EU Risk Management Plan for BIMERVAX emulsion for injection

RMP version to be assessed as part of this application:

RMP Version number: 1.4

Data lock point for this RMP: 30 August 2023

Date of final sign-off: See e-signature page

Rationale for submitting an updated RMP: Type II variation (C.I.13) to provide results from final CSR of HIPRA-HH-5 clinical trial. This updated version of the RMP also includes results from the already approved final CSR of HIPRA-HH-10, HIPRA-HH-1 and HAN-01 clinical trials.

Summary of significant changes in this RMP:

RMP Part/Module	**RMP v1.4**
PART I PRODUCT(S) OVERVIEW	No changes.
PART II SAFETY SPECIFICATION	
PART II Module SI Epidemiology of the Indication(s) and Target Populations	Updated according to current information.
PART II Module SII Non-Clinical Part of the Safety Specification	No changes.
PART II Module SIII Clinical Trial Exposure	Updated studies HIPRA-HH-10, HIPRA-HH-5, HIPRA-HH-1 and HAN-01 to completed studies and inclusion of relevant information. Updated overall exposure according to CSRs of studies HIPRA-HH-10, HIPRA-HH-5, HIPRA-HH-1 and HAN-01.
PART II Module SIV Populations Not Studied in Clinical Trials	No changes.
PART II Module SV Post-Authorisation Experience	Updated with an estimation for post-authorisation exposure data up to 30 August 2023.

PART II Module SVI Additional EU Requirements for the Safety Specification	No changes.
PART II Module SVII Identified and Potential Risks	No changes.
PART II Module SVIII Summary of Safety Concerns	No changes.
PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)	
PART III.1 Routine Pharmacovigilance Activities	No changes.
PART III.2 Additional Pharmacovigilance Activities	Removed completed studies HIPRA-HH-10, HIPRA-HH-5, HIPRA-HH-1 and HAN-01.
PART III.3 Summary Table of Additional Pharmacovigilance Activities	Removed completed studies HIPRA-HH-10, HIPRA-HH-5 HIPRA-HH-1 and HAN-01.
PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES	No changes.
PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	
PART V.1 Routine Risk Minimisation Measures	No changes.
PART V.2 Additional Risk Minimisation Measures	No changes.
PART V.3 Summary of Risk Minimisation Measures	Removed completed studies HIPRA-HH-10, HIPRA-HH-5, HIPRA-HH-1 and HAN-01.
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN	
I. The medicine and what it is used for	No changes.
II. Risks associated with the medicine and activities to minimise or further characterise the risks	II.B – Removed completed studies HIPRA-HH-10, HIPRA-HH-5, HIPRA-HH-1 and HAN-01. II.C – Removed completed studies HIPRA-HH-10, HIPRA-HH-5, HIPRA-HH-1 and HAN-01.
PART VII ANNEXES TO THE RISK MANAGEMENT PLAN	

Annex 1 – Eudravigilance interface	No changes.
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Updated the status of HIPRA-HH-10, HIPRA-HH-5, HIPRA-HH-1 and HAN-01 studies from on-going to completed.
Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan	Removed completed studies HIPRA-HH-10, HIPRA-HH-5 HIPRA-HH-1 and HAN-01.
Annex 4 – Specific adverse drug reaction follow-up forms	Minor format and wording update on VAED and Myocarditis/Pericarditis questionