Risk Management Plan

for COVID-19 Vaccine (inactivated, adjuvanted) Valneva

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Datum: 23.06.2022 11:36:59

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List of Abbreviations

ADZ1222	AstraZeneca COVID-19 vaccine
AE	Adverse Event
AESI	Adverse Event of Special Interest
AU	Antigen Unit
CCDS	Company Core Data Sheet
COVID-19	Coronavirus Disease 2019
CpG	Cytosine Phospho-Guanine
COPD	Chronic Obstructive Pulmonary Disease
DART	Developmental and Reproductive Toxicology
DLP	Data Lock Point
ECDC	European Centre for Disease Control
EEA	European Economic Area
EFD	Embryofoetal Development
ERD	Enhanced Respiratory Disease
EU	European Union
FDA	Food and Drug Administration
GD	Gestation Day
GLP	Good Laboratory Practices
HLT	High Level Term
ICSR	Individual Case Safety Report
MHRA	Medicines and Healthcare products Regulatory Authority
mRNA	Messenger Ribonucleic Acid
MSSR	Monthly Summary Safety Report
NHP	Non-Human Primate
PPND	Pre-and Postnatal Development
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
rHA	Recombinant Human Albumin
RMP	Risk Management Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SmPC	Summary of Product Characteristics

SOC	System Organ Class
TESSy	The European Surveillance System
Th1	T Helper Cell Type 1
Th2	T Helper Cell Type 2
UK	United Kingdom
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
WHO	World Health Organisation

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Part I: Product Overview

Table 1: Product(s) Overview

Active substance(s) (INN or common name)	COVID-19 Vaccine (inactivated, adjuvanted) Valneva COVID-19 vaccine (inactivated, adjuvanted, adsorbed)
Pharmacotherapeutic group(s) (ATC Code)	Viral vaccines (JO7BX03)
Marketing Authorisation Applicant	Valneva Austria GmbH Campus Vienna Biocenter 3 1030 Vienna Austria
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	n.a.
Marketing authorisation procedure	Centralised
Brief description of the product	Type of product Bio(techno)logical / classical biological / Vaccine
	Summary of mechanism of action COVID-19 Vaccine (inactivated, adjuvanted) Valneva is a purified, inactivated, and adjuvanted whole virus SARS-CoV-2 (Wuhan strain hCoV-19/Italy/INMI1-isl/2020) vaccine grown on Vero cells. The vaccine process makes the virus unable to replicate and delivers intact spike proteins on the virus surface. Adjuvants are added to increase the magnitude of vaccine-mediated immune responses. Following administration, COVID-19 Vaccine (inactivated, adjuvanted) Valneva induces 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 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.
	Important information about its composition This is a multi-dose vial which contains 10 doses of 0.5 mL. One dose (0.5 mL) contains 33 Antigen Units (AU) of inactivated SARS-CoV-2 virus[1,2,3]. [1] Strain hCoV-19/Italy/INMI1-isl/2020 [2] Produced on Vero cells (African green monkey cells) [3] Adsorbed on aluminium hydroxide (0.5 mg Al^{3+} in total) and adjuvanted by 1 mg CpG 1018 (cytosine phospho-guanine) in total. List of excipients:

	Sodium chloride Sodium phosphate dibasic anhydrous Potassium phosphate mono anhydrous (E340) Potassium chloride (E508) Water for injections Recombinant human albumin (rHA) produced in yeast (Saccharomyces cerevisiae).
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	COVID-19 Vaccine (inactivated, adjuvanted) Valneva is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 to 55 years of age.
Dosage in the EEA	1 dose (0.5 mL) contains 33 Antigen Units (AU) of inactivated SARS-CoV-2 virus[1,2,3] [1] Strain hCoV-19/Italy/INMI1-isl/2020 [2] Produced on Vero cells (African green monkey cells) [3] Adsorbed on aluminium hydroxide (0.5 mg Al^{3+} in total) and adjuvanted by 1 mg CpG 1018 (cytosine phospho-guanine) in total.
Pharmaceutical form(s) and strengths	Suspension for injection (injection). White to off-white suspension (pH 7.5 ± 0.5).
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication and target population

Indication

Active immunization of individuals between 18 and 55 years of age to prevent COVID-19 disease caused by SARS-CoV-2.

Incidence

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), the causative etiology of 'Corona Virus Disease-2019' (COVID-19), has caused high morbidity and mortality globally.(Nalbandian, Sehgal et al. 2021) It was first identified in Wuhan city, Hubei province, China in early December 2019.(She, Jiang et al. 2020) Coronaviruses (CoV) were identified as human pathogens in the 1960s. They are enveloped positive stranded RNA viruses that belongs to the Coronaviridae family (subfamily Coronavirinae) of the Nidovirales Order.(Shereen, Khan et al. 2020) There are currently seven human CoVs known to infect humans causing diseases ranging from mild form or common cold to severe and/or fatal infections.(Dhama, Sharun et al. 2020)
On March 11, 2020, the WHO declared COVID-19 a global 'pandemic'.(Li, Wang et al. 2020) Since the first reports of cases from Wuhan at the end of 2019, cases have been reported in all continents. Globally, over 200 million confirmed cases of COVID-19 have been reported. with 4,852,764 deaths worldwide.(Hopkins) Estimates of SARS-CoV-2 incidence change rapidly. Since 31 December 2019 and as of 02 August 2021, the overall number of people who had been infected with SARS-CoV-2 was over 199,024,295 worldwide. In the EU and the UK, the number of confirmed cases had accumulated to over 51,584,667 including 1,134,188 reported deaths. (Worldometers.info 2021)

Surveillance data reported to the WHO Regional Office for Europe and the European Centre for Disease Prevention and Control (ECDC) shows that between 28 June and 11 July 2021 the Delta variant was dominant in the majority (19 countries) of the 28 countries who reported sufficiently complete genetic sequencing information.(ECDC 2021)

Prevalence

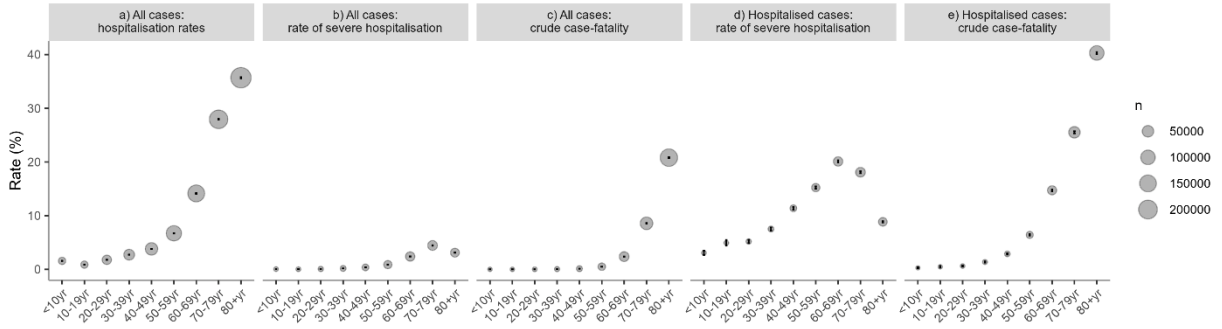
Based on pooled data collected by ECDC from official national sources in 30 countries, the 14-day case notification rate for the EU/EEA for week 31 (week ending Sunday 8 August 2021), was 209.2 per 100 000 population (country range: 5.1–930.6), compared to 214.0 (country range: 4.3–1 242) in week 30.
The rate per 100 000 population was <40 in five countries (Czechia, Hungary, Poland, Romania and Slovakia), 40–<100 in nine countries, 100–<300 in nine countries and 300 or higher in seven countries. Increasing trends were observed in 19 countries.(ECDC. 2021) Based on data reported by 27 countries, the 14-day case notification rate in people aged 65 years and older for the EU/EEA, was 66.8 per 100 000 population (country range: 5.2-333.5), compared to 63.8 (country range: 4.9–492.1) in week 30. The rate per 100 000 population was <20 in 10 countries, 20–<50 in six countries, 50–<150 in eight countries and 150 or higher in three countries (Cyprus, Iceland and Spain). Increasing trends were observed in 15 countries.(ECDC. 2021)

Demographics of the population in the proposed indication and risk factors for the disease:

COVID-19 is now recognized as a multi-organ disease with a broad spectrum of manifestations.(Nalbandian, Sehgal et al. 2021)
The predominant pathophysiologic mechanisms of acute COVID-19 include the followings: direct viral toxicity, endothelial damage and microvascular injury, immune system dysregulation and stimulation of a hyperinflammatory state, hypercoagulability with resultant in situ thrombosis and macrothrombosis and maladaptation of the angiotensin-converting enzyme 2 (ACE2) pathway.(Gupta, Madhavan et al. 2020)
Most cases of COVID-19 are mild or moderate and do not require hospitalisation or advanced medical care. (ECDC 2021)
Severity of COVID-19 is associated with increased age, male sex, and pre-existing medical conditions (Treskova-Schwarzbach, Haas et al. 2021) (Figliozzi, Masci et al. 2020).

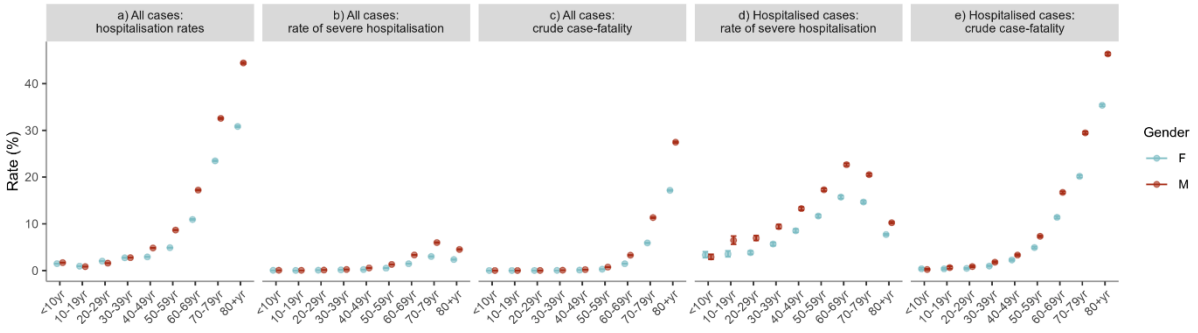
With regards to mortality among hospitalised COVID-19 cases, high certainty evidence in age-/sex-adjusted analyses has been identified for diabetes mellitus, renal disease, and dementia, while moderate certainty evidence has been noted for ischaemic heart disease, stroke, solid organ tumours, and obesity. Mortality among cases detected in the community setting is associated with a history of heart failure, stroke, diabetes, and end-stage renal disease. High or moderate certainty evidence reveals a strong association between hospitalisation for COVID-19 and diabetes, heart failure, COPD, renal disease, obesity, and ischaemic heart disease in the community setting (ECDC. 2021).
According to European Surveillance System TESSy, COVID-19 case-based data, accessed on 02 August 2021, (Figure 1 and Figure 2), the risk of hospitalisation and death increases sharply with age.
The reduced risk of severe hospitalisation among the oldest age groups may reflect clinical decisions about the use of limited ICU or ventilator capacity and is a pattern that is observed in many countries. Males have a higher risk of severe outcomes than females, and this sex difference tends to becomes more marked in the older age groups. Values of case-fatality may be underestimated for countries with deaths under-reported relative to cases in TESSy.
Age and age-sex-specific attack rates are shown in the figures below for five indicators of severity across all (a–c) and hospitalised (d–e) cases.

Figure 1: Age-specific rates of hospitalization (a), severe hospitalization (b, d) and case-fatality (c, e) all cases and hospitalized cases, EU/EEA countries to 25 July 2021*. (ECDC. 2021)



*Data source ECDC, COVID-19 situation update for the EU/EEA as of July 2021:

Figure 2: Age-specific rates of hospitalization (a), severe hospitalization (b, d) and case-fatality (c, e) all cases and hospitalized cases, EU/EEA countries to 25 July 2021*. (ECDC. 2021)



*Data source ECDC, COVID-19 situation update for the EU/EEA as of July 2021:

The main existing treatment options

Several medicinal products have been studied or are currently undergoing clinical trials to assess their safety and efficacy as potential agents for prophylaxis or treatment of COVID-19. These include corticosteroids, the antiviral nucleotide analogue remdesivir, systemic interferons, monoclonal antibodies against components of the immune system such as interleukin-6 (IL-6), other immune modulators, and monoclonal antibodies against components of SARS-CoV-2. Clinical trials of therapeutic interventions for COVID-19 have focused on adult patients.(ECDC 2021)

As of July 2021, several vaccines have been authorized for emergency use globally.
Four COVID-19 vaccines have received conditional marketing authorisation in the EU/EEA, following evaluation by European Medicines Agency (EMA), and are part of the EU Coronavirus Vaccines Strategy Portfolio: Comirnaty (BNT162b2) developed by BioNTech/Pfizer, COVID-19 Vaccine Moderna (mRNA-1273), Vaxzevria (previously COVID-19 Vaccine AstraZeneca) (AZD1222), and COVID-19 Vaccine Janssen (Ad26.COV 2.5).(ECDC. 2021)

The continued efforts in the development of additional safe and effective COVID-19 vaccines are considered essential to address the current ongoing pandemic in reducing and most importantly preventing future outbreaks.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

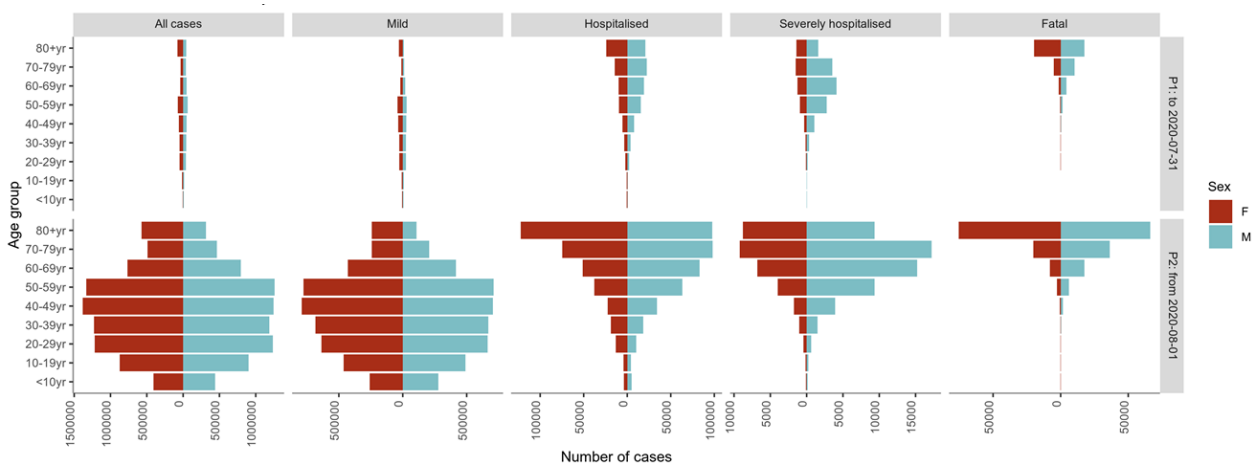
The natural history of coronavirus disease 2019 (COVID-19) has yet to be fully described. Considering its ability to spread and the relatively low case-fatality rates initially reported in China, SARS-CoV-2 was thought to be more similar to influenza than SARS-CoV-1. (Petersen, Koopmans et al. 2020)

Globally, as of 16 August 2021, there have been 207.173.086 confirmed cases of COVID-19, including 4.361.996 deaths, reported to WHO.(WHO 2021)

Age-sex distributions of all cases reported at different levels of severity are shown below. Cases reported to TESSy are older than the general population, with very few cases in people aged below 20 years. This reflects the age distribution of people who met the requirements for being

tested and is unlikely to reflect the actual distribution of infections in the population. Males and older age groups are over-represented among more severe cases (hospitalised, severely hospitalised or fatal).

Figure 3: Age-sex distribution of cases at different levels of severity and by time period, pooled data for EU/EEA countries*. (ECDC 2021)



*Data source ECDC, COVID-19 situation update for the EU/EEA as of August 2021:

As of August 8, 2021, there have been 1,212,033 deaths across the whole of Europe due to the coronavirus (COVID-19) since the first recorded European death in France on February 15, 2020. The United Kingdom currently has the highest number of deaths in Europe and has recorded 130,356 coronavirus deaths as of August 8. In Italy, there have been 128,220 confirmed deaths as a result of the coronavirus.(Statista 2021)

Important co-morbidities

According to ECDC, important underlying health conditions reported among adult patients with severe COVID-19 disease include cardiac disorder. diabetes, hypertension, history of heart failure, ischaemic heart disease, chronic obstructive pulmonary disease (COPD), chronic respiratory disease, chronic kidney disease, immune compromised status, cancer neurologic conditions and smoking (Table 2). (ECDC 2021)

Table 2: Preconditions among COVID-19 Patients in EU/EEA and UK, by Severity of Disease. Case-based Data from TESSy 7 as of October 2021 (ECDC 2021)

Precondition	Mild (%)	Hospitalized (%)	Severe (%)	Fatal (%)
Cardiac disorder, excluding hypertension	8.6	23.3	30.7	24.1
Diabetes	4.8	16.5	19.8	18.4
Cancer, malignancy	3	8.9	9.7	10.9
Chronic lung disease, excluding asthma	1.9	4	4.9	4.1
Current smoking	1,3	0.3	0.4	0.1
Hypertension	0.9	3.4	4.2	4.5

Precondition	Mild (%)	Hospitalized (%)	Severe (%)	Fatal (%)
Neuromuscular disorder, chronic neurological	0.7	2	1.5	3.3
Asthma	0.6	1.3	1.7	1.2

Part II: Module SII - Non-clinical part of the safety specification

Toxicity

A repeat dose toxicology study was conducted in rats, with the highest human dose used in the clinical study VLA2001-201.
A pre- and post-natal development (PPND) study has been performed with the human Phase 3 dose of VLA2001.

Single Dose Toxicity

No formal single dose toxicology study was performed. As the intended clinical dosing includes more than one injection, an acute dose toxicology study will not add scientific value.

Repeat Dose Toxicity and Local Tolerance

Repeat Dose IM Toxicity Study of in Rats with a 3 Week Recovery

The objectives of this GLP study were to determine the potential toxicity of VLA2001, a Vero cell inactivated whole virus vaccine candidate for the prevention of COVID-19, when given by IM injection on three occasions at a 2-weekly interval (Days 1, 15, 29) to Han Wistar rats, and to evaluate the potential reversibility of any findings (Study 514449).

Methods

The study design was as follows:

Table 3 : Experimental Design

Group No.	Treatment	Dose Level (AU/0.4 mL/dose)	Dose Volume (mL)	Number of Animals			
				Main Study		Recovery	
				Males	Females	Males	Females
1	Control (0.9% [w/v] sodium chloride solution)	0	0.4	10	10	5	5
2	VLA200+CpG 1018	42*	0.4	10	10	5	5

AU=antigen unit; CpG 1018=cytosine phospho-guanine; w/v=weight/volume.
Dose of 42 AU corresponds to 28AU if measured with the second-generation ELISA

Mortality, clinical observations, body weights, food consumption, body temperature, ophthalmology, clinical pathology parameters (haematology, coagulation, clinical chemistry, and urinalysis), α1-acid glycoprotein and α2-macroglobulin analysis, immunogenicity analysis, organ weights and macroscopic and microscopic examinations were evaluated during study.

Results

There were no unscheduled deaths related to VLA2001. There were no clinical signs of systemic toxicity that were related to VLA2001, but there were transient local signs at the site of administration with swollen hind limbs in a few VLA2001-treated animals. There were no ophthalmology or urine analysis findings related to VLA2001.

There was minimal body weight loss (<3%) on Days 2, 16 and 30 (the day after administration), when compared to the controls. Food consumption was lower (18% to 29% in males and 12% to 19% in females) in animals that received VLA2001 only in the 4-day period after each administration. There was a slightly higher body temperature in VLA2001-treated animals 4hours post-dose, when compared to the controls and the values recorded pre-dose and pre-treatment.

VLA2001 clinical pathology findings included differences in white blood cell numbers, lower platelet numbers, prolongation of activated partial thromboplastin time and higher fibrinogen, lower triglycerides, total protein, calcium, and differences in plasma proteins (lower albumin and higher globulin), when compared with controls. There were also higher inflammatory proteins noted the day after dosing, when compared with controls. These effects had recovered or lessened at Day 51.

Plasma concentrations of α1-acid glycoprotein and α2-macroglobulin were higher than controls the day after injection, but recovered at the next collection, 7 or 21 days after administration. VLA2001 vaccine is highly immunogenic in rat. After receiving a single dose of the VLA2001 vaccine, there were low but detectable antibody titres. Antibody titres significantly increased and reached a plateau following the second immunization. The third immunization did not further increase antibody titres.

Macroscopically, the only test item-related gross finding was an enlargement of the draining lymph nodes. Group mean spleen weights in males and females and liver weights in females were higher, when compared with controls. There was no recovery of the macroscopic or organ weight (spleen and liver) findings. Microscopically at Day 31, test item-related findings were observed at the administration sites (necrosis/inflammation of the myofiber), sciatic nerve (inflammation), femorotibial joint (inflammation), spleen (increased cellularity in the white pulp), and popliteal/iliac/inguinal lymph nodes (increased cellularity of lymphoid and plasma cells). All these microscopic findings were still observed at the end of the recovery period although incidence was lower indicating partial recovery.

Conclusion

In conclusion, IM administration of VLA2001 on three occasions at 2 weekly intervals (Days 1, 15 and 29) to Han Wistar rats was associated with transient body weight loss, lower food consumption, a transient increase in body temperature and inflammatory proteins, clinical pathology differences, higher spleen and liver weights, and microscopic findings at and around the administration sites, the spleen and draining lymph nodes. After a 3-week treatment, free period microscopic findings were still evident, but with relative lower incidences at the administration sites and spleen, indicating partial recovery. The observations would be considered physiological and immunological responses to the vaccine.

Reproductive and Development Toxicity

A pre- and post-natal development (PPND) study was performed with the human Phase 3 dose of VLA2001.

The test dose applied to rats, 26.4 AU/0.4 mL total daily dose, amounts to 80% of the human dose (33 AU).

The clinical trial lot used in the Phase 3 study VLA2001-301 was used in the study on reproductive toxicity described in this section.

The study analysed both, Embryofoetal Development (EFD) phase and Littering phase. The study involved female Han Wistar rats (n=44 in each phase, 2 rats were kept as a reserve, one for each group). The design of the test is summarized in Table 4.
The objective of this GLP study was to determine the potential toxicity of VLA2001 when given before and after pregnancy via i.m. injection to female Han Wistar rats (n=90 F) during pre- and post-natal development. In addition, 45 male rats were used for mating.

Each female rat received 2 injections of 0.2 ml, (a total dose volume of 0.4 ml), i.m. into a hind limb. Overall, each animal received three doses, the first one at 22 days prior to mating while the second and the third dose were administered 9 days prior to the mating (EFD phase) and on the gestation day (GD) 6 (littering phase), respectively.

Table 4: Pre and Post Natal Development Study of VLA2001 Vaccine in rats

EFD phase					
Group No	**Treatment**	**Dose level (AU/0.4 ml/dose)**	**Dose Volume per site (ml)**	**Total dose volume (ml)**	**Animal numbers** **EFD Phase** **Females**
1	Control	0	0.2	0.4	1501-1522
2	VLA2001	26.4	0.2	0.4	2501-2522
Littering phase					
Group No	**Treatment**	**Dose level (AU/0.4 ml/dose)**	**Dose Volume per site (ml)**	**Total dose volume (ml)**	**Animal numbers**
					Littering Phase
					Females
1	Control	0	0.2	0.4	1601-1522
2	VLA2001	26.4	0.2	0.4	2601-2522

Source: Study No. 491250

Results of the study

No deaths neither any clinical signs related to the test product were reported in the PPND study (Study No: 491250). This included also local reactions at the dosing site.
Body weights and the weight gains of tested animals were not affected by VLA2001. Also, there were no test item related effects on food consumption of animals in either the EFD or Littering phase.

There was no evidence of test item related effects on mating behaviour, yet the overall pregnancy rate was reported to be small; of the 88 females paired, the number of those pregnant or birth giving was 68 (overall pregnancy rate on study of 77%), which was classified as a lower threshold of a normal range. The study authors are of the opinion that the overall number of animals used in the study is enough to conclude that the somewhat lower pregnancy rate had nothing to do with VLA2001.

Genotoxicity

Genotoxicity studies of an inactivated vaccine is not considered necessary. (WHO 2005)

Carcinogenicity

Carcinogenicity studies of an inactivated vaccine is not considered necessary. (WHO 2005)

Safety Pharmacology

As one potential cause for vaccine mediated enhanced respiratory disease (VAERD) or antibody disease enhancement (ADE) may be a strong Th2 response, the pronounced Th1 skewed response observed for VLA2001 observed in all species tested indicated a minimal risk of VAERD or ADE upon infection.

Administration of VLA2001 adjuvanted with alum and CpG 1018 was determined as safe in cynomolgus macaques. No clinically significant observations were made upon injection.
Finally, data from a repeat-dose toxicity study in rats did not suggest that VLA2001 might overtly affect vital functions.
Thus, dedicated safety pharmacology studies were not conducted in line with applicable and relevant guidelines (WHO, 2005).

Other toxicity-related information or data

No other toxicity studies have been performed with VLA2001.

Part II: Module SIII - Clinical trial exposure

Valneva is conducting first-in-human trials of vaccine candidate VLA2001 in the United Kingdom and in New Zealand to obtain safety and immunogenicity data in different age groups in order to evaluate its COVID-19 vaccine candidate (VLA2001) and provide information on the clinical development of VLA2001, an inactivated, whole virus, adjuvanted SARS-CoV-2 vaccine.

Overall, one Phase 1/2 (VLA2001-201), and two Phase 3 trials (VLA2001-301 and VLA2001-304) have been initiated and currently ongoing. A summary is provided below for each trial.

Phase 1/2 study: VLA2001-201 and pivotal phase 3 study: VLA2001-301

The vaccine candidate VLA2001 was evaluated in the Phase1/2 Study (VLA2001-201), where three dose regimens were administered to participants aged 18 to 55 years. Based on the safety and immunogenicity data obtained in this study, the high dose regimen (33 AU) was selected for further evaluation in the Study VLA2001-301, which is a randomized, observer blind, controlled, superiority Phase 3 study to compare the immunogenicity of VLA2001 against ADZ1222 (Vaxzevria), in adults aged 30 years and above. The VLA2001-301 study evaluates the superiority of VLA2001 compared to AZD1222 administered in 2-dose immunization schedule 4 weeks apart in adults aged 30 years and older.

The VLA2001-201 study comprised dose-escalation and dose-level -finding evaluations of the vaccine candidate VLA2001, where three distinct dose levels (low, medium and high) were evaluated. The study vaccine was administered using a 2-dose schedule, 21 days apart. Dose levels were administered to participants aged 18 to 55 years. The vaccine was safe and well tolerated. The whole-virus, inactivated, COVID-19 vaccine at the 33 AU dose level was selected and advanced to the Phase 3 for further evaluation because the reactogenicity profile for the high dose level (33 AU) of VLA2001 was like the other two dose levels, however with significantly improved immunogenicity results.

The Phase 1/2 Study (VLA2001-201) was divided into 2 Parts (Part A and Part B) and comprised the evaluation of safety and immunogenicity data for the first 150 participants (50 participants have been recruited to each dose group, namely low, medium and high dose groups). The clinical study protocol was amended to include a third part in the study (Part C) that consists of a Booster phase. Part A includes data up to Day 36, Part B includes data from Day 37 to Day 208 and Part C includes data of the participants who entered the booster phase up to 6 months after the booster administration. The study is still ongoing.

The total number of participants in the VLA2001-201 study was considered sufficient to obtain initial safety data considering that inactivated vaccines are a well-established, safe vaccine technology. The number of participants per group allow for a 95% confidence that an adverse event (AE) with a true underlying incidence of about 2% would be observed in the present study.

The Phase 3 VLA2001-301 study (which is ongoing) represents the pivotal study to evaluate safety and efficacy in terms of immunogenicity of VLA2001. The study is designed to demonstrate superiority of VLA2001 in terms of inducing neutralizing antibodies as well as non-inferiority for seroconversion rates of neutralizing antibodies compared to AZD1222, for which efficacy has been demonstrated.

Recruitment of adolescents into the pivotal Phase 3 trial VLA2001-301 has commenced. The adolescent part of the trial consists of an observer-blind, randomised, placebo-controlled part to investigate VLA2001 with regards to safety, tolerability, and immunogenicity in approximately 660 adolescents aged 12-17 years of age. At the time of writing this plan the 16 sentinel adolescent participants have received two doses of VLA2001.

Cumulative Patient Exposure in the Development Program of VLA2001

Overall, an estimated 4,487 healthy subjects have been enrolled in the VLA2001 clinical program, of which approximately 3,492 subjects have received VLA2001, and 995 subjects have received the comparator vaccine AZD122.

Table 5: Estimated Cumulative Subject Exposure by Trial

Trial	Treatment	Number of Subjects
VLA2001-201		
	VLA2001	153
VLA2001-301		
Adult trial	VLA2001	3017
	Comparator (AZD1222)	995
Adolescent Trial	VLA2001	16
	Placebo	0

An estimate of cumulative exposure to VLA2001 by age, sex (Table 6, Table 7) and racial group is provided in tabulations below (Table 8, Table 9) based on Demographic Data by Clinical Trial Type (i.e. VLA2001-201, VLA2001-301 and VLA2001-304).

Cumulative Summary Tabulations of Demographic Data by Clinical Trial: Age and Sex

VLA2001-201

Table 6: Cumulative Subject Exposure to VLA2001 by Age and Sex

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

VLA2001-301

Table 7: Cumulative Subject Exposure to VLA2001 by Age and Sex

Adult Trial				
	Number of Subjects			
Age Range (years)	**Male**	**Female**	**Diverse**	**Total**
18-29	555	483	2	1040
30-55	1121	834	3	1958
≥55	14	5	0	19
Total	**1690**	**1322**	**5**	**3017**

Adolescent Trial				
	Number of Subjects			
Age Range (years)	**Male**	**Female**	**Diverse**	**Total**
<18	9	7	0	16
Total	**9**	**7**	**0**	**16**

Cumulative Summary Tabulations of Demographic Data by Clinical Trial: Race and Gender

VLA2001-201

Table 8: Cumulative Subject Exposure to VLA2001 by Race and Gender

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

VLA2001-301

Table 9: Cumulative Subject Exposure to VLA2001 by Race and Gender

Adult Trial				
	Number of Subjects			
Race Group	**Male**	**Female**	**Diverse**	**Number of Subjects**
White/White European	1577	1218	5	2800
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	**1690**	**1322**	**5**	**3017**

Adolescent Trial				
	Number of Subjects			
Race Group	**Male**	**Female**	**Diverse**	**Number of Subjects**
White	8	7	0	15
Mixed	1	0	0	1
Total	**9**	**7**	**0**	**16**

Cumulative Summary Tabulations of Treatment Exposure by Clinical Trial: Duration

A summary of exposure to study treatment by VLA2001 is presented in Table 10 and Table 11 for individual clinical studies. The mean (SD) duration of exposure indicates the number of days between first and second study vaccination.

VLA2001-201

Table 10: Exposure to VLA2001 in the VLA2001-201 study (Safety Analysis Set)

VLA2001 treatment	Number of participants	Exposure duration (days)
Low dose	51	21.9
Medium dose	51	21.1
High dose	51	21.5

Exposure duration is calculated as: Date of last dose of study drug – Date of first dose of study drug + 1.

VLA2001-301

Table 11: Exposure to VLA2001 in the VLA2001-301 study (Safety Population)

Age Range and treatment type	Number of participants	Exposure duration (days)
18 to <30 years VLA2001	1040	28.9
≥30 years VLA2001	1977	29.0
≥30 years AZD1222	995	29.2

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Detailed descriptions of all exclusion criteria for clinical studies VLA2001-201 and VLA2001-301 are provided in the individual Clinical Trial Protocols. Phase 1/2 exclusion criteria were more detailed and differed from criteria in Phase 3 of the study. Participants were excluded from the studies according to the general criteria listed below:

Receipt of medications and / or vaccination intended to prevent COVID-19

Reason for exclusion: To avoid confounding the assessment of serological or clinical immune response in the study population.

Is it considered to be included as missing information? No.
Rationale: Minimal potential clinical impact on the target population.

Women who are pregnant or breastfeeding

Reason for exclusion: To avoid use in a vulnerable population.

Is it considered to be included as missing information? Yes.
Rationale: There is limited experience with use of COVID-19 Vaccine (inactivated, adjuvanted) Valneva 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) Valneva in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. It is unknown whether COVID-19 Vaccine (inactivated, adjuvanted) Valneva is excreted in human milk.

Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination

Reason for exclusion: Immunocompromised participants may have impaired immune responses to vaccines and would therefore limit the ability to demonstrate efficacy, which is the primary pivotal endpoint.

Is it considered to be included as missing information? Yes.
Rationale: Participants with known or suspected defect in the immune system, such as participants with congenital or acquired immunodeficiency were not specifically included in the study population in order to avoid factors that could confound an understanding of the interpretation of the safety and efficacy of VLA2001. However, representation of the vulnerable population to COVID-19 illness, may provide further understanding of immune responses in this population in our future studies.

History of allergy to any component of the vaccine

Reason for exclusion: Patients with known allergy/hypersensitivity to the active ingredient or comparator were excluded from the clinical studies as these individuals may have a higher risk of hypersensitivity reactions, including anaphylaxis.

Considered to be included as missing information? No.

Rationale: VLA2001 can be potentially contraindicated in patients with known hypersensitivity to the active substance and other vaccine components known from a patient's history, therefore use in this patient population is not applicable.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical studies are limited in size and, therefore, unlikely to detect very rare adverse reactions, or adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 12: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Available data on COVID-19 Vaccine (inactivated, adjuvanted) Valneva administered to pregnant women are insufficient to inform on vaccine-associated risks in pregnancy. Therefore, administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. Until DLP, 8 pregnancies were reported, thereof 5 participants' pregnancies and 3 partner pregnancies. Six participants continued with study visits. One pregnancy was terminated voluntarily. No follow-up information is available at the time of this RMP version. The earliest pregnancy test dates May 2021.

Type of special population	Exposure
Breastfeeding women	Breastfeeding women were not included in the clinical development program with COVID-19 Vaccine (inactivated, adjuvanted) Valneva. Data are not available to assess the effects of COVID-19 Vaccine (inactivated, adjuvanted) Valneva on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COVID-19 Vaccine (inactivated, adjuvanted) Valneva and any potential adverse effects on the breastfed newborn / infant / toddler from COVID-19 Vaccine (inactivated, adjuvanted) Valneva or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptible to disease prevented by the vaccine. There were no clinical trial cases indicative of exposure during breastfeeding.
Patients with unstable health conditions and co-morbidities, e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD)	Not included in the clinical development program. COVID-19 Vaccine (inactivated, adjuvanted) Valneva 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 condition or treatment of the condition.
Population with relevant different ethnic origin	Please refer to Table 13 below for exposure information by ethnic origin from the pivotal clinical trial VLA2001-301.
Subpopulations carrying relevant genetic polymorphisms	No data available.
Paediatric population	Safety and effectiveness in individuals younger than 18 years of age has not yet been established.

Table 13: VLA2001-301 Exposure by ethnic origin

	VLA2001 **Age under 30** **(N=1.040)**	**VLA2001** **Age 30 and Above** **(N=1977)**	**AZD1222** **(N=995)**	**Overall** **(N=4.012)**
Ethnicity (only >1% shown in this table)				
White	955 (91,8)	1.844 (93,3)	927 (93,2)	3.726 (92,9)
Mixed	39 (3,8)	38 (1,9)	23 (2,3)	100 (2,5)
Asian	23 (2,2)	54 (2,7)	22 (2,2)	99 (2,5)

	VLA2001 Age under 30 (N=1.040)	VLA2001 Age 30 and Above (N=1977)	AZD1222 (N=995)	Overall (N=4.012)
Ethnicity (only >1% shown in this table)				
Black	12 (1,2)	15 (0,8)	6 (0,6)	33 (0,8)

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

COVID-19 Vaccine (inactivated, adjuvanted) Valneva was approved in Bahrain on 28 February 2022, with first doses administered from 14 April 2022. The vaccine was furthermore approved in the UK on 13 April 2022. No exposure data are available yet at data lock of this RMP.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Vaccines in general are not considered to present a risk for abuse. The potential for misuse of Covid-19 Vaccine (inactivated, adjuvanted) Valneva is negligible as it is being available at authorised vaccination sites via national vaccination programmes.

Part II: Module SVII - Identified and potential risks

Below factors were taken into consideration for the generation of the safety specifications and are not determined to be identified or potential risks.

The vaccine construct and the formulation.

VLA2001 is a highly purified, inactivated, whole virus SARS-CoV-2 vaccine grown on serum-free Vero cells. The vaccine production platform, developed by Valneva, uses an inactivated whole-virus approach, where live wild-type virus is grown in cell culture and then inactivated (i.e. making it unable to replicate and infect cells) via chemical treatment. Valneva uses β-propiolactone inactivation in order to preserve the native surface structure of the S-glycoprotein. Each VLA2001 Final Bulk Vaccine is filled into multidose 6R Type I vials with a filling volume of 5.95 mL, closed with 20MM injection stopper Flurotec® and secured with Aluminium caps - Flip-off caps. The VLA2001 Final Vaccine Lot is representing a multidose vial presentation of 10 doses.

The VLA2001 Final Vaccine Lot is a suspension and stored at +2-8°C. A retest date of 12 months is anticipated under these storage conditions. The volume for administration is 0.5 mL, resulting in the final dose of antigen and adjuvants as summarized in Table 14.

Table 14: Composition of VLA2001 (dose, 0.5mL)

Active substance	
SARS-CoV-2 inactivated	Antigen Units/dose[1] 33 AU
Excipients and buffer components	
Aluminium Hydroxide	0.5 mg Al^{3+}/dose
CpG 1018	1 mg/dose
Dulbecco's Phosphate Buffered Saline (DPBS) [3)]	
rHA	≤50 µg/dose

[1] This antigen unit/dose is considered equivalent to the high dose group in the clinical Phase 1/2 study VLA2001-201. Previously the value of 33AU/dose have been used in VLA2001-201 to describe the high dose. However, this was a calculated value based on 1st generation ELISA measured on viral concentrate, since no direct measurement was feasible on final product. For the clinical Phase 3 material, antigen units are measured on final product with an improved 2nd generation ELISA. Equivalence has been shown by retesting of VLA2001-201 material with the 2nd generation ELISA, showing comparable data (i.e. 35AU/0.5mL for DP high /Alum/CpG 1018).

VLA2001 is adjuvanted with the licensed adjuvant cytosine phospho-guanine (CpG) 1018 (produced by Dynavax, contained in HEPLISAV-B®) in combination with aluminium hydroxide.

VLA2001 has been developed using the same manufacturing platform as that used for the commercial vaccine IXIARO®, a purified, inactivated, whole virus, aluminium hydroxide-adjuvanted Japanese encephalitis vaccine that has been approved by regulatory authorities worldwide (including the Food and Drug Administration (FDA), European Medicines Agency (EMA) and Therapeutic Goods Administration (TGA). It is similar in composition to VLA2001, with a good safety profile consistent with findings from pre-licensure clinical studies. As of March 2021, 4.286.101 individuals worldwide have been vaccinated with IXIARO (IXIARO PSUR 012, May 2021).
VLA2001 has demonstrated excellent purity and overall, a biological, chemical and physical profile comparable to that of IXIARO®.

Adjuvants

CpG 1018:

Numerous toxicology studies and human clinical studies with CpG 1018 have established a robust safety profile for CpG 1018. CpG 1018 as an adjuvant is contained in a Hepatitis B vaccine (Heplisav-B) which was approved by the EMA in 2020 and by the FDA in 2017.

VLA2001 is immunogenic in mice and non-human primates. In mice, an increase in immunogenicity (dose sparing effect) was observed when CpG 1018 was used together with Aluminum Hydroxide. The presence of CpG 1018 skewed the immune response towards a pronounced Th1 response. A strong Th1 response is important to minimize potential risks for enhanced respiratory disease (ERD) or antibody disease enhancement (ADE) upon infection. One potential cause for ERD or ADE is a strong Th2 response. In addition, neutralizing antibodies could be measured at the highest immunization dose (3,0 AU) in the presence of

CpG 1018, the measured neutralizing titre was in a similar range as the neutralizing titre determined for the plasma pool derived from convalescent donors.

Aluminium hydroxide

After almost a century, aluminium salts maintain their dominance as adjuvants in human vaccines. This reflects the fact that aluminium adjuvants are extremely effective at enhancing antibody responses, are well tolerated, do not cause pyrexia and have the strongest safety record of any human adjuvants. (Petrovsky 2015)

SVII.1 Identification of safety concerns in the initial RMP submission

The safety concerns for COVID-19 vaccine are listed in Table 15 below.

Table 15: 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 patients
	Use in patients with autoimmune or inflammatory disorders
	Use in frail patients with unstable health conditions and co-morbidities, e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD)
	Long-term safety data
	Interaction with other vaccines

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reactogenicity – interim analysis of clinical trial VLA2001-301

Solicited AEs were collected in the eDiary by the study participants for seven consecutive days after each vaccination, starting on the day of vaccination. Per definition these were considered related to the study vaccine.
Solicited injection site reactions include injection site pain, itching, tenderness, redness and swelling/induration.
Solicited systemic reactions include fever/body temperature, fatigue, headache, nausea/vomiting, muscle pain.

Solicited Injection Site Reactions

The most common injection site reactions after either vaccination were tenderness and injection site pain.
In participants aged 18-29 years receiving VLA2001, overall rates of solicited injection site reactions were 80,9% vs. 73,2% compared to participants 30 years and above receiving VLA2001. Rates of participants aged 18-29 years with injection site tenderness were 76,4% vs. 66,8% and with injection site pain 52,9% vs. 45,5% compared to participants 30 years and above receiving VLA2001.
The duration of solicited injection site reactions was similar between treatment groups (generally 1-2 days).
Overall, the rates of solicited injection site reactions after first and second vaccination with VLA2001 were comparable.

Systemic Adverse Reactions

The most common systemic reactions after either vaccination were fatigue, headache and muscle pain.

In participants aged 18-29 years receiving VLA2001, overall rates of solicited systemic reactions were 76,9% vs. 70.2%. Rates of participants aged 18-29 years with fatigue were 57,3% vs. 51,2%, with muscle pain 44,0% vs. 37,0% and with headache 40,6% vs. 39,8% compared to participants 30 years and above receiving VLA2001.

Overall, the rates of solicited systemic reactions after first and second vaccination with VLA2001 were comparable.

Important potential risks considered for Valneva's Japanese encephalitis vaccine IXIARO

Valneva's Japanese encephalitis vaccine IXIARO is manufactured using the same Vero cells platform as COVID-19 Vaccine (inactivated, adjuvanted) Valneva.

No important risks have been defined for IXIARO. The current version of the RMP for IXIARO, is version 7.0 dated 28 January 2019.

The following neurological events are considered important potential risks for IXIARO:

- Convulsion
- Acute disseminated encephalomyelitis
- Acute encephalitis
- Acute myelitis
- Central nervous system inflammation
- Guillain-Barré syndrome
- Meningitis

At the time of licensure of IXIARO, potential risks defined were based on known class effects. The most common adverse events associated with a JE vaccine were derived from the known safety profile of JE-VAX. This formalin-inactivated, mouse brain derived vaccine was the only JE vaccine in use outside Asia for travelers and at that time was licensed in the US, Canada, Israel and Australia for the vaccination of travelers and military personnel.

JE-VAX safety concerns regarding a single case of acute disseminated encephalomyelitis following JE vaccination led to the suspension of the recommendation of routine JE vaccination of the general population in Japan in May 2005 (Global Advisory Committee on Vaccine Safety, 2005). The neural tissue substrate of JE-VAX had raised concerns about the possibility of neurological adverse events following immunization, postulated to be due to neural tissue remnants. Reports had been received from South Korea and Japan of acute encephalomyelitis following JE vaccination. Surveillance in Japan suggested that the rate of severe neurological AEs following JE vaccination was 1.8 cases per 1 million doses of vaccine (Tsai 2000) .

Since IXIARO is manufactured in a mammalian cell culture substrate in lieu of mouse brain tissue these severe neurological adverse effects were not expected following vaccination. Neurologic adverse reactions were not seen in clinical studies with IXIARO. Serious treatment-related neurological events were not reported in any treatment group during the studies with IXIARO. The safety profile of IXIARO has remained unchanged and positive since licensure, as discussed in the PSURs.

It is suggested to add the symptoms defined as potential risks in IXIARO's RMP to the list of AESIs for COVID-19 Vaccine (inactivated, adjuvanted) Valneva. Of the symptoms listed above, Guillain-Barré syndrome and encephalitis including ADEM are already considered AESIs for

COVID-19 vaccines. It is suggested to add the symptoms of convulsion, central nervous system inflammation, acute myelitis, and meningitis to this list, see suggested AESIs below.

Adverse Events of Special Interest (AESIs)

The following events are considered AESIs for COVID-19 vaccines according to regulatory guidance, but have not been confirmed by clinical evidence to date:

- COVID disease enhancement
- Sudden death
- Guillain-Barré syndrome, and other peripheral and polyneuropathies
- Multiple sclerosis, transverse myelitis, acute myelitis and other demyelinating disorders
- Optic neuritis
- Encephalomyelitis / encephalitis (incl. ADEM)
- Myasthenia gravis
- Bell's palsy
- Seizure disorders (incl. febrile)
- Convulsion Myocardial infarction
- Myopericarditis / pericarditis
- Deep vein thrombosis
- Pulmonary embolism
- Disseminated intravascular coagulation
- Immune thrombocytopenia
- Stroke and other cerebrovascular events
- Venous thromboembolism
- Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia
- Rheumatoid arthritis, polyarthritis
- Autoimmune thyroiditis
- Chronic Fatigue Syndrome (ME/PVFS
- Fibromyalgia
- Post Orthostatic Tachycardia Syndrome
- Narcolepsy
- Paediatric inflammatory multisystem syndrome (or otherwise a recent definition condition associated with COVID in children and adolescents)
- Kawasaki syndrome
- Central nervous system inflammation
- Meningitis
- Multisystem inflammatory syndrome
- Appendicitis
- Pregnant women – pre-term labour, stillbirth, maternal or neonatal death, pre-eclampsia or eclampsia, haemorrhage, foetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low weight birth, neonatal renal failure, chorioamnionitis, major structural congenital malformations

Convulsion, central nervous system inflammation, acute myelitis and meningitis have been added to this list as AESIs specific to IXIARO, which is manufactured using the same Vero cells platform as COVID-19 Vaccine (inactivated, adjuvanted) Valneva.

No AESIs reported in clinical trial VLA2001-301 were assessed as related to vaccination with COVID-19 Vaccine (inactivated, adjuvanted) Valneva by the investigators.

CpG1018

The risk of acute myocardial infarction as well as well as the risk of occurrence of potentially immune-mediated disorders (including inflammatory disorders) and exacerbation of potentially immune-mediated disorders (including inflammatory disorders) have been discussed in context with the adjuvant CpG1018 for the vaccine Heplisav-B, a vaccine which contains CpG 1018 and was licensed in the EU in 2020 and in the US in 2017.

Hypothetic risk of acute myocardial infarction:

CpG 1018 acts by stimulating a single, well-defined cellular receptor, toll-like receptor 9 (TLR9). TLR9 is a transmembrane receptor present in the endosomal membrane, with the DNA-binding domain exposed to the lumen of the endosomes. The distribution of cell types that express TLR9 is more restricted than for most other TLRs, especially in humans and non-human primates. In humans, TLR9 expression by antigen-presenting cells is limited to plasmacytoid dendritic cells (pCD) and memory B cells. In mice, TLR9 stimulation of dendritic cells, but not B cells is essential for the adjuvant activity of CpG 1018, and this is likely true in humans as well.

While there are data indicating that activation of TLR9 can have proinflammatory effects with putative impact on the course of myocardial infarction and induce development of atherosclerotic lesions in vitro and in mice, the differences in cellular distribution of TLR9 between rodents and humans together with the extremely large margins (>50-100) to the concentrations and doses with proinflammatory and proatherogenic effects did not support a clinically relevant correlation. Some published evidence in fact suggested that CpG adjuvants could ameliorate myocardial reperfusion damage and provide with cardioprotective effects in mice model (Hilbert, Markowski et al. 2018);Heplisav-B EPAR 2020).

There is no plausible molecular-biological mechanism triggered by CpG 1018 adjuvanted vaccine to cause acute myocardial infarction. The finding of excess cardiovascular risk in the Heplisav-B clinical programme was unexpected and largely confined to one study. The available outcomes of the post-marketing surveillance study HBV-025 provided compelling and reassuring evidence that there is no increased cardiovascular risk with the CpG 1018 adjuvant.

Nevertheless, while the risk of myocardial infarction remains hypothetic, myocardial infarction is considered an AESI for COVID-19 vaccines and will be monitored during administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva post-marketing.

Hypothetic risk of the occurrence of potentially immune-mediated disorders and exacerbation of potentially immune-mediated disorders:

It has been discussed whether the TLR9 activation and subsequent immunostimulatory activity of CpG 1018 could increase the risk to develop autoimmunity in particular systemic autoimmune disease (e.g. systemic lupus erythematosus) which are in part caused by generation of anti-dsDNA antibodies. This concern was based on evidence from studies in animal models for autoimmunity where TLR9 stimulation was demonstrated to enhance development of / exacerbate autoimmune disease. There are also reports that demonstrate that TLR9 may have a protective role against autoimmunity so there is clearly a complex relationship between TLR9 and autoimmunity.
There is no plausible molecular-biological mechanism triggered by CpG 1018 adjuvanted vaccine in relation to immune-mediated adverse events. There was no signal detected across the Heplisav-B clinical program for immune-mediated AEs.

Nevertheless, while immune-mediated disorders remain a hypothetic risk, the following AESIs have been considered for CpG 1018 and will be monitored during administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva post-marketing:

AESIs considered for CpG 1018:

Gastrointestinal disorders:

- Crohn's disease
- Ulcerative proctitis

Musculosceletal disorders:

- Psoriatic arthropathy
- Spondyloarthritis, including reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis

Neuroinflammatory disorders:

- Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy)
- Tolosa Hunt syndrome
- Polyneuropathies associated with monoclonal gammopathy
- Narcolepsy
- Optic neuritis
- Transverse Myelitis

Skin disorders:

- Erythema nodosum
- Lichen planus
- Rosacea
- Sweet's syndrome

Vasculitides:

- 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), necrotising vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others:

- Idiopathic pulmonary fibrosis
- Raynaud's phenomenon
- Sarcoidosis
- Steven-Johnson syndrome
- Uveitis

Aspects of the formulation

VLA2001 is a highly purified, whole virus, SARS-CoV-2 vaccine produced on serum-free Vero cells and inactivated with β-propiolactone. The viral strain is derived from a Chinese tourist from Hubei diagnosed in a hospital in Rome (Stefanelli et al, 2020). VLA2001 is adjuvanted with the licensed adjuvant cytosine phospho-guanine (CpG) 1018 (produced by Dynavax, contained in HEPLISAV-B®) in combination with Aluminium Hydroxide.

Adjuvants

Aluminium Hydroxide

Whole virus inactivated SARS-CoV-2 vaccine candidates adjuvanted with alum have shown acceptable safety profile in phase 1 and 2 studies published so far (Table 16).

Table 16: Overview of published data for whole virus inactivated alum adjuvanted SARS-CoV-2 vaccine candidates.

	Sinopharm/Wuhan Institute	Sinopharm/Beijing Institute	CoronaVac	Institute of Medical Biology	VLA2001
Cell line	Vero cells	Vero cells	Vero cells	Vero cells	Vero cells
Inactivation	β-propiolactone	β-propiolactone	β-propiolactone	Formaldehyde and β-propiolactone	β-propiolactone
Adjuvant	Alum	Alum	Alum	Alum	Aluminium Hydroxide **+CpG1018**
Buffer	PBS without preservatives	PBS and sodium chloride	PBS and sodium chloride	Buffered saline	PBS and sodium chloride
Injection	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Publications	Xia et al. JAMA (Xia, Duan et al. 2020)	Xia et al. Lancet(Xia, Zhang et al. 2021)	Zhang et al. MedRxiv(Zhang, Guo et al. 2021)	Pu et al. MedRxiv (Pu, Yu et al. 2020)	First in-human study initiated in Dec. 2020

Summary of the published safety profile revealed that the most common adverse reaction was injection site pain, the most common systematic adverse event was fever. No severe adverse reactions related to the vaccine were observed, no serious adverse events were reported in any of the published studies of alum-only adjuvanted inactivated vaccine candidates against SARS-CoV-2 so far.

CpG 1018

COVID-19 Vaccine (inactivated, adjuvanted) Valneva also contains CpG 1018 as additional adjuvant to Aluminium Hydroxide. CpG 1018 has an established robust safety profile as it is contained in a Hepatitis B vaccine which is approved by FDA and EMA.

HEPLISAV-B is a hepatitis B virus vaccine comprised of recombinant, yeast cell-derived hepatitis B surface antigen (HBsAg) and CpG 1018. HEPLISAV-B is a sterile liquid dosage form that is administered as an IM injection. The CpG 1018 in HEPLISAV-B is the same synthetic 22-mer phosphonothioate oligodeoxynucleotide (PS ODN) containing an immunostimulatory sequence that is an agonist for TLR9 as in VLA2001. However, HEPLISAV-B contains 3 mg CpG 1018 while VLA2001 contains 1 mg CpG 1018/dose.

Cumulatively, 10,049 subjects (10,038 subjects 18 years of age and older and 11 subjects below 18 years old) and 386 adult subjects with chronic kidney disease 18 years of age and older have received HEPLISAV-B in clinical trials.

HEPLISAV-B was well tolerated in clinical trials in healthy adults [Dynavax Package Insert 2020]. The reactogenicity profile of HEPLISAV-B was like Engerix-B (an alum adjuvanted HBV vaccine) in time course and severity. Compared with Engerix-B, HEPLISAV-B caused more local reactions and fewer systemic reactions. Common adverse reactions from HEPLISAV-B included injection site pain, erythema, and swelling, headache, malaise, myalgia, and fatigue. SAEs, autoimmune adverse events, and deaths were infrequent in the HEPLISAV-B clinical program and similar in frequency between HEPLISAV-B and Engerix-B. No deaths have been considered by the investigator to be related to HEPLISAV-B. Interim analyses of an ongoing post-marketing study of over 30,000 HEPLISAV-B recipients and more than 35,000 Engerix-B recipients has raised no safety concerns.

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Not all potential or identified risks for the vaccine are considered to meet the level of importance or severity necessitating inclusion in the list of safety concerns in the RMP, e.g. risks with minimal and temporary clinical impact on patients in relation to the severity of the disease prevented.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk

No important risks have been identified for COVID-19 Vaccine (inactivated, adjuvanted) Valneva.

Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Risk-benefit impact

Enhanced respiratory disease has been reported in animal models for SARS-CoV-1 vaccines. Although several NHP studies for SARS-CoV-2 vaccines including inactivated vaccines showed no evidence of enhanced disease, disease enhancement remains a theoretical safety concern. Therefore, COVID-19 manifestations and complications associated with COVID-19 (such as - but not limited to - pneumonia, neurological or vascular complications, severe pneumonia, severe neurological or vascular events, acute respiratory distress syndrome, renal complications, sepsis, septic shock, death) have been closely monitored as AESIs in the pivotal clinical trial.

Missing Information

Use in Pregnancy and while breast feeding

Risk-benefit impact

The safety profile of the vaccine is not known in pregnant or breastfeeding women due to their exclusion from the pivotal clinical study. Accordingly, maternal COVID-19 impact to either embryo or foetus is also not known. It is important to obtain long term follow-up on women who were pregnant at or around the time of vaccination so that any potential negative consequences to the pregnancy or to the embryo or foetus can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy or on the embryo or foetus.

Use in immunocompromised patients

Risk-benefit impact

The safety profile of the vaccine is not known in immunocompromised individuals due to their exclusion from the pivotal clinical study. The efficacy of the vaccine may be lower in immunocompromised individuals, thus decreasing their protection from COVID-19.

Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Risk-benefit impact

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.

Use in patients with autoimmune or inflammatory disorders

Risk-benefit impact

There is no information on the safety of the vaccine in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.

Interaction with other vaccines

Risk-benefit impact

COVID-19 Vaccine (inactivated, adjuvanted) Valneva will be used in individuals who also may receive other vaccines. Studies to determine if co-administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva with other vaccines may affect the efficacy or safety of either vaccine have not been performed.

Long term safety data

Risk-benefit impact

The long-term safety of COVID-19 Vaccine (inactivated, adjuvanted) Valneva is unknown at present, however further safety data are being collected in ongoing Study VLA2001-301 for up to 1 year following administration of dose 2 of COVID-19 Vaccine (inactivated, adjuvanted) Valneva and in parallel from post-authorisation / post-marketing cohort study which will be evaluating the effectiveness of the VLA2001 inactivated vaccine to prevent serious COVID19 infection in conditions of usual care utilizing primary data collected prospectively through the COVIDRIVE platform up to 2 years post vaccination.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII 3.1 Important Identified Risks

No important risks have been identified.

SVII.3.1.1 Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Table 17: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Potential mechanism	This potential risk is theoretical because it has not been described in association with the COVID-19 Vaccine (inactivated, adjuvanted) Valneva nor has it been reported from any other late phase clinical trial of other human vaccines. Animal models of SARS-CoV-2 infection have not shown evidence of VAED after immunization, whereas cellular immunopathology has been demonstrated after viral challenge in some animal models administered SARS-CoV-1 (murine, ferret and non-human primate models) or MERS-CoV (mice model) vaccines. (Lambert, Ambrosino et al. 2020) (Haynes, Corey et al. 2020) This potential risk has been included based on animal data with these related betacoronaviruses. Historically, disease enhancement in vaccinated children following infection with natural virus has been observed with an inactivated respiratory syncytial virus vaccine.(Openshaw, Culley et al. 2001) Potential mechanisms of enhanced disease may include both T cell-mediated [an immunopathological response favouring T helper cell type 2 (TH2) over T helper cell type 1 (TH1)] and antibody-mediated immune responses (antibody responses with insufficient neutralizing activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells). (Graham 2020)
Evidence source and strength of evidence	No evidence of harm has been identified in nonclinical studies with COVID-19 Vaccine (inactivated, adjuvanted) Valneva nor from the phase 3 clinical trial VLA2001-301 until data lock point for this version of the Risk Management Plan.
Characterisation of the risk	If VAED/VAERD were to occur in vaccinated individuals, it may manifest as a modified and/or more severe clinical presentation of SARS-CoV-2 viral infection upon subsequent natural infection. This may result in individuals assumed to be at lower risk for severe COVID-19 having more severe disease, for individuals at known risk for severe COVID-19 (e.g. older or immunocompromised) having higher rates of fatal outcomes, or for observation of an unfavourable imbalance in severe COVID-19 cases in vaccinated individuals when compared to those not vaccinated. It is challenging if not impossible to assess for VAED/VAERD on an individual case basis, given the lack of specific clinical or laboratory markers at this time, rather surveillance for this theoretical risk needs to be at population level.
Risk factors and risk groups	It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titres or in those demonstrating waning immunity. (Graham 2020; Munoz, Cramer et al. 2021)

Preventability	An effective vaccine against COVID-19 that produces high neutralizing titres and a TH1 predominant CD4+ T cell response and strong CD8+ T cell response, is expected to mitigate the risk of VAED/VAERD. (Graham 2020; Lambert, Ambrosino et al. 2020)
Impact on the risk-benefit of the biologic product	Vaccine-associated enhanced disease (including VAERD) may present as severe disease or modified/unusual clinical manifestations of a known disease presentation and may involve one or multiple organ systems. Subjects with VAED/VAERD may experience rapid clinical deterioration and will likely require non-invasive or invasive mechanical ventilation, and patients diagnosed with acute respiratory distress syndrome have poorer prognosis and potentially higher mortality rate.
Public health impact	As this safety concern is currently theoretical in relation to administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva, there is no public health impact noted at this time.

SVII.3.2 Presentation of Missing Information

Table 18: Important Missing Information

Missing Information	Evidence source	Population in need of further characterisation
Use in pregnancy and while breast feeding	The safety profile of COVID-19 Vaccine (inactivated, adjuvanted) Valneva is not known in pregnant or breastfeeding women due to their exclusion from the pivotal clinical study VLA2001-301. There may be pregnant women who choose to be vaccinated despite the lack of safety data. It will be important to follow up these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo / foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy is not yet fully understood, and the pregnant woman's baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19. These factors and the extent to which the pregnant woman may be at risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine.	The lack of data will be communicated in the product labelling. A post-authorisation pregnancy registry is planned.
Use in immunocompromised patients	COVID-19 Vaccine (inactivated, adjuvanted) Valneva has not been studied in individuals with overt immunocompromised conditions. Therefore, further safety data will be sought in this population.	Safety data will be collected in individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressants in the post-authorisation safety study.

Missing Information	Evidence source	Population in need of further characterisation
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	COVID-19 Vaccine (inactivated, adjuvanted) Valneva 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 condition or treatment of the condition. Therefore, further safety data will be sought in this population.	Safety data will be collected in individuals who are frail due to age or debilitating disease in the post-authorisation safety study and through routine pharmacovigilance.
Use in patients with autoimmune or inflammatory disorders	There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders.	Safety data will be collected in individuals with autoimmune or chronic inflammatory diseases, including those who may be on immunosuppressants in the post-authorisation safety study.
Interaction with other vaccines	There are limited data on the interaction of COVID-19 Vaccine (inactivated, adjuvanted) Valneva with other vaccines at this time.	Data on concomitant vaccination will be collected in the post-authorisation safety study.
Long term safety data	At this time, 6-month post dose 2 safety data are available for subjects who received COVID-19 vaccine in study VLA2001-201, while 1 month safety data are available for subjects who received COVID-19 vaccine in study VLA2001-301. The study is ongoing.	At the time of vaccine availability, the long-term safety of COVID-19 Vaccine (inactivated, adjuvanted) Valneva is not fully known, however further safety data are being collected in ongoing Study VLA2001-301 for up to 1 year following administration of dose 2 of COVID-19 Vaccine (inactivated, adjuvanted) Valneva and from post-authorisation safety study.

Part II: Module SVIII - Summary of the safety concerns

Table 19: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None 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 patients
	Use in frail patients with unstable health conditions and co-morbidities, e.g. diabetes, chronic neurological disease, cardiovascular disorders, chronic obstructive pulmonary disease (COPD)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance for the lifecycle of a product is a critical component to the detection, assessment, understanding and mitigation of individual case safety reports (ICSRs). Objectives of routine pharmacovigilance include having processes in place to ensure the ongoing and timely collection, processing, follow-up, and analysis of ICSRs and aggregate data globally, following global safety Standard Operating Procedures and regulatory guidance. Valneva monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations. Valneva gathers data for signal detection and evaluation commensurate with product characteristics.

III.1.1 ICSR Reporting

To address the unique challenges associated with a mass vaccination campaign work is ongoing to ensure that the necessary pharmacovigilance infrastructure is in place to address the expected rapid increase in post-marketing individual case safety reports (ICSRs) for processing and regulatory reporting. This will in turn facilitate the rapid provision of high quality data to support the detection and evaluation of potential safety issues. Some of the measures put in place include scaling of infrastructure and systems, recruitment, and training of additional resources, and implementation of specific processes and procedures.

All ICSRs received for COVID-19 Vaccine (inactivated, adjuvanted) Valneva will be processed and reported in accordance with the requirements specified in the EMA guidance document entitled “Detailed Guidance on ICSRs in the context of COVID-19 - Validity and coding of ICSRs (EMA/174312/2020)” (EMA 2020c).

Spontaneous cases of confirmed vaccination failure will be reported within the required 15 days of receipt.

For all ICSRs received for COVID-19 Vaccine (inactivated, adjuvanted) Valneva, in addition to data regarding the subject demographics and adverse reaction (including outcome), the following data will also be proactively sought, if not available with the initial report:

- Individual’s medical history (inclusive of autoimmune disorders) and concomitant medications.
- Vaccination history.
- Vaccination schedule, including batch number.

Furthermore, in case of a suspected quality defect, detailed specific information regarding batch release specifications, expiry date(s), and distribution and administration-related data (eg, storage and handling conditions for vaccines in the healthcare institutions where vaccination took place) will also be requested.

