in the Kingdom of Bahrain on 28 February 2022 (emergency use authorisation). In the EU, it was authorised on 24 June 2022 (centralised marketing authorisation). 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, direct healthcare professional communication letters (DHPC) were prepared and submitted to authorities and healthcare professionals in Austria, Germany, Denmark and Bulgaria to inform them about the extension of the shelf life of the vaccine.

Rapporteur assessment comment: Safety reasons were not the trigger for the DHPC.

1.3.2. Changes to reference safety information

The MAH refers to updates of the summary of product characteristics (SmPC) during the interval. The SmPCs in effect were dated 25 July 2022, 21 September 2022, 22 November 2022 and 17 February

2023. The shelf life was extended from 15 to 18 and finally to 21 months for the finished product. Besides, the in-use shelf life has been updated to 6 hours when stored below 25°C or up to 48 hours when stored at 2-8°C.

Rapporteur assessment comment:

The MAH states that no changes have been made to the safety sections during the reporting interval. Proposals in terms of new safety information and key risk minimisation recommendations are not made.

1.3.3. Estimated exposure and use patterns

Clinical trial exposure. According to the MAH, a cumulative total of 4,094 subjects received COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in five ongoing clinical trials. The studies included 2,234 male, 1,855 female, and 5 diverse adult participants. In addition, the vaccine was administered to 10 male and 11 female adolescents (≥ 12 and < 18 years old).

trial	male	female	diverse	total
VLA2001-201 (completed)	83	70	0	153
VLA2001-301 (adult part)	1,690	1,322	5	3,017
VLA2001-304	146	160	0	306
VLA2001-307	87	91	0	178
COV-BOOST	228	212	0	440
total	2,234	1,855	5	4,094

Table 1: Cumulative number of adult clinical trial participants by trial and gender. Summary of data from the tables in section 5.1 of the PSUR by the assessor.

Post-authorisation exposure. The MAH notes that a total of 1,171,700 COVID-19 vaccine (inactivated, adjuvanted, adsorbed) doses were distributed in the Kingdom of Bahrain (n = 300,500) and the EU (n = 871,200; Austria, n = 76,800; Denmark, n = 43,200; Germany, n = 751,200). 2,109 vaccine doses were administered in Austria, and 7,087 doses in Germany. No information on the number of doses administered is available for the total EU, Denmark, and the Kingdom of Bahrain.

Rapporteur assessment comment:

According to the tables, most of the study participants were/are white/white European. The gender ratio appears to be quite balanced.

It remains unclear why the 21 adolescents (≥ 12 and < 18 years of age) exposed in the VLA2001-301 study (adolescent part, PSUR p. 16) are not included in the cumulative number of subjects treated. 4,094 adults and 21 adolescents equal 4,115 individuals exposed, not 4,094. Besides, not all of the studies listed are still ongoing, so the total number of subjects is likely to have been exposed in completed and ongoing studies rather than in ongoing studies (PSUR pp. 15-16). The totals of male and female study participants in Table 9 (PSUR p. 18, trial VLA2001-307, columns "male" and "female") are obviously not correct. The figures should be corrected in subsequent reports.

Compared to the last PSUR, the number of vaccine doses distributed, especially in Germany and the Kingdom of Bahrain, has increased: 1,171,700 doses in the present PSUR versus 562,400 doses in the last PSUR, of which in Germany 751,200 now versus 249,600 six months ago and in the Kingdom of Bahrain 300,500 now versus 200,000 six months ago. It is appreciated that figures of administered vaccine doses are now given at least for two EU countries – Austria and Germany. The disproportion between distributed and administered doses is substantial.

Note: The statement "during the reporting interval [and cumulatively]" in section 5.2 of the PSUR (PSUR pp. 19-20, text and Table 12), as well as in the executive summary (PSUR p. 5), cannot be correct. Already in the reporting interval of the first PSUR, 572,400 vaccine doses were distributed, so that now not all distributed vaccine doses can fall within the reporting interval of the second PSUR. In the next report, care should be taken to present the post-marketing exposure data as clearly as possible.

1.3.4. Data in summary tabulations

Appendix 3 (PSUR p. 75) lists serious adverse events from clinical trials up to the data cut-off date of 27 February 2023. According to the MAH, during the reporting period (28 August 2022 to 27 February 2023), no serious adverse reactions were reported for the trials VLA2001-201, VLA2001-301, VLA2001-304 and VLA2001-307. In September 2021, one study participant experienced atrial fibrillation following the 1st vaccine dose and recovered. For the COV-BOOST trial, two serious adverse reactions are reported – liver injury (grade 4) and myocardial infarction (grade 3). All three events were considered possibly related to the administration of COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

No individual case safety reports (ICSRs) had been received in the reporting interval of the first PSUR, covering the period between 28 February 2022 and 27 August 2022. Appendix 4 (PSUR pp. 76-81) now lists a total of 31 adverse events reported for 12 patients during the reporting period, three of which were serious and affected one patient. The Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) of the serious adverse events were anaphylactic reaction, dyspnoea, and off label use. The most common MedDRA PT among non-serious adverse events was off label use (n = 8).

Rapporteur assessment comment:

Appendix 3, PSUR p. 75: When compared to the previous PSUR, the eight serious adverse events with a causality rating of "not related" or "unlikely" have been removed from the line listing. All these events occurred in the VLA2001-304 study. An ambiguous terminology had already been noticed in the last PSUR (covering the period between 28 February 2022 and 27 August 2022). In its response to the request for supplementary information in the preceding PSUR assessment report, dated 14 February 2023, the MAH defined a "serious adverse reaction" as a "serious adverse event considered at least as possibly related to the medicinal product". This commonly used terminology should be followed when preparing reports. Unfortunately, the title of Appendix 3 now again mentions serious adverse events, whereas section 6 of the PSUR (except for the heading of section 6.2) and Tables 17-19 address serious adverse reactions. It should be noted that Module VII of the Guidelines on Good Pharmacovigilance Practices (GVP, section VII.B.5.6) refers to "summary tabulations of serious adverse events from clinical trials" (https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf). The MAH is kindly asked to consider this in subsequent reports.

The information on the study participants who had serious adverse reactions (Appendix 3, PSUR p. 75) includes protected personal data (for example, one subject ID and two study sites are specified). This is acceptable provided that the PSUR or such parts of it are not published.

Appendix 4, PSUR pp. 76-81: In contrast to the reporting interval of the first PSUR, ICSRs were now received. However, in the 6th monthly summary safety report (SSR), covering the period from 01 December 2022 to 31 December 2022, the MAH had stated that it had received a cumulative total of 23 ICSRs with three serious and 58 non-serious adverse events in 23 patients. In the present (2nd) PSUR, covering the period from 28 August 2022 to 27 February 2023, Appendix 4 lists a cumulative total of 31 spontaneously reported adverse events in 12 patients, thereof three serious. These figures are obviously inconsistent.

Note: A MedDRA PT should not actually be designated as serious or non-serious, only the event, reaction, or report.

Overall, 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 no safety concerns were identified in the phase 1/2 trial VLA2001-201 by an independent Data Safety Monitoring Board (DSMB). The majority of adverse events were mild or moderate. Two participants reported severe solicited adverse events (headache and fatigue), and 18.3% of the participants reported unsolicited adverse events up to day 208 that were considered related to the vaccine, none of which were severe or serious. Two participants had severe unsolicited adverse events (increased blood bilirubin and vaccination complications after COVID-19 vaccination outside the study) which were considered not related to VLA2001. One non-related serious adverse event (event term: chilblains, also considered an adverse event of special interest [AESI]) was reported. In the booster part of the study, one participant reported a severe unsolicited adverse event (periarthritis). A synopsis of the final clinical study report is provided in Appendix 6.1 (PSUR pp. 89-105).

Ongoing clinical trials. Trial VLA2001-301: The MAH states that, in an interim analysis of the main part of the trial with data up to day 208 in 4,012 participants treated (thereof 3,017 in the VLA2001 dose group), no safety concerns were identified by the DSMB. More than 90% of the participants reported any adverse event, 1.0% had any serious adverse event, and 13 reported an AESI. In the booster part, an interim analysis with data up to day/study visit B2 in 958 participants treated (712 primed with VLA2001 and 246 primed with AZD1222) showed similar incidences of adverse events in both groups (78.7% and 77.6%, respectively; three serious adverse events in the AZD1222 primed group and four serious adverse events in the VLA2001 primed group; one AESI). Overall, serious adverse events reported by more than one participant who had received VLA2001 were appendicitis (four participants in the main part), appendicitis perforated (two participants in the main part), seizure (two participants [one participant in the main part and one participant in the adult booster part]), and spontaneous abortion (two participants in the main part). None of the 73 serious adverse events in the VLA2001 group was considered to be treatment related. With regard to the adolescent part of the study, the MAH notes that recruitment of adolescent participants was stopped due to low enrolment after recruitment of 16 sentinel participants followed by six randomised participants (three randomised to VLA2001 and three randomised to placebo). Up to the cut-off date for this PSUR (27 February 2023), no serious adverse event and no AESI has been reported in the adolescent part of the study. Trial VLA2001-304: 306 participants were enrolled in a non-randomised manner to receive VLA2001 on days 1 and 29. In 17 subjects, a total of 18 serious adverse events were reported. One participant with a medical history of intermittent atrial fibrillation experienced atrial fibrillation which was considered possibly related and classified as suspected unexpected serious adverse reaction (SUSAR). Up to the cut-off date for this PSUR, no AESI has been reported. Trial VLA2001-307: As of the cut-off date for this PSUR, no serious adverse event and no AESI has been reported in this study. Trial COV-BOOST: 219 participants received VLA2001 and 220 participants received a half-dose of VLA2001 as a booster after two vaccinations with Vaxzevria or Comirnaty. As of the cut-off date for this PSUR, five serious adverse events in the VLA2001 group (two of which were considered possibly related to VLA2001 by the investigator) and one in the half-dose VLA2001 group were reported.

In summary, 91 serious adverse events have been described in participants who received VLA2001 in the MAH's ongoing trials for COVID-19 vaccine (inactivated, adjuvanted, adsorbed). According to the MAH, the majority of these serious adverse events were mild to moderate in intensity, and no participants died as a result of serious adverse events reported in clinical trials during the reporting period.

Pregnancy and breastfeeding. The MAH notes that no pregnancy cases have been reported from post-marketing experience. In study VLA2001-201, there were two pregnancies among participants who received VLA2001. Both resulted in full-term healthy live births. No congenital anomalies and no post-natal medical problems were reported for either baby. In trial VLA2001-301, there were 29 participant pregnancies and 10 partner pregnancies among participants who received VLA2001. Among the 29 participant pregnancies, 11 had a normal outcome; seven had a negative outcome, including one foetal death, one premature birth, one emergency caesarean section at 39 weeks gestation, and four miscarriages (two in the first trimester and two for which the gestation period was not specified); two pregnancies were ongoing as of the cut-off date for this report (27 February 2023); and the outcome had not been reported for nine pregnancies. Of the 10 partner pregnancies of participants who received VLA2001, seven had a normal outcome; two pregnancies were ongoing as of the cut-off date for this report; and the outcome had not been reported for one pregnancy (the participant's partner did not consent to follow up). In study VLA2001-307, one pregnancy was reported on 25 January 2023.

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 trials. The MAH notes that during the reporting interval, no other studies have been conducted with COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

Vaccination errors. During the reporting interval and cumulatively, one non-serious ICSR involved a vaccination error (wrong vaccine administered). From all available data, the MAH did not identify any pattern of (potential) vaccination errors.

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

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

- E. Hildt's overview of COVID-19 vaccines licensed in the EU describes the compositional characteristics of the six different COVID-19 vaccines licensed in the EU, their efficacy, and the impact of various factors on efficacy (Hildt E. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2022;65(12):1237-43, doi: 10.1007/s00103-022-03600-4). PRAC assessor's addendum: One of the vaccines discussed is COVID-19 vaccine (inactivated, adjuvanted, adsorbed).
- The questionnaire survey by Lv et al. showed that an inactivated COVID-19 vaccine had a good safety profile in patients with chronic liver disease, and that there is a correlation between self-reported adverse reactions and vaccine anxiety (Lv L et al. Hum Vaccin Immunother 2022;18(6):2136435, doi: 10.1080/21645515.2022.2136435). The study was conducted in patients with chronic liver disease attending a tertiary care hospital in Taizhou, China. PRAC assessor's addendum: Although the trade name of the vaccine is not clearly indicated in the article, it was not COVID-19 vaccine (inactivated, adjuvanted, adsorbed). The overall incidence of adverse reactions after COVID-19

vaccination was 44.4% (71/160), and the most common adverse reaction was local injection site reaction, accounting for 80.3% of adverse reactions (57/71).

- The retrospective study by Fei et al. found a mean onset of inactivated COVID-19 vaccine-associated ocular complications of 13.2 ± 11.9 days (range, 3-30 days; Fei et al. Hum Vaccin Immunother 2022;18(6):2138051, doi: 10.1080/21645515.2022.2138051). PRAC assessor's addendum: The study included eight eyes of five patients, and the cases reported were three anterior uveitis, one herpetic keratitis and iridocyclitis, and one posterior uveitis. The patients had received CoronaVac (Sinovac) and/or BBIBP-CorV (Beijing Institute of Biological Products, Sinopharm).
- The multicenter retrospective cohort study by Li et al. investigated the safety and immunogenicity of two doses of CoronaVac in subjects ≥ 40 years old. The authors conclude that the safety, immunogenicity and cellular immunity memory of CoronaVac in the elderly (≥ 60 years old) living with chronic diseases are comparable to that of healthy individuals (Li et al. Commun Med (Lond) 2022;2(1):151, doi: 10.1038/s43856-022-00216-2). PRAC assessor's addendum: Of 1,302 participants recruited, 969 could be evaluated – 740 individuals with underlying medical conditions and 229 as healthy controls. The authors note that the higher incidence of adverse events in the adult (40-59 years old) comorbidities population was the main driving factor for the difference between the comorbidities cohort and healthy control in the overall incidence of adverse events. More specifically, the major inter-group difference was contributed by the systemic adverse events, mainly fatigue. In the elderly (≥ 60 years old), comorbidities and healthy group did not show significant difference in the overall (15.6% versus 11.1%, P = 0.290), the first dose (9.71% versus 6.48%, P = 0.354) or the second dose (9.93% versus 6.48%, P = 0.354) vaccination. No severe adverse events were reported.
- The meta-analysis by Li et al. included eight studies with 79,334 subjects of which 48,123 had received two doses of COVID-19 inactivated vaccines, and 31,211 two doses of placebo (Li X et al. Front Med (Lausanne) 2022;9:1015184, doi: 10.3389/fmed.2022.1015184). The authors sum up that short-term, mild to moderate adverse reactions occurred, but serious adverse events were rare and no placebo or vaccine-related deaths were reported. PRAC assessor's addendum: The vaccines used in the studies were CoronaVac (Sinovac), BBIBP-CorV (Sinopharm), inactivated SARS-CoV-2 vaccine (Vero cell) (Shenzhen Kangtai Biological Products), BBV152 vaccine (Bharat Biotech International), and SARS-CoV-2 vaccine (Vero cells) (Institute of Medical Biology, Chinese Academy of Medical Sciences).

The MAH states that its 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).

Other periodic reports. The MAH refers to its monthly submitted summary safety reports (SSRs), five of them during the reporting interval. The reporting intervals of all five SSRs cover the period from 01 August 2022 to 31 December 2022.

Rapporteur assessment comment:

Study VLA2001-301: In addition to the study visit (B2), it would have been helpful to indicate the period after booster vaccination in which this study visit occurred.

In the first PSUR, two cases each of osteoarthritis and tibial fracture were mentioned. It is unclear why these cases are now no longer listed in the section on serious adverse events reported by more than one participant. Also, the current PSUR no longer indicates that the SUSAR included three episodes of atrial fibrillation. This had been described in the first PSUR. The MAH should clarify these discrepancies.

The presentation of data on pregnancies is appreciated. However, without further details, it is difficult to interpret the negative outcomes described.

The MAH does not specify how many published and unpublished manuscripts it reviewed. The criteria

used to select the five literature articles "identified for discussion" are not specified. The MAH is kindly asked to specify in subsequent reports the literature search and the criteria used to select the article(s) discussed.

1.3.6. Lack of efficacy in controlled clinical trials

According to the MAH, from interventional, non-interventional, retrospective studies and from the review of published literature no new safety data emerged that indicated a lack of efficacy with COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

1.3.7. Late-breaking information

The MAH states that during the preparation of this PSUR, no potentially important new safety and efficacy/effectiveness findings arose for COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

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 2: Summary of safety concerns, EU risk management plan v1.0 dated 21 June 2022 (PSUR p. 37, Table 14).

2.2. Signal evaluation

The MAH 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 during the reporting interval.

Concerning the use in patients with autoimmune or inflammatory disorders, one ICSR was received during the reporting interval. A 72-year-old male reported vaccination site warmth (outcome *recovered*) after the first vaccination with COVID-19 vaccine (inactivated, adjuvanted, adsorbed). Regarding the use in frail patients with unstable health conditions and comorbidities, one ICSR was received during the reporting interval from a 64-year-old male patient with a medical history of diabetes mellitus, hypertension and COPD, reporting an anaphylactic reaction and dyspnoea (outcome *recovered*) following the first vaccination with COVID-19 vaccine (inactivated, adjuvanted, adsorbed). The MAH's review of the

two ICSRs did not reveal any trends for the adverse event profile compared with the adverse event profile defined in the SmPC.

The MAH notes that it did not receive any ICSRs on the important potential risks or the other missing information. Further assessment of these safety concerns was therefore not possible.

Rapporteur assessment comment:

No data is presented that alters the classification of risks or missing information. No signals have been raised.

2.3. Evaluation of risks and safety topics under monitoring

As already in the first PSUR, the MAH notes that, during the reporting interval, 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 lists fatal reports and the experience in special patient populations as additional safety topics under monitoring.

Safety topics *fatal reports, angioedema, autoimmune disorders, cardiomyopathy, peripheral neuropathy,* and *menstrual disorders*: No ICSRs were received during the reporting interval and cumulatively. Therefore, these safety topics could not be further evaluated.

Safety topic *experience in special patient populations*: In the age group < 18 years, the case of a 17-year-old male was received, reporting an injection site reaction after vaccination (outcome *recovered*). In the age group ≥ 65 years, three ICSRs described mild general symptoms like temperature elevation, vaccination site warmth and unevaluable event (outcome *recovered*).

Safety topic *hypersensitivity*: During the reporting interval, one ICSR was received, reporting an anaphylactic reaction and dyspnoea (outcome *recovered*) following the first vaccination with COVID-19 vaccine (inactivated, adjuvanted, adsorbed).

The MAH queried its global vaccine safety database for AESIs including those considered for adjuvant CpG1018. During the reporting interval and cumulatively, it identified one ICSR related to the AESI anaphylaxis.

Rapporteur assessment comment:

The MAH's statement in section 15.2 is exactly the same as in the last PSUR. It is unclear whether a new request was received from the health authorities or whether this section of the PSUR was not updated.

The MAH's statement "the Pharmacovigilance Risk Assessment Committee concluded that there is no evidence of a causal relationship of menstrual disorders with vaccines against COVID-19" (PSUR p. 36) is not quite correct. The following can be taken from the Pharmacovigilance Risk Assessment Committee (PRAC) 24-27 October 2022 meeting highlights: "After reviewing the data, the Committee concluded that there is at least a reasonable possibility that the occurrence of heavy menstrual bleeding is causally associated with these vaccines [Comirnaty and Spikevax] and therefore recommended the update of the product information". The MAH should take care to ensure that its statements in subsequent reports are accurate.

Apart from this, in view of the virtually unchanged data situation, 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 summarises results of the ongoing study VLA2001-301. Immunogenicity of COVID-19 vaccine (inactivated, adjuvanted, adsorbed) was at least similar to the comparator AZD1222. The vaccine 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. During the reporting interval, 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). Besides, no new information on efficacy and effectiveness of the vaccine became available.

Rapporteur assessment comment: There are no new data on efficacy that alters previous assessments, and which are described in the approved product information. Note to reference 13: The MAH should indicate when it accessed the website. At the time of writing this assessment report, according to the WHO Coronavirus (COVID-19) Dashboard, the numbers of confirmed COVID-19 cases were considerably higher (specifically, over 767 million) than the "more than 609 million" reported in both the first and second PSURs.

4. Benefit-risk balance

The data presented in the current PSUR do not reveal any new safety issues. 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. In the 6th monthly summary safety report (SSR), covering the period from 01 December 2022 to 31 December 2022, the MAH had stated that it had received a cumulative total of 23 ICSRs with

three serious and 58 non-serious adverse events in 23 patients. In the present (2nd) PSUR, covering the period from 28 August 2022 to 27 February 2023, Appendix 4 lists a cumulative total of 31 spontaneously reported adverse events in 12 patients, thereof three serious. The MAH is kindly asked to briefly address these apparent discrepancies (12 versus 23 patients).

2. In the first PSUR, two cases each of osteoarthritis and tibial fracture were mentioned. It is unclear why these cases are now no longer listed in the section on serious adverse events reported by more than one participant. Also, the current PSUR no longer indicates that the SUSAR included three episodes of atrial fibrillation. This had been described in the first PSUR. The MAH should clarify these discrepancies.

6. MAH responses to Request for supplementary information

Question 1: *In the 6th monthly summary safety report (SSR), covering the period from 01 December 2022 to 31 December 2022, the MAH had stated that it had received a cumulative total of 23 ICSRs with three serious and 58 non-serious adverse events in 23 patients. In the present (2nd) PSUR, covering the period from 28 August 2022 to 27 February 2023, Appendix 4 lists a cumulative total of 31 spontaneously reported adverse events in 12 patients, thereof three serious. The MAH is kindly asked to briefly address these apparent discrepancies (12 versus 23 patients).*

MAH's response: During the preparation of the 6th monthly summary safety report (SSR), the MAH was in the process of transitioning to a new safety database and a new case processing team. To ensure timely submission of SSR 06 to EMA, the report had to be compiled right after completion of data migration. Although the migrated data was complete, the MAH had included case tabulations covering also cases of medication errors by mistake.

This error led to the incorrect sum of 23 ICSRs included and discussed in this SSR.

The MAH ensures that the information provided in Appendix 4 of PSUR #2 (reporting period: 28-Aug-2022 to 27-Feb-2023) is accurate and consistent with the information in Valneva's global safety database, i.e. a total of 12 ICSRs have been reported for COVID-19 Vaccine (inactivated, adjuvanted) Valneva to date.

Rapporteur assessment comment:

Cases of medication error should be summarised and discussed in the PSUR. In section 9.2 on vaccination errors, the MAH states that "During the reporting interval and cumulatively, there was one non-serious ICSR report involving a vaccination error (Wrong vaccine administered) received". Therefore, the MAH's response is not entirely comprehensible. Also, a search in EudraVigilance yielded more than 12 ICSRs even considering the data lock point of the PSUR. *{Confidential information removed}*

The MAH is kindly requested to recheck the number of ICSRs in its database. Issue not resolved.

Question 2 (1): *In the first PSUR, two cases each of osteoarthritis and tibial fracture were mentioned. It is unclear why these cases are now no longer listed in the section on serious adverse events reported by more than one participant.*

MAH's response: This is due to the SAEs reported by more than one participant being presented in a slightly different way in the two PSURs:

PSUR #1 for period 2022Feb28 to 2022Aug27 -> Section "Ongoing Clinical Trials" starts with a summary and in the 4th paragraph lists SAEs reported by more than one participants across all ongoing trials.

PSUR #2 for period 2022Aug28 to 2023Feb27 was oriented to the DSUR finalized shortly prior to the PSUR, and presents SAE reported by more than one participant per study.

Tibia fracture and osteoarthritis occurred in one participant each for VLA2001-301 and VLA2001-304 studies, so they are only comprised when listing SAE in SAEs reported by more than one participants across all ongoing trials, and not when listing SAE reported by more than one participant per study.

We ask the rapporteur to clarify what type of presentation is preferred for the next PSUR.

Question 2 (2): *Also, the current PSUR no longer indicates that the SUSAR included three episodes of atrial fibrillation. This had been described in the first PSUR. The MAH should clarify these discrepancies.*

MAH's response: It is still correct that the respective participant had three episodes of atrial fibrillation, as described in PSUR #1. The second episode was classified as SAE based on hospitalization and was later classified as SUSAR. We apologize for not having described the event with the same level of detail in PSUR #2.

Rapporteur assessment comment:

The MAH asks which presentation of serious adverse events in trials is preferred by the PRAC rapporteur. The PRAC rapporteur considers a cumulative presentation of events to be more meaningful and informative than a presentation by individual trial, as this allows less frequent events to be better captured. In addition, the adverse events per study should be reported, so that an increased incidence in a particular study in eventually a specific population can be identified.
The MAH's answers to Question 2 are acceptable. Issue resolved.

7. Comments from Member States

No comments from member states were received.

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-Aug-2022 to 27-Feb-2023

Date of Report: 14-Apr-2023

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:

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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] 20 April 2023

EXECUTIVE SUMMARY

Introduction

This is the second 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 summarizes the safety data received and processed by Valneva Austria GmbH (herein referred to as Valneva) from worldwide sources for the reporting interval covering 28-Aug-2022 to 27-Feb-2023.

The periodicity of this PSUR is based on the Emergency Use Authorization in the Kingdom of Bahrain, which is considered 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) neutralizing 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 immunization 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: 17-Feb-2023.

Worldwide Marketing Authorisation Status

The first Emergency Use Authorization 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 authorized 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 Authorization), EU (Centralized), United Arab Emirates (Emergency Use Authorization), and United Kingdom (Conditional Marketing Authorization).

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

During the reporting interval, Direct Healthcare Professional Communication letters (DHPC) were prepared and submitted to authorities and Healthcare professionals in Austria, Germany, Denmark and Bulgaria to inform them about the extension of the shelf life for COVID-19 vaccine (inactivated, adjuvanted).

Changes to Reference Safety Information

Several updates were made to the Summary of Product Characteristics (SmPC) for COVID-19 vaccine (inactivated, adjuvanted) during the interval, the SmPCs in effect were dated 25 Jul 2022, dated 21 Sep 2022, dated 22 Nov 2022 and dated 17 Feb 2023.

During the reporting interval, the shelf life was extended from 15 to 18 and finally to 21 months for the finished product. Furthermore, the in-use shelf life has been updated to 6 hours when stored below 25 °C or up to 48 hours when stored at 2-8 °C.

No changes to the safety sections were made during the reporting interval.

Summary of Clinical Trials

During the reporting interval, there were 4 ongoing clinical trials with VLA2001, 1, 1 Phase 2/3 trial (VLA2001-307), 2 Phase 3 trials (VLA2001-301 and VLA2001-304), and 1 Phase 2 trial (COV BOOST).

Furthermore, 1 clinical trial (Phase 1/2 trial (VLA2001-201)) was completed with VLA 2001 during the reporting period.

Further details of the completed and ongoing clinical trials are presented in Section 7.2.

Clinical Trial Exposure

Cumulatively, a total of 4.094 subjects received COVID-19 vaccine (inactivated, adjuvanted, adsorbed) in 5 ongoing clinical trials.

Post-Authorisation Exposure

During the reporting interval, a total of 1.171.700 COVID-19 vaccine (inactivated, adjuvanted, adsorbed) doses were distributed in Kingdom of Bahrain and EU region.