The following ICSR follow-up approach will apply:

Table 20: ICSR follow-up approach

	Priority Group 1	**Priority Group 2**	**Priority Group 3**
Type of ICSR	• Serious unexpected ICSRs • Serious expected ICSRs • Vaccination failure • Invalid cases • Non-serious cases containing at least one Adverse Event of Special Interest • ICSRs on exposure during pregnancy or lactation	• Non-serious unexpected ICSRs • Occupational / Accidental exposure • Overdose	• Non-serious expected ICSRs • Special Situations without associated ADRs o Medication errors o Misuse / Abuse o Off-label use o Unexpected therapeutic benefit o Suspected transmission of an infectious agent via the product o Counterfeit product
Timing of follow-up attempts	Initial: target within 5 business days of ICSR receipt date Subsequent: approx. 5 business days post initial attempt	Initial: target within 5 business days of ICSR receipt date a Subsequent: approx. 5 business days post initial attempt	Target within 1-2 weeks of ICSR receipt date
Required minimum number of attempts	3	2	0-1
Follow-up is required for	Missing batch number Missing event outcome(s), including information on recovery / sequelae or foetal outcome for pregnancy exposure cases Missing information considered sufficient to characterise the case. Missing medical confirmation. Missing minimum criteria for valid case. Missing full description of the event (including specific body site if applicable.	Missing batch number	Missing batch number
Method of follow-up attempts	1. Email or fax 2. Letter 3. Telephone	1. Email or fax 2. Letter 3. Telephone	1. Email or fax 2. Letter 3. Telephone

For pregnancy exposure cases, an additional follow-up attempt should be performed after the estimated date of delivery or 10 months after initial receipt of the report.

For solicited ICSRs, follow-up attempts will be performed where possible depending on the programme, data collection method and frequency of analysis.

Routine pharmacovigilance activities beyond the receipt and review of individual ICSRs

Signal detection

Routine signal detection activities for the COVID-19 Vaccine (inactivated, adjuvanted) Valneva will be performed on a weekly basis.

Sources include data from the MAH's global safety database, which will be screened on a weekly basis. Data will be retrieved from regulatory authorities' databases, e.g., EudraVigilance and further authorities' databases as applicable on a weekly basis. The frequency of these searches will be adapted to the actual case volumes. Sources further include aggregated data from active surveillance systems or studies.

Sources of data will include all scientific information concerning the use of COVID-19 Vaccine (inactivated, adjuvanted) Valneva and the outcome of the use, i.e. quality, non-clinical and clinical data, in accordance with GVP Module IX Signal Management, section IX.B.1. Sources of data and information. Batch-specific analysis in accordance with the principles in section P.I.B.5 of the EU GVP module on "Vaccines for Prophylaxis against Infectious Diseases".

In addition, global literature will be reviewed on a weekly basis for individual case reports and broader signal detection purposes via PubMed. Regulatory authority safety alerts will be monitored.

Signal detection activities will include routine as well as specific review of ICSRs consistent with the AESI lists provided in PART II. SVII.1.1 – Risks not considered important for inclusion in the list of safety concerns in the RMP.

Where possible, coverage data will be used, e.g., ECDC for EEA and other databases, as applicable. In addition – considering that coverage data may not be available for all countries / regions worldwide, an additional analysis by doses distributed will be performed for a global comparison of safety data.

Observed vs. expected analysis will be conducted for reports with fatal outcomes, events provided in the AESI list, where suitable expected rates published in the scientific literature (e.g., ACCESS study) or other appropriate sources are available.

Safety signal evaluation will cover the collection, analysis and assessment of information to evaluate potential causal associations between and event and the vaccine and will include subsequent qualitative or quantitative characterisation of the relevant risk to determine appropriate continued pharmacovigilance and risk mitigation actions.

Cluster analysis will be performed on an ad hoc basis where justified, based on results of scheduled signal detection methods, using qualitative or quantitative methods, as appropriate. Justifications and methods will be documented.

Summary table of data sources, signal detection activities and frequencies

Table 21: Summary table of data sources, signal detection activities and frequencies

Data source	Frequency of review
Valneva's global post-authorsation safety database, including	Weekly

all spontaneous and solicited ICSRs, including reports downloaded from EVDAS, MHRA, and other regulatory databases as applicable	
Aggregate review of the Clinical Trial Databases	As per study milestones / interim or final analyses
Literature (PubMed)	Weekly
EudraVigilance Data Analysis System (EVDAS) Electronic Monitoring 8eRMR)	Bi-weekly
Product quality complaint data	Monthly
PRAC recommendations on signals	Monthly
Batch specific analysis	Weekly

Monthly Summary Safety Reports (MSSRs)

In addition to routine 6-monthly PSUR compilation, monthly summary safety reports (MSSRs) will be compiled to support timely and continuous benefit-risk evaluations. Topics covered by the monthly summary safety reports will include:

- Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately)
- Interval and cumulative number of reports, overall and by age groups and in special populations (e.g., pregnant women)
- Interval and cumulative number of reports per HLT and SOC
- Exposure data, e.g., data on doses administered as presented by ECDC for EEA, and others as applicable.
- In addition – considering that coverage data may not be available for all countries / regions worldwide, an additional analysis by doses distributed will be performed for a global comparison of safety data.
- Changes to reference safety information in the interval, and current CCDS
- Ongoing and closed signals in the interval
- AESI reports – numbers and relevant cases
- ICSRs with fatal outcome – numbers and relevant cases
- Batch-specific analysis in accordance with the principles in section P.I.B.5 of the EU GVP module on “Vaccines for Prophylaxis against Infectious Diseases”
- Monthly reports and PSURs will include results of the observed versus expected analysis (ACCESS database) for AESIs as appropriate and will present the results and details of the statistical approach.

Periodic Safety Update Reports (PSURs)

Six-monthly PSURs will be submitted for the first 2 years of licensure, and thereafter annually for 2 years.

Specific adverse reaction follow-up questionnaires

Follow-up questionnaires will be used to collect targeted information as follows:

- Vaccine Associated Enhanced Disease Questionnaire
- Pregnancy Questionnaire

For details, please see Annex 4 “Specific adverse drug reaction follow-up forms”.

Potential for medication errors

Large scale public health approaches for mass vaccination may represent changes to standard vaccine treatment process, thereby potentially introducing the risk of medication errors related to:

- reconstitution and administration
- vaccination schedule
- storage conditions
- errors associated with a multi-dose vial, and
- confusion with other COVID vaccines.

These potential medication errors are mitigated through the information in the SmPC and available educational materials for healthcare providers

- SmPC (section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of the COVID-19 mRNA vaccine
- Medical information hotlines will be available for healthcare providers to obtain information on use of the vaccine.

Traceability

The SmPC, includes instructions for healthcare professionals:

"In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded."

Self-adhesive labels will include expiry date, batch number product name and a 2D barcode as per member state requirements.

Traceability will be available for every shipping container of COVID-19 Vaccine (inactivated, adjuvanted) Valneva, which are outfitted with a device that provides real-time monitoring of geographic location and records temperature 24 hours per day, 7 days a week while in transit. Alarm /escalation systems are in place for any temperature excursions.

Vaccination cards will be available as per local regulatory requirements. Vaccination cards will contain the following elements:

- Placeholder space for the vaccinee's name
- Placeholder space for the name of the vaccine (brand name) and manufacturer of the vaccine
- Placeholder for the batch number of the vaccine
- Placeholder space for the date the vaccine was administered

Cold-Chain Handling and Storage

Store and transport refrigerated (2°C - 8°C).
Do not freeze.

III.2 Additional pharmacovigilance activities

Post-marketing Safety Studies

Post-Authorization Safety Study:

Study title:

A non-interventional post-authorisation safety study (PASS) of safety concerns (potential risks, missing information) as well as adverse events of special interest among recipients of the COVID-19 Vaccine (inactivated, adjuvanted) Valneva in Europe: A retrospective study using health care databases.

Study countries:
Study will be conducted using linked health care databases in EU countries where COVID-19 Vaccine (inactivated, adjuvanted) Valneva will be launched. In line with the launch plan, the health care databases of three countries are considered (France, Italy, Germany).

Rationale and study objectives:

Primary objective:
To estimate the incidence of adverse events of special interest (AESIs), that are medically attended - including the potential risk of vaccine associated enhanced disease (VAED) and vaccine associated respiratory disease (VAERD)- following the administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the real-world immunisation setting.

Secondary objectives:
- For each AESI, to compare the observed incidence rate with the observed rate an external comparator population of unvaccinated or vaccinated with other COVID-19 vaccines depending on the population vaccination status.
- To quantify the association between COVID-19 Vaccine (inactivated, adjuvanted) Valneva and each AESI for which a risk window after vaccination can be defined, using estimates of relative risk.
- To determine the proportion of vaccinees who fail to receive both vaccine doses.
- To describe the use of COVID-19 Vaccine (inactivated, adjuvanted) Valneva and the risk of AESIs, including the potential risk of VAED/VAERD, use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders, autoimmune or autoinflammatory disorders), as well as interaction with other vaccines.
- To characterize the long-term safety of COVID-19 Vaccine (inactivated, adjuvanted) Valneva.

Study design:
A retrospective cohort study of adults (age ≥ 18 years) vaccinated with COVID-19 Vaccine (inactivated, adjuvanted) Valneva will be conducted. Study population will be identified the health care databases of EU countries where the vaccine will be launched and with available health care databases (France, Italy, Germany).

Methods and study conduct will be based on the VAC4EU and ACCESS resources. An external (parallel) reference population of unvaccinated individuals or of individuals vaccinated with the other available COVID-19 vaccines will be used to compare incidence rates of AESIs, including VAED and VAERD. In addition, where risk windows can be defined and where assumptions are met, a self-controlled case series analysis will be conducted.

Study population:
Adult (aged ≥18 years) who receive at least one dose of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the real-world immunisation setting.

Study variables:

1. Patient characteristics: Socio-demographics, medical history (incl. past SARS-CoV-2 infections and history of hospitalization for COVID-19), comorbidities (at index date and during follow-up), incl. COPD, diabetes, chronic neurological disease, cardiovascular disorders, autoimmune or autoinflammatory disorders.
2. Exposure to COVID-19 Vaccine (inactivated, adjuvanted) Valneva and other vaccines during follow-up: Number of doses and interval between doses.
3. Adverse events of special interest that are medically attended: All AESIs listed in the RMP for COVID-19 Vaccine (inactivated, adjuvanted) Valneva, including VAED and VAERD, as well as those of the MHRA guidance on Pharmacovigilance and Risk Management Plan Requirements for COVID-19 vaccines in the UK (see appendix A). In addition, death will also be sought. One exception is paediatric inflammatory multisystem syndrome given that the PASS study will be restricted to the adult population.

Milestones:

Study is expected to end 3 years after the start of vaccination campaign with COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the EU.

Plans for disseminating and communicating study results:

Study protocol will be registered in the EU PAS register.

Pregnancy Registry

Study name and title:
Pregnancy Registry of Women Exposed to COVID-19 Vaccine (inactivated, adjuvanted) Valneva immediately before or during Pregnancy as part of the C-VIPER Registry Consortium (Pregistry-sponsored)

Rationale and study objectives:
There are very limited data on safety and health status in pregnant women. The study objective is to estimate the risk of the most common obstetric outcomes, i.e. pregnancy losses, placentation disorders, gestational diabetes, premature delivery, and COVID-19, neonatal outcomes, i.e. congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission, and COVID-19, among pregnant women exposed to COVID-19 Vaccine (inactivated, adjuvanted) Valneva from 30 days prior to the first day of the LMP to end of pregnancy and their offspring relative to a matched unexposed reference group. The study will also cover the corresponding AESIs listed in section SVII.1.1. “Risks not considered important for inclusion in the list of safety concerns in the RMP” -, pre-term labour, stillbirth, maternal or neonatal death, pre-eclampsia or eclampsia, haemorrhage, fetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low weight birth, neonatal renal failure, chorioamnionitis, major structural congenital malformations.

Study design:
This study will utilize data from a prospective registry, C-VIPER, an international, prospective, observational cohort study of pregnant women vaccinated from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy to prevent COVID-19. It includes follow-up of liveborn infants to one year of age.
Women will be followed through the end of their pregnancy, i.e., abortion, stillbirth, or live birth, and until the child reaches 12 months of age.

Study population:
Women aged ≥18 years old who receive COVID-19 Vaccine (inactivated, adjuvanted) Valneva at any tine while they are pregnant or who become pregnant within a predefined period, e.g., 30 days pre-LMP, after being vaccinated will be eligible for inclusion in the treated cohort. A minimum of 500 women exposed to COVID-19 Vaccine (inactivated, adjuvanted) Valneva, including 200 exposed during the first trimester, will be recruited. Unexposed women from IRCEP will be matched to COVID-19 Vaccine (inactivated, adjuvanted) Valneva exposed women from C-VIPER by country and gestational age at enrolment.

Post-marketing observational study using existing secondary health data sources through the COVIDRIVE platform

Study name and title:
A post-authorisation study to evaluate the effectiveness of the COVID-19 Vaccine (inactivated, adjuvanted) Valneva to prevent serious COVID19 infection in conditions of usual care utilizing primary data collected prospectively through the COVIDRIVE platform up to 2 years post-vaccination.

Primary study objective:
To estimate effectiveness against hospitalization due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with COVID-19 Vaccine (inactivated, adjuvanted) Valneva.

The secondary and exploratory objectives of COVIDRIVE’s master protocol are stratifications to the first objective aiming to estimate COVID-19 Vaccine (inactivated, adjuvanted) Valneva’s

effectiveness against COVID-19 hospitalization within populations of special interest, by SARS-CoV-2 genetic variants, by time since last dose and by time between doses.
The Applicant is applying for an indication for COVID-19 Vaccine (inactivated, adjuvanted) Valneva to be used for primary series immunization in adults.

Primary endpoint:

1. To confirm CVE of COVID-19 Vaccine (inactivated, adjuvanted) Valneva against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients.

Exploratory endpoints:

2. To confirm CVE of COVID-19 Vaccine (inactivated, adjuvanted) Valneva against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients,
   i. by SARS-CoV-2 genetic variants.
   ii. within populations of special interest (e.g., specific age groups, specific immunocompromised or chronic conditions, pregnant women).
   iii. by time since last COVID-19 vaccine dose.
   iv. by time between last two COVID-19 vaccine doses.
   v. by number of VLA2001 doses (1,2,3…) doses given
   vi. by number and type(s) of the COVID-19 vaccine doses given prior to the last
   vii. by number and type(s) of the COVID-19 vaccine doses given prior to the last
2. To study the potential occurrence of **vaccine-associated enhanced disease (VAED)** by describing **the clinical and laboratory features of critical COVID-19 disease** (1) cases, by **COVID-19 vaccine exposure status and time since vaccination**. (2)

[1] Critical COVID-19 disease is defined as being admitted to Intensive Care Unit (ICU) due to laboratory confirmed SARS-CoV-2.
[2] It is postulated that the potential VAED risk may change with waning vaccine induced immunity, hence with time since vaccination as a proxy.

Study design:
This will be a retrospective, longitudinal cohort study using population-based automated health care data to ascertain vaccination details, patient characteristics, and outcomes of interest. The study observation period starts on the date of the first VLA2001 post-authorization cohort study which will be evaluating the effectiveness of the VLA2001 inactivated vaccine to prevent serious COVID19 infection in conditions of usual care utilizing primary data collected prospectively through the COVIDRIVE platform up to 2 years postvaccination if other censoring rules apply (eg, death, leaving database). A minimum prior period of one year of database history will be required to collect information on patient characteristics and prior risks.

Study population:
All patients vaccinated with COVID-19 Vaccine (inactivated, adjuvanted) Valneva with a date of administration (preferably batch date) and a minimum of 12 months of prior history in the database.

Milestones: The interim and final analysis are anticipated to be triggered 6 and 12 months after initiation of use of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the participating countries assuming a constant COVID-19 attack rate. Therefore, the anticipated timelines for the interim and final reports are 9 and 16 months after study initiation.

III.3 Summary Table of additional Pharmacovigilance activities

Table 22: Planned additional pharmacovigilance activities

Study	Summary of objectives	Safety concerns addressed	Milestones / Due dates
Pregnancy Registry	To estimate the risk of the most common obstetric outcomes, i.e. pregnancy losses, placentation disorders, gestational diabetes, premature delivery, and COVID-19, neonatal outcomes, i.e. congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission, and COVID-19, among pregnant women exposed to COVID-19 Vaccine (inactivated, adjuvanted) Valneva from 30 days prior to the first day of the LMP to end of pregnancy and their offspring relative to a matched unexposed reference group.	Use in pregnancy and corresponding AESIs	Registration in the EU PAS Register 20 January 2021. Start of data collection of VLA2001 exposures 01 August 2022. Annual Reports: 31 August 2023 31 August 2024 31 August 2025 31 August 2026 Semiannual Reports: 28 February 2023 29 February 2024 28 February 2025 28 February 2026 28 February 2027 Final Study Report: 31 August 2027
Post-Authorisation Safety Study	To estimate the incidence of adverse events of special interest (AESIs), including the potential risk of vaccine associated enhanced disease (VAED) and vaccine associated respiratory disease (VAERD), that are medically attended following the administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the real-world immunisation setting. A retrospective study using health care databases.	VAED and VAERD Use in immunocompromised patients Use in frail patients Use in patients with autoimmune or inflammatory disorders Long-term safety data	Study Protocol: June 2022 Registration in the EU PAS Register: upon protocol finalisation Request for data extraction: launch of VLA2001 in the EU Progress reports: 12 and 24 months after start of vaccination campaign. Final study report: 36 months after start of vaccination campaign.
Post-Authorisation Safety Study	To evaluate the risk of adverse events of special interest (AESIs) that are medically attended. A prospective multi-centre cohort study.	VAED and VAERD Use in immunocompromised patients Use in frail patients Use in patients with autoimmune or inflammatory disorders Long-term safety data	Study is expected to end 36 months after start of enrolment with delivery of the final study report (30 months for data collection and 6 months for database lock, data analysis, and study report).

Post-Authorisation Efficacy Study	To estimate effectiveness against hospitalization due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with COVID-19 Vaccine (inactivated, adjuvanted) Valneva.	VAED and VAERD	The interim and final analysis are anticipated to be triggered 6 and 12 months after initiation of use of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the participating countries assuming a constant COVID-19 attack rate. Therefore, the anticipated timelines for the interim and final reports are 9 and 16 months after study initiation.
Clinical Study VLA2001-201	To evaluate the tolerability, safety and immunogenicity of the inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 of a two-dose schedule in healthy adults aged 18 to 55 years.	Long-term safety data	Interim CSR submitted as part of licensure application Q4 2021. Interim CSR including follow-up to Month 6 planned to be submitted mid-2022. Final CSR submission planned Q4 2022.
Clinical Study VLA2001-301	To demonstrate the superiority of VLA2001 (Wuhan strain) compared to AZD1222 in adults aged 30 years and older. To examine the immunogenicity of VLA2001 in adolescents aged ≥12 to <18 years compared to adults 18-29 years of age. To evaluate the safety and tolerability of VLA2001 in adults and adolescents aged ≥12 years and older.	Long-term safety data	CSR submitted as part of licensure rolling review procedure Q4 2021. Addendum CSR with extended immunogenicity and safety follow-up (including Day 71) planned to be submitted until 31 August 2022. Interim CSR report including primary endpoint in adolescents planned to be submitted Q3 2022. Final CSR submission planned Q2 2023.

Part IV: Plans for post-authorisation efficacy studies

Post-marketing observational study using existing secondary health data sources through the COVIDRIVE platform

Study name and title:
A post-authorisation study to evaluate the effectiveness of the COVID-19 Vaccine (inactivated, adjuvanted) Valneva to prevent serious COVID19 infection in conditions of usual care utilizing primary data collected prospectively through the COVIDRIVE platform up to 2 years post-vaccination.

Primary study objective:
To estimate effectiveness against hospitalization due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with COVID-19 Vaccine (inactivated, adjuvanted) Valneva.

The secondary and exploratory objectives of COVIDRIVE's master protocol are stratifications to the first objective aiming to estimate COVID-19 Vaccine (inactivated, adjuvanted) Valneva's effectiveness against COVID-19 hospitalization within populations of special interest, by SARS-CoV-2 genetic variants, by time since last dose and by time between doses.
The Applicant is applying for an indication for COVID-19 Vaccine (inactivated, adjuvanted) Valneva to be used for primary series immunization in adults.

Primary endpoint:

3. To confirm CVE of COVID-19 Vaccine (inactivated, adjuvanted) Valneva against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients.

Exploratory endpoints:

4. To confirm CVE of COVID-19 Vaccine (inactivated, adjuvanted) Valneva against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients,
   i. by SARS-CoV-2 genetic variants.
   ii. within populations of special interest (e.g., specific age groups, specific immunocompromised or chronic conditions, pregnant women).
   iii. by time since last COVID-19 vaccine dose.
   iv. by time between last two COVID-19 vaccine doses.
   v. by number of VLA2001 doses (1,2,3…) doses given
   vi. by number and type(s) of the COVID-19 vaccine doses given prior to the last
   vii. by number and type(s) of the COVID-19 vaccine doses given prior to the last
3. To study the potential occurrence of **vaccine-associated enhanced disease (VAED)** by describing **the clinical and laboratory features of critical COVID-19 disease** [(1)] cases, by **COVID-19 vaccine exposure status and time since vaccination**. [(2)]

[1] Critical COVID-19 disease is defined as being admitted to Intensive Care Unit (ICU) due to laboratory confirmed SARS-CoV-2.
[2] It is postulated that the potential VAED risk may change with waning vaccine induced immunity, hence with time since vaccination as a proxy.

Study design:

This will be a retrospective, longitudinal cohort study using population-based automated health care data to ascertain vaccination details, patient characteristics, and outcomes of interest. The study observation period starts on the date of the first VLA2001 post-authorization cohort study which will be evaluating the effectiveness of the VLA2001 inactivated vaccine to prevent serious COVID19 infection in conditions of usual care utilizing primary data collected prospectively through the COVIDRIVE platform up to 2 years postvaccination if other censoring rules apply (eg, death, leaving database). A minimum prior period of one year of database history will be required to collect information on patient characteristics and prior risks.

Study population:
All patients vaccinated with COVID-19 Vaccine (inactivated, adjuvanted) Valneva with a date of administration (preferably batch date) and a minimum of 12 months of prior history in the database.

Milestones: The interim and final analysis are anticipated to be triggered 6 and 12 months after initiation of use of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the participating countries assuming a constant COVID-19 attack rate. Therefore, the anticipated timelines for the interim and final reports are 9 and 16 months after study initiation.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

The product information is sufficient to mitigate the current identified and potential risks of COVID-19 Vaccine (inactivated, adjuvanted) Valneva. The necessary information to ensure appropriate use of the product is included in the relevant sections of the SmPC. No additional measure for risk minimisation is considered necessary at this point in time. The proposed minimisation measures are summarised in Table 23**:** below for each safety concern.

Table 23: Description of routine risk minimization measures by safety concern

Safety concern	**Routine risk minimisation activities**
Important Potential Risk	
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Missing Information	
Use in pregnancy and while breast feeding	Routine risk communication: SmPC section 4.6 Fertility, pregnancy and lactation. Package Leaflet section 2. What you need to know before you are given COVID-19 Vaccine (inactivated, adjuvanted) Valneva. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in immunocompromised patients	Routine risk communication: SmPC section 4.4 Special warnings and precautions for use. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in patients with autoimmune or inflammatory disorders	Routine risk communication: SmPC section 5.1 Pharmacodynamic properties. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Interaction with other vaccines	Routine risk communication: SmPC section 4.5 Interaction with other medicinal products and other forms of interaction. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Long term safety data	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

V.2. Additional Risk Minimisation Measures

No additional risk minimisation activities are suggested. Routine risk minimisation activities as described in Part V.1 are considered sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 24: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up Questionnaire (see Annex 4). Additional pharmacovigilance activities: COVIDRIVE study. Post-authorisation safety studies.
Use in pregnancy and while breast feeding.	Routine risk minimisation measures: SmPC section 4.6, PL section 2. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up Questionnaire (see Annex 4). Additional pharmacovigilance activities: Pregnancy registry.
Use in immunocompromised patients	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Sub-population in post-authorisation safety studies.
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Sub-population in post-authorisation safety studies.
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Sub-population in post-authorisation safety studies.
Interaction with other vaccines	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Post-authorisation safety studies.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Clinical study extension of VLA2001-201 and VLA2001-301. Post-authorisation safety studies.

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for COVID-19 Vaccine (inactivated, adjuvanted) Valneva. The RMP details important risks of COVID-19 Vaccine (inactivated, adjuvanted) Valneva, how these risks can be minimised, and how more information will be obtained about COVID-19 Vaccine (inactivated, adjuvanted) Valneva's risks and uncertainties (missing information).

COVID-19 Vaccine (inactivated, adjuvanted) Valneva 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how COVID-19 Vaccine (inactivated, adjuvanted) Valneva should be used.

Important new concerns or changes to the current ones will be included in updates of COVID-19 Vaccine (inactivated, adjuvanted) Valneva’s RMP.