Overview of Individual Case Safety Reports (ICSRs)

Cumulative and interval summary tabulations of adverse drug reactions (serious and non-serious) received during the reporting interval is provided in Appendix 4.

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. One ICSR with MedDRA preferred terms related to the list of AESIs was identified but did not suggest any trends for the AE profile compared to the AE profile in the current SmPC. (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 a good 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 that has a major impact on the benefit risk evaluation.

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 good 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.

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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
SMQ	Standardised MedDRA Query
SSR	Summary Safety Report

Acronym	Abbreviation Definition
UK	United Kingdom
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
WWMA	Worldwide Marketing Authorisation

1 INTRODUCTION

This is the second periodic safety update report (PSUR) for Coronavirus Disease (COVID-19) vaccine (inactivated, adjuvanted, adsorbed) compiled for regulatory authorities which follows the International Conference on Harmonization 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-Aug-2022 to 27-Feb-2023.

The periodicity of this PSUR is based on the Emergency Use Authorization in the Kingdom of Bahrain, which is considered 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: 17 Feb 2023 (refer to Appendix 1).

2 WORLDWIDE MARKETING AUTHORISATION STATUS

COVID-19 vaccine (inactivated, adjuvanted, adsorbed) is currently authorized in various regions for the active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 to 50 years of age. The first Emergency Use Authorization 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 authorized 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 Authorization), EU (Centralized), United Arab Emirates (Emergency Use Authorization), and United Kingdom (UK) (Conditional Marketing Authorization).

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, Direct Healthcare Professional Communication letters (DHPC) were prepared and submitted to authorities and Healthcare professionals in Austria, Germany, Denmark and Bulgaria to inform them about the extension of the shelf life for COVID-19 vaccine (inactivated, adjuvanted).

4 CHANGES TO REFERENCE SAFETY INFORMATION

Several updates were made to the Summary of Product Characteristics (SmPC) for COVID-19 vaccine (inactivated, adjuvanted) during the interval, the SmPCs in effect were dated 25 Jul 2022, dated 21 Sep 2022, dated 22 Nov 2022 and dated 17 Feb 2023.

During the reporting interval, the shelf life was extended from 15 to 18 and finally to 21 months for the finished product . Furthermore, the in-use shelf life has been updated to 6 hours when stored below 25 °C or up to 48 hours when stored at 2-8 °C.

No changes to the safety sections 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 4.094 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
VLA2001-307	VLA2001	178
COV-BOOST	VLA2001	440
TOTAL	VLA2001	**4094**

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 (completed)

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 (completed)

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

Table 9: Cumulative Participant Exposure to VLA2001 by Age and Gender – Trial VLA2001-307

Age Range (years)	Number of Participants		
	Male	Female	Total
18-29	27	40	67
30-55	37	27	64
≥56	23	24	47
Total	**64**	**65**	**178**

Table 10: Cumulative Participant Exposure to VLA2001 by Race and Gender - Trial VLA2001-307

Race Group	Number of Participants		
	Male	Female	Total
White	79	82	161
Latin American	0	1	1
Asian	3	3	6
Māori	0	1	1
Other	5	4	9
Total	**87**	**91**	**178**

COV-BOOST Trial

Table 11: 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)
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 1.171.700 COVID-19 vaccine (inactivated, adjuvanted, adsorbed) doses were distributed in Kingdom of Bahrain and EU region.

Table 12: Interval Actual Exposure Data (Administered and Distributed) from Post-Authorisation Experience Presented by Region / Country

Region / Country	Total Doses Administered[a]	Total Doses Distributed
	Interval	
Kingdom of Bahrain	Not available	300.500
EU		
Austria	2.109	76.800
Denmark	Not available	43.200
Germany	7.087	751.200
Total (EU Countries)	**Not available**	**871.200**
Total	**Not available**	**1.171.700**

[a] https://www.data.gv.at/en/data/austrian-covid-19-open-data-information-portal/

6 DATA IN SUMMARY TABULATIONS

6.1 Reference Information

The Medical Dictionary for Regulatory activities (MedDRA) version 25.1 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 all serious adverse reactions from Company-sponsored interventional CTs is provided in Appendix 3.

6.3 Cumulative and Interval Summary Tabulations from Post-Authorisation Data

Cumulative and interval summary tabulations of adverse drug reactions (serious and nonserious) received during the reporting interval is provided in Appendix 4.

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

Protocol VLA2001-201 A Phase I/II Randomised, Two Parts, Dose-Finding Study to Evaluate the Safety, Tolerability and Immunogenicity of an Inactivated, Adjuvanted SARS-CoV-2 Virus Vaccine Candidate (VLA2001), Against COVID-19 In Healthy Subjects:

- **Study period**: *16 Dec 2020 to 06 Apr 2022*

Trial VLA2001-201 (Phase 1/2) was the first-in-human trial of VLA2001. The trial was a randomised, dose-escalation and dose-finding, multicentre trial with 3 dose groups (low, medium and high). The primary objective of this trial was to evaluate the tolerability, safety, and immunogenicity of VLA2001 in a 2-dose primary immunization schedule (Day 1; Day 22) in healthy adults aged 18 to 55 years. The trial was conducted in 3 parts: Part A (covering the follow-up from Day 1 to Day 36) and Part B (covering the follow-up from Day 37 to Day 208). A Booster Part (Part C, covering the follow-up from Visit 7 to Visit 10) was also added to the trial. Trial participants who have completed the 2 initial vaccinations and have been followed for 8-9 months, were offered 1 dose of VLA2001 (high dose) as a booster vaccination. Electronic diaries were used to solicit local and systemic adverse events (AEs) within 7 days after each vaccination.

In this trial, VLA2001 was found to be generally safe and well tolerated across all dose groups tested, with no safety concerns identified by an independent Data Safety Monitoring Board (DSMB). The majority of adverse events (AEs) were mild or moderate and only 2 participants reported severe solicited AEs (headache and fatigue). The majority of solicited AEs resolved quickly. Only 18.3% of trial participants reported unsolicited AEs up to Day 208 which were considered related to the vaccine; no related severe unsolicited AEs were reported. There were no serious related AEs. One non-related serious adverse event (SAE; event term: chilblains, also considered adverse event of special interest [AESI]) was reported. The Investigator reported the event as mild in severity. No action was taken with regard to the trial vaccine and the event resolved.

The high dose was selected for Phase 3 trials.

For information on the Synopsis of the final Clinical Study Report please refer to Appendix

7.2 Ongoing Clinical Trials

Overall, 2 Phase 3 Valneva-sponsored clinical trials (VLA2001-301 and VLA2001-304) and 1 Phase 2/3 trial (VLA2001-307) were ongoing during the reporting period. The Phase 3 VLA2001-301 trial includes an Adult Part, an Adult Booster Part, and an Adolescent Part.

In addition, 1 Phase 2 non-Valneva-sponsored clinical trial (Phase 2 COV-BOOST Trial) included VLA2001 as booster vaccination in 1 of 3 groups in the trial. Analysis of the study part concerning VLA2001 is completed; study is ongoing for further sub-studies.

Phase 3 Trial – VLA2001-301

- Study period: 28-Apr-2021 to 13-Mar-2023 (Data analysis ongoing)
- Summary:

VLA2001-301 is a Phase 3, randomized, observer-blind, controlled, superiority trial to compare the immunogenicity of VLA2001 to AZD1222 in terms of GMT of SARS-CoV-2-specific neutralizing antibodies. AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 Spike surface glycoprotein. Development of AZD1222, previously referred to as ChAdOx1 nCoV-19, was initiated by the University of Oxford with subsequent transfer of development activities to AstraZeneca.

Main Part (Adult Population):

Participants in VLA2001-301 are adults aged 18 years older who are either generally healthy or have a stable medical condition. Approximately, 3,000 participants 30 years of age and older have been randomized in a 2:1 ratio to receive 2 IM doses of either VLA2001 (n=2,000) or AZD1222 (n=1,000) at the recommended dose level (33 AU), 28 days apart, on Days 1 and 29. Approximately 1,000 participants who are under 30 years of age have been placed in a non-randomized treatment group and receive VLA2001, 28 days apart. The primary objectives of this trial are to demonstrate the superiority of VLA2001 compared with AZD1222, in terms of GMT of neutralizing antibodies, at 2 weeks after the second vaccination in adults aged 30 years and older and to evaluate the safety and tolerability of VLA2001 at 2 weeks after the second vaccination.

The last participant's last visit took place on Oct 10, 2022. Data analysis was ongoing at the cut-off date for this PSUR.

An interim analysis with data up to Day 208 in 4,012 participants treated (3,017 in the VLA2001 dose group and 995 in the AZD1222 dose group) is available. In this analysis, VLA2001 was found to be generally safe and well tolerated, with no safety concerns identified by the DSMB. Overall, 94.1% of participants reported any AE up to Day 208. The incidences of AEs were similar in the VLA2001 (age 18-29 years) group, and the VLA2001 (age ≥30 years) group (94.4% and 91.7%, respectively) compared with the AZD1222 group (98.5%). The majority of AEs were mild in severity. There were no deaths in this study as of up to Day 208. Overall, 1.0% of participants had any SAEs up to Day 208. The incidences of SAEs were similar between treatment groups. Up to Day 208 91.1% of participants reported any treatment-related AE. The

incidences were 91.8% and 87.2% in the VLA2001 (age 18-29 years) group, and the VLA2001 (age ≥30 years) group, respectively, compared with the AZD1222 group (98.1%). No serious solicited AEs were reported up to Day 208. 13 participants reported an AESI up to Day 208.

Adult Booster Part:

In the Booster Part, all participants, except those who already received a licensed COVID-19 vaccine outside of the trial, were offered a booster dose with VLA2001.

An interim analysis with data up to Day B2 in 958 participants treated (712 primed with VLA2001 and 246 primed with AZD1222) is available. Overall, in this analysis 78.4% participants reported any AE. The incidences of AEs were similar in the VLA2001 primed and the AZD1222 primed groups (78.7% and 77.6%, respectively). The majority of AEs reported were mild in severity, and 73.9% of participants had AEs that were treatment related. The incidences of treatment-related AEs were similar in the VLA2001 primed group and the AZD1222 primed group (74.2% and 73.2%, respectively). There were no deaths in this study up to Day B2. Overall, 0.7% of participants had SAEs. The number of SAEs was similar between both study groups (3 events in the AZD1222 primed group and 4 events in the VLA2001 primed group). None of the SAEs was considered to be treatment related. One AESI was reported up to visit B2.

In total in the adult part of the study (including adult main and booster part), 94 SAEs in 82 participants have been reported (73 in the VLA2001 group and 21 in the AZD1222 group). There were no deaths in this study up to the cut-off date for this PSUR.

The majority of these SAEs were mild to moderate in intensity. The only SAEs reported by more than 1 participant who received VLA2001 in Trial VLA2001-301 were appendicitis (4 participants in the Main Part), appendicitis perforated (2 participants in the Main Part), seizure (2 participants [1 participant in the Main Part and 1 participant in the Adult Booster Part]), spontaneous abortion (2 participants in the Main Part). None of the SAEs was considered to be treatment related.

Adolescent Part:

This protocol was amended on 10 August 2021 to include adolescent participants ≥12 to <18 years old, to determine the safety and tolerability of VLA2001 in this age group. For safety reasons, the first 16 adolescents were enrolled in an open-label, non-randomized manner. A DSMB review of the accrued safety data after all 16 sentinel participants completed the 7-day e-diary period after vaccination was favourable. Randomization of the remaining participants across all sites was initiated and is ongoing.

At least 660 participants were planned to be recruited and randomized in a 1:1 ratio to receive 2 IM doses of either VLA2001 (n=330) or placebo (n=330). It was planned for adolescents who initially received placebo in this trial to subsequently receive 2 doses of VLA2001. However, the protocol was amended on 06 September 2022 and recruitment of adolescent participants was stopped due to low enrolment after recruitment of 16 sentinel participants followed by 6 randomized participants (3 randomized to VLA2001 and 3 randomized to placebo). The study

design ensures a safety follow-up of 6 months after the last VLA2001 vaccination/booster for all enrolled study participants.

The sentinel adolescent participants received a booster vaccination with VLA2001 at Visit V5ab and will have follow-up visits 14 days after the booster dose (i.e., Visit V6ab) and 6 months after the booster dose (i.e., Visit V7ab). None of the randomized participants will receive a booster dose. Participants in the placebo group will receive a 2-dose primary immunization (28 days apart) with VLA2001 at Visit V4p and Visit V5p.

Due to the fact that the placebo group will receive a dose of VLA2001 at Visit V4p, all adolescent participants will be unblinded at this point in time. Visit V5p, V6p, V7p and V8p will only be performed by the participants initially randomized to the placebo group.

The adolescent study was ongoing at the cut-off date for this PSUR. No SAE and no AESI has occurred in the adolescent study part up to the cut-off date for this PSUR.

Phase 3 Trial – VLA2001-304

- Study period: 09-Aug-2021 to 18-Nov-2022 (Data analysis ongoing)
- Summary:

VLA2001-304 is a Phase 3, multicenter, open-label, single arm study to assess the safety, tolerability, and immunogenicity of VLA2001 in older adults. Participants aged >56 years and older who are either generally healthy or are with a stable medical condition were enrolled. A total of 306 participants were enrolled in a non-randomized manner to receive VLA2001 at the recommended dose level, 28 days apart, on Days 1 and 29. The study protocol was amended in order to investigate a booster dose of VLA2001 in older adults. All participants except those who had already received a licensed COVID-19 vaccine outside of the study have been offered a booster dose with VLA2001. All eligible and willing participants have received a booster VLA2001 vaccination at Visit B1 and have been followed up 14 days and 6 months after the booster vaccination.

In study VLA2001-304, a total of 18 SAEs were reported in 17 subjects.