I. The medicine and what it is used for

COVID-19 Vaccine (inactivated, adjuvanted) Valneva is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals between 18 and 55 years of age (see SmPC for the full indication). It contains COVID-19 vaccine (inactivated, adjuvanted, adsorbed) as the active substance and it is given intramuscularly.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of COVID-19 Vaccine (inactivated, adjuvanted) Valneva, together with measures to minimise such risks and the proposed studies for learning more about COVID-19 Vaccine (inactivated, adjuvanted) Valneva's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.
If important information that may affect the safe use of COVID-19 Vaccine (inactivated, adjuvanted) Valneva is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of COVID-19 Vaccine (inactivated, adjuvanted) Valneva are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of

COVID-19 Vaccine (inactivated, adjuvanted) Valneva. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 25: List of Important Risks and Missing Information

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

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 26: Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Evidence for linking the risk to the medicine	VAED is considered a potential risk because it has not been seen in human studies with with this or other COVID-19 vaccines being studied. It has not been seen in vaccine studies in animal models of the SARS-CoV-2 virus either. However, in selected vaccine studies in animal models as well as in some laboratory studies in animal cells infected with 2 other related coronaviruses (SARS-CoV-1 and MERS-CoV), abnormalities in immune responses or cellular responses indicative of VAED were observed. Because of this, VAED is considered a potential risk. In the past there have been other examples of particularly respiratory viruses where VAED has been observed. For example, some children who received an inactivated respiratory syncytial virus vaccine (a different type of virus), had worse signs of disease when they were subsequently infected with respiratory syncytial virus. VAED is thought to occur by several mechanisms where the immune response is not fully protective and actually either causes the body to have an inflammatory reaction due to the type of immune response with specific types of T-cells, or the body does not produce enough strong antibodies to prevent SARS-CoV-2 infection of cells or produces weak antibodies that actually bind to the virus and help it to enter cells more easily, leading to worse signs of disease.
Risk factors and risk groups	It is thought that the potential risk of VAED may be increased in individuals producing a weak antibody response or in individuals with decreasing immunity over time.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Efficacy Study. Post-Authorisation Safety Studies.

Table 27: Missing Information: Use in pregnancy and while breast feeding

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Pregnancy registry.

Table 28: Missing Information: Use in immunocompromised patients

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.

Additional pharmacovigilance activities	Sub-population in post-authorisation safety studies.

Table 29: Missing Information: Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Sub-population in post-authorisation safety studies.

Table 30: Missing Information: Use in patients with autoimmune or inflammatory disorders

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Sub-population in post-authorisation safety studies.

Table 31: Missing Information: Interaction with other vaccines

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-authorisation safety studies.

Table 32: Missing Information: Long term safety data

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Clinical study extension of VLA2001-201 and VLA2001-301. Post-authorisation safety studies.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of COVID-19 Vaccine (inactivated, adjuvanted) Valneva.

II.C.2 Other studies in post-authorisation development plan

Pregnancy Registry

Purpose of the study: to estimate the risk of the most common obstetric outcomes, i.e. pregnancy losses, placentation disorders, gestational diabetes, premature delivery, and COVID-19, neonatal outcomes, i.e. congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission, and COVID-19, among pregnant women exposed to COVID-19 Vaccine (inactivated, adjuvanted) Valneva from 30 days prior to the first day of the LMP to end of pregnancy and their offspring relative to a matched unexposed reference group.

Post-Authorisation Safety Study

Purpose of the Study: to estimate the incidence of adverse events of special interest (AESIs), including the potential risk of vaccine associated enhanced disease (VAED) and vaccine associated respiratory disease (VAERD), that are medically attended following the administration of COVID-19 Vaccine (inactivated, adjuvanted) Valneva in the real-world immunisation setting. A retrospective study using health care databases.

Post-Authorisation Study

A post-authorisation study to evaluate the effectiveness of the COVID-19 Vaccine (inactivated, adjuvanted) Valneva to prevent serious COVID-19 infection in conditions of usual care utilizing primary data collected prospectively through the COVIDRIVE platform up to 2 years post-vaccination.

Clinical Study VLA2001-201

Purpose of the Study: to evaluate the tolerability, safety and immunogenicity of the inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 of a two-dose schedule in healthy adults aged 18 to 55 years.

Clinical Study VLA2001-301

Purpose of the Study: to demonstrate the superiority of VLA2001 (Wuhan strain) compared to AZD1222 in adults aged 30 years and older. To examine the immunogenicity of VLA2001 in adolescents aged ≥12 to <18 years compared to adults 18-29 years of age. To evaluate the safety and tolerability of VLA2001 in adults and adolescents aged ≥12 years and older.

Annex IV - Specific adverse drug reaction follow-up forms

Annex IV.1 – Pregnancy Questionnaire

Valneva Date of Receipt: _____ Case ID# : _____

PREGNANCY QUESTIONNAIRE

1. Reporter Information:

Reporter's First and Last Name:

Is the Reporter a Healthcare Professional: ☐ Yes ☐ No
If yes, what is the specialty:

Reporter's Address (no, street, city, postal code, country):

Reporter's Telephone and Fax:

Reporter's Signature and Date *(DD/MM/YY)*:

2. Patient Details:

Initials: **Date of birth** *(DD/MM/YYYY)*: **Age in Years**: **Weight in kg** **Height in cm**

Race: ☐ White ☐ Black ☐ Asian ☐Other_____ ☐ Refused or Unknown

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Other _____ ☐ Unknown

Medical history (including previous pregnancies) _____

3. Covid-19 Vaccine:

Dose 1 received ☐ Yes ☐ No If yes, date of vaccination *(DD/MM/YY)*: Batch/Lot number:

Dose 2 received ☐ Yes ☐ No If yes, date of vaccination *(DD/MM/YY)*: Batch/Lot number:

If dose 2 was not received, was the dose not administered due to the adverse event? ☐ Yes | ☐ No

If yes please specify:_____

4. Adverse Event Details after vaccination:

Adverse Event(s) (Check any/both as applicable)	**Start Date** (DD/MM/YY)	**Stop Date** (DD/MM/YY)	**Outcome**	
			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown
			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown

5. Current pregnancy details:

Method and Date of pregnancy positive test *(DD/MM/YYYY)*

Was pregnancy known when product administered? ☐ *No* ☐ *Yes*

First day of last menstrual period *(DD/MM/YYYY)* **Estimated delivery date**

Complications during pregnancy: ☐ Pre-eclampsia ☐ Diabetes ☐ Infection

☐ Other *(please specify)*

_____

Hospitalization during pregnancy: ☐ No ☐ Yes (*please specify reasons):*

7. Concomitant Drugs/ Vaccines: *Please include drugs used to treat the event(s) during pregnancy or 30 days before pregnancy. List all medications including over-the-counter drugs and supplements.*

Concomitant Drug Name	Indication	Daily Dose	Route	Start Date *(DD/MM/YY*	Stop Date *(DD/MM/YY)*	Withdrawn
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

8. Pregnancy outcome:

Please provide and attach results of relevant laboratory test and procedures

Mode of delivery: ☐ Spontaneous ☐ Cesarean section ☐ Other, *please specify*:

Date of delivery *(DD/MM/YYYY)*:

☐ **Term labor, (***please specify gestational age)*:

☐ **Pre-term labor, (***please specify gestational age)*:

☐ **Fetal Death / Stillbirth** *(pregnancy loss ≥20 weeks of gestation)*

☐ **Spontaneous abortion,** *(pregnancy loss <20 weeks of gestation)*

☐ **Elective termination, (***please specify gestational age)*:

☐ **Ectopic pregnancy**

Neonate: ☐ Single ☐ Multi *(please specify #)* **Sex:**

☐ **Live birth, with no congenital anomalies**

☐ **Live birth, with congenital anomalies** *(please specify)*

Weight of the baby*(kg)*

Height of the baby*(cm)*

Cranial circumference*(cm)*

Apgar score

☐ **Neonatal illness** (*please specify diagnoses, hospitalization, therapy)*

☐ **Stillbirth** **Was an autopsy performed** *(If yes please attach the autopsy report)*

Comments *(please specify all pregnancy outcome relevant info)*

Thank you for completing this form

Annex IV.2 – Vaccine Associated Enhanced Disease Questionnaire

Valneva Date of Receipt: _____ Case ID#:_____

VACCINE ASSOCIATED ENHANCED DISEASE QUESTIONNAIRE

1.Reporter information

Reporter's first and last name

Is the reporter a Healthcare professional ☐ Yes ☐ No
If yes what is the specialty:

Reporter's Address (no, street, city, country):

Reporter's telephone and fax:

Reporter's signature and date *(DD,MM,YY)* :

2.Patient details.

Initials **Sex**: ☐ Male ☐ Female **Date of birth** *(DD,MM,YYYY)* **Age** (years)

Race: ☐ White ☐ Black or African American ☐ Native American ☐ Alaska Native ☐ Native Hawaiian ☐ Asian ☐ Aboriginal and Torres Strait Islander ☐ Other ☐ Refused or Unknown

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknow

3.Covid-19 vaccine:

Dose 1 received ☐ Yes ☐ No If yes, date of vaccination *(DD/MM/YY)*: Batch/Lot number:

Dose 2 received ☐ Yes ☐ No If yes, date of vaccination *(DD/MM/YY)*: Batch/Lot number:

If dose 2 was not received, was the dose not administered due to the adverse event? ☐ Yes | ☐ No

4.Adverse event details.

Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*	**Outcome**	
			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown
			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown

Please provide details of any signs and symptoms experienced in relation to diagnosed or suspected COVID-19 illness (including date of onset for each and eventual worsening):

SARS-CoV-2 test/antibodies:

Did the patient have testing for SARS-CoV-2? ☐ Yes ☐ No ☐Unknown
If yes, specify type of testing and date *of test, whether IgM /IgG or both and the titer*

In the absence of a positive test, what findings suggested a diagnosis of COVID-19 infection or VAED?

Does the patient have SARS-CoV-2 antibodies at diagnosis? ☐ Yes ☐ No ☐Unknown

How many days from the SARS-CoV2 diagnosis did it take before the SARS-CoV2 antigen test became negative

In the event of death, please provide the date and cause of death (*please provide copy of autopsy report, if available):*
Was the patient hospitalized for the adverse event(s)? ☐ Yes ☐ No
If yes, please provide the admission and the discharge dates *(DD/MM/YY)*

Please provide the discharge report information and histology results

Was/Is the patient admitted to an Intensive Care Unit? ☐ Yes ☐ No ☐ Unknown
If 'Yes', please provide case summary:

Have any pre-existing diseases worsened during the SARS-CoV-2 ☐ Yes ☐ No ☐ Unknown
If 'Yes', please specify the details:

5.Patient Covid-19 treatment

Therapy	**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*	**Daily dose/ Any additional information**
Remdesivir			
Hydroxychloroquine			
Monoclonal antibodies			
Azithromycine			
Corticosteroids			
Bamlavinimab			
Etesevimab			
Plasmapheresis			
Other (please *specify)*			

6. Please provide information on any new or worsening symptoms/signs during the COVID-19 illness

Respiratory	**Cardio-vascular**	**Hematology & Immune system**	**Renal system**	**Gastro-intestinal and hepatic system**	**Central nervous system**	**Other systems**
☐Dyspnea ☐Tachypnea ☐Hypoxemia ☐Cough ☐Cyanosis ☐COVID-19 pneumonia ☐Acute respiratory distress syndrome ☐Lower respiratory tract infection ☐Respiratory failure ☐Pulmonary hemorrhage ☐ Radiographic abnormalities	☐Heart failure ☐Acute cardiac injury ☐Acute myocardial infarction ☐Arrhythmia ☐Pericarditis ☐Myocarditis ☐Cardiogenic shock ☐Other:	☐Coagulopathy ☐ Thrombocytopenia ☐Deep vein thrombosis ☐Disseminated intravascular coagulation ☐Vasculitis ☐Limb ischemia ☐Pulmonary embolism ☐Other:	☐Renal disfunction ☐Acute kidney injury ☐Other:	☐Vomiting ☐Diarrhea ☐Jaundice ☐Abdominal pain ☐Acute liver injury ☐Other:	☐Altered mental status ☐Convulsions/seizures ☐Cranial nerve involvement ☐Encephalopathy ☐Meningitis ☐Cerebrovascular accident ☐Other:	☐Acute arthritis ☐Dermatologic ☐Chilblains ☐Erythema multiforme ☐Multisystem inflammatory syndrome ☐Multiorgan failure *Specify*: ☐Death ☐Other:

☐Other:						

7.Relevant Medical History/Concurrent Diseases

Medical History			Start date	Stop date	Is the patient treated for this condition?	
Respiratory or gastrointestinalinfection	☐ Yes	☐ No				
Lymphoma	☐ Yes	☐ No				
HIV positive	☐ Yes	☐ No				
Systemic lupus erythematosus	☐ Yes	☐ No				
Vasculitis	☐ Yes	☐ No				
Other autoimmune disorders	☐ Yes	☐ No				
Hypertension	☐ Yes	☐ No				
Diabetes	☐ Yes	☐ No				
Heart Disease (*please specify*)	☐ Yes	☐ No				
Lung Disease (*please specify*)	☐ Yes	☐ No				
Kidney disease (*please specify*)	☐ Yes	☐ No				
Liver disease (*please specify*)	☐ Yes	☐ No				
Coagulation disorders	☐ Yes	☐ No				
Obesity	☐ Yes	☐ No				
Current or Former Smoker *If Yes, please provide details*	☐ Yes	☐ No				

8.Concomitant Drugs/ Vaccines

Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations. Add vaccine administered within the last month

Concomitant Drug Name	Indication	Daily Dose	Route	Start Date *(DD/MM/YY*	Stop Date *(DD/MM/YY)*	Withdrawn
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

9.Lab test/ diagnostic procedures *Please provide and attach results of relevant laboratory test and procedures*

Lab test /Diagn. procedure	Date and Results
Imaging for COVID-Pneumonia (e.g., CXR, CT)	
Hypoxemia,OR,Hypercapnia (PaCO2) OR acidosis (pH)	
Hematology results	
Chemistry results	
Elevated cytokines	

Thank you for completing this form.