One participant with a medical history of intermittent atrial fibrillation since 2011 had an SAE (reported in the PSUR covering the interval 28 Feb 2022 to 27 Aug 2022), which was initially reported by the Investigator as unrelated. Upon further review, the Investigator changed the event to possibly related during the reporting period for the current DSUR and this event was reported as suspected unexpected serious adverse reaction (SUSAR). The event was considered severe, and it resolved within 16 days.

One participant (Trial VLA2001-304) withdrew consent due to a non-VLA2001 related SAE (oesophageal adenocarcinoma) in March 2022.

No death and no AESI has occurred in study VLA2001-304 up to the cut-off date for this PSUR.

Phase 2/3 Trial – VLA2001-307

- Study period: 09-May-2022 to ongoing
- Summary:

VLA2001-307 is a Phase 2/3 multicenter, open-label clinical trial investigating the safety, tolerability, and immunogenicity of a VLA2001 booster vaccination (standard dose of 0.5 mL in participants ≥18 years to ≤50 years of age, or a double dose of 1.0 mL in participants aged >50 years). Approximately 275 participants, either generally healthy or with a stable medical condition, are planned to be enrolled in the trial, with approximately 25% of participants who are>65 years of age enrolled into the cohorts with participants >50 years of age.
The VLA2001 booster is given to adults at least 6 months after vaccination with an mRNA COVID-19 vaccine, with or without confirmed SARS-CoV-2 infection, or to unvaccinated adults at least 4 months after confirmation of natural SARS-CoV-2 infection.

Immunogenicity will be assessed at Visit 1 (pre-booster, Day 1) and at Visit 2 (14 days after booster, Day 15). Safety will be assessed for at least 6 months after the booster vaccination. This trial was initiated during the reporting period and remains ongoing.

No SAE, no AESI and no death have been reported in study VLA2001-307 up to the cut-off date for this PSUR.

COV-BOOST Trial

The COV-BOOST trial is a multicenter, randomized, controlled, Phase 2 trial of a third dose booster vaccination against COVID-19. Participants were aged 30 years and older and were at least 70 days post 2 doses of the Oxford-AstraZeneca vaccine or at least 84 days post 2 doses of the Pfizer-BioNTech vaccine, with no history of laboratory-confirmed SARS-CoV-2 infection (Munro et al, 2021). The study consisted of 3 groups, one of them including VLA2001 as a booster shot. In that group, participants were randomised to receive either Pfizer-BioNTech, VLA2001, half-dose of VLA2001, Janssen Ad26, or control (a quadrivalent meningococcal conjugate vaccine) in a 1:1:1:1:1 manner.

In the COV-BOOST trial, a total of 219 participants received VLA2001 and 220 participants received a half-dose of VLA2001 as a booster after 2 vaccinations of Oxford-AstraZeneca or Pfizer-BioNTech. As of the cut-off date for this PSUR and per the report in Munro 2021, 5 SAEs 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. All vaccines showed no safety concerns.

Appendix 3:Table 19: Serious Adverse Reactions from the COV-BOOST TrialTable 19 shows Serious Adverse Reactions from the COV-BOOST Trial.

<u>Summary Valneva's VLA2001 clinical program</u>

Cumulatively, in the ongoing trials in Valneva's VLA2001 clinical program up to the cut-off date for this PSUR, 91 SAEs have been reported in participants who received VLA2001. The majority of these SAEs were mild to moderate in intensity. The only SAEs reported by more

than 1 participant who received VLA2001 in Trial VLA2001-301 were appendicitis (4 participants in the Adult Part), appendicitis perforated (2 participants in the Adult Part), seizure (2 participants [1 participant in the Adult Part and 1 participant in the Booster Part]), spontaneous abortion (2 participants in the Adult Part); and atrial fibrillation (2 participants) in Trial VLA2001-304.

In the ongoing trials in Valneva's VLA2001 clinical program, 1 suspected unexpected serious adverse reaction (SUSAR) has been reported in the VLA2001 trials as of the cut-off date for this PSUR. One participant in Trial VLA2001-304 had an SAE of atrial fibrillation during the previous reporting period (28 Feb 2022 to 27 Aug 2022), which was initially reported by the Investigator as unrelated. Upon further review, the Investigator changed the event causality to possibly related during the reporting period for the current DSUR and this event was reported as a SUSAR. The event was considered severe, and it resolved within 16 days.

One participant (Trial VLA2001-304) withdrew consent during the reporting period due to a non-VLA2001 related SAE (oesophageal adenocarcinoma). One participant (Trial VLA2001-201) withdrew consent due to a non-serious AE not related to VLA2001 (COVID-19). Two participants in Trial VLA2001-301 withdrew consent due to non-serious AEs (hypercalcaemia and worsening of anxiety) not related to VLA2001.

No SARs (related SAEs) were reported in clinical trials of VLA2001 during the reporting period (28 Aug 2022 - 27 Feb 2023).

Appendix 3:Table 18 presents a cumulative table of the number of SARs that have been reported during clinical trials of VLA2001, from its initiation to the data lock point (27 Feb 2023) for this reporting period, organized by SOC.

Cases with a Fatal Outcome

No participants died as the result of SAEs reported in clinical trials during the reporting period.

Pregnancy and Lactation

In study VLA2001-201, there were 2 pregnancies during the study among participants who received VLA2001. A participant in the Main Part of the study had a positive serum pregnancy test on 25 January 2021. She received her first and only VLA2001 vaccine dose on 18 January 2021. The pregnancy resulted in a full-term healthy live birth by caesarean section. A participant in the Booster Part of the study received her VLA2001 booster dose on 29 September 2021 and had a positive urine pregnancy test on 20 December 2021. The pregnancy resulted in a full-term healthy live birth at 39 weeks gestation. No congenital anomalies and no post-natal medical problems were reported for either baby.

In Trial VLA2001-301, there have been 29 participant pregnancies and 10 partner pregnancies during the study as of the cut-off date for this PSUR (27 Feb 2023) among participants who received VLA2001. Among the 29 participant pregnancies, 11 had a normal outcome; 7 had a negative outcome, including 1 foetal death, 1 premature birth, 1 emergency caesarean section at 39 weeks gestation, and 4 miscarriages (2 in the first trimester and 2 for which the gestation period was not specified); 2 pregnancies were ongoing as of the cut-off date for this report; and the outcome had not been reported for 9 pregnancies.

Of the 10 partner pregnancies of participants who received VLA2001, 7 had a normal outcome; 2 pregnancies were ongoing as of the cut-off date for this report; and the outcome had not been reported for 1 pregnancy (the participant's partner did not consent to follow up).

In study VLA2001-307, one pregnancy was reported on 25 Jan 2023.

No pregnancies were reported in study VLA2001-304 (all participants were ≥56 years of age). No pregnancy cases have been reported from post-marketing experience.

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 was one non-serious ICSR report involving a vaccination error (Wrong vaccine administered) received. No patterns of vaccination errors or potential vaccination errors were identified for COVID-19 vaccine (inactivated, adjuvanted, adsorbed) from all available data.

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, 5 literature articles were identified for discussion which are summarised below:

1. Eberhard Hildt, Overview of COVID-19 vaccines licensed in the EU-from technology via clinical trial to registration[1]

As of July 2022, six different COVID-19 vaccines are licensed in the EU including two mRNA-based vaccines, two adenoviral vector-based vaccines, one subunit vaccine and the inactivated virus vaccine VLA2001. Although these vaccines are based on different technologies, they all share the use of the spike protein of SARS-CoV-2 as antigen. This overview describes the characteristics of their composition, their efficacy, and the impact of various factors on efficacy. Another aspect of this overview is the description of the approval process and the identification of factors that have contributed to the unprecedented speed in the development and approval of vaccines against a pandemic pathogen.

2. Li Lv, et. al., Adverse reactions to inactivated COVID-19 vaccination in patients with chronic liver disease: The effect of anxiety[2]

The aim of this study was to evaluate the safety of the inactivated COVID-19 vaccine in patients with chronic liver disease, and the effect of anxiety on adverse reactions. A questionnaire survey for self-administered post-vaccination adverse reaction monitoring was conducted from June 17, 2021, to August 11, 2021, in patients with chronic liver disease attending a tertiary care hospital in Taizhou, China. This study showed that the inactivated COVID-19 vaccine had a good safety profile in patients with chronic liver disease, and that there is a strong correlation between reported adverse reactions and vaccine anxiety.

3. Ping Fei et al., Inflammatory ocular events after inactivated COVID-19 vaccination[3]

The purpose of this retrospective study was to report potential vaccine-induced inflammatory ocular adverse events following inactivated COVID-19 vaccination. In previous investigations COVID-19 vaccine-associated uveitis has been reported with onset ranging from 1 to 30 days following vaccine administration while in this study the mean time between vaccination and ocular complications onset was 13.2 ± 11.9 days (range 3– 30 days).

4. Chunmei Li et. al., Retrospective study of the immunogenicity and safety of the CoronaVac SARS-CoV-2 vaccine in people with underlying medical conditions[4]

This large cohort study investigated the safety and immunogenicity of CoronaVac in participants ≥ 40 years old who received two does of CoronaVac inactivated vaccines. The results of this study highlighted the comparable safety, immunogenicity, and cellular immunity memory of CoronaVac in seniors and people living with chronic diseases.

5. Xiaoming Li et al., Efficacy and safety of COVID-19 inactivated vaccine: A meta-analysis[5]

The authors of the study screened several databases for randomized controlled trials related to COVID-19 inactivated vaccines. In this analysis eight studies with 79,334 subjects were included of which 48,123 had received two doses of COVID-19 inactivated vaccines, and 31,211 had received two doses of placebo. Two doses of inactivated COVID-19 vaccines in people over 18 years of age effectively prevented SARS-CoV-2 infection and its associated hospitalizations. Short-term, mild to moderate adverse reactions had occurred, but serious adverse events were rare and no placebo or vaccine-related deaths had been reported.

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 13 below.

Table 13: 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. 2	01-Aug-2022 to 31-Aug-2022	31-Aug-2022	EMA
COVID-19 Vaccine (inactivated, adjuvanted) Valneva, SSR No. 3	01-Sep-2022 to 30-Sep-2022	30-Sep-2022	EMA
COVID-19 Vaccine (inactivated, adjuvanted) Valneva, SSR No. 4	01-Oct-2022 to 31-Oct-2022	31-Oct-2022	EMA
COVID-19 Vaccine (inactivated, adjuvanted) Valneva, SSR No. 5	01-Nov-2022 to 30-Nov-2022	30-Nov-2022	EMA
COVID-19 Vaccine (inactivated, adjuvanted) Valneva, SSR No. 6	01-Dec-2022 to 31-Dec-2022	31-Dec-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.

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)

The global vaccine safety database was queried for AESI for the cumulative period up to 27-Feb-2023 according to prespecified search strategies (refer to [Table 23] or [Appendix 8] for search strategies).

Total List of AESI

- Acute disseminated encephalomyelitis
- Amniotic cavity infection
- Anaphylaxis
- Multiple sclerosis
- Multisystem inflammatory syndrome in children
- Myasthenia gravis

- Appendicitis
- Autoimmune thyroiditis
- Bell's palsy
- Cerebral venous sinus thrombosis
- 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
- Myocardial infarction
- Myocarditis, Pericarditis
- Narcolepsy
- Neonatal death
- 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, one ICSR with MedDRA PT related to the following AESIs were identified.

- **Anaphylaxis**

For more details on the case please refer to section Hypersensitivity 15.2.2.3.

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).

Results and Discussion

During the reporting interval one case of a 17 year old male from [redacted] was received, reporting an injection site reaction after the vaccination with the vaccine. The outcome of the reaction was reported as recovered.

Conclusion

The review of the ICSR did not suggest any trends for the AE profile compared to the AE profile as defined in the SmPC.

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).

Results and Discussion

During the reporting interval three ICSRs were received from patients over 65 years of age. The reports were received from patients 69-, 72- and 74-years of age and described only mild general

symptoms like temperature elevation (1), vaccination site warmth (1) and unevaluable event (1). The outcome of the reaction was reported as recovered. All patients had received several doses from other vaccines in the past, therefore all cases were also coded as Off label use.

Conclusion

The review of the ICSR did not suggest any trends for the AE profile compared to the AE profile as defined in the SmPC.

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).

Results and Discussion

During the reporting interval one ICSR was received from a 64-year old male patient with a medical history of Diabetes mellitus, Hypertension and COPD from [redacted]. The patient reported an anaphylactic reaction (1) and dyspnea (1) after the first vaccination with COVID-19 vaccine Valneva. The outcome of the reaction was reported as recovered without treatment.

Conclusion

The review of the ICSR did not suggest any trends for the AE profile compared to the AE profile as defined in the SmPC.

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 including symptoms of angioedema. 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 14 reflective of EU RMP v1.0, dated 21-Jun-2022.

Table 14: 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 involving pregnancies or use during breastfeeding. 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 involving immunocompromised patients. 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).

Results and Discussion

During the reporting interval one ICSR was received from a 72-year old male patient with a medical history of pancreatitis from [redacted]. The patient reported vaccination site warmth after the first vaccination with COVID-19 vaccine Valneva. The outcome of the reaction was reported as recovered without treatment.

Conclusion

The review of the ICSR did not suggest any trends for the AE profile compared to the AE profile as defined in the SmPC.

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).

Results and Discussion

During the reporting interval one ICSR was received from a 64-year old male patient with a medical history of Diabetes mellitus, Hypertension and COPD from [redacted]. The patient reported an anaphylactic reaction (1) and dyspnea (1) after the first vaccination with COVID-19 vaccine Valneva. The outcome of the reaction was reported as recovered without treatment.

Conclusion

The review of the ICSR did not suggest any trends for the AE profile compared to the AE profile as defined in the SmPC.

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 from post-authorisation safety studies. 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 reporting any interaction with other vaccines. 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 15). 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.[6]

Table 15: 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)**

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 (%)
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.[7,8,9,10,11,12] 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.[13]

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.

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. [6,14,15,16,17]

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 a good safety profile in the past.[18,19,20] 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 good 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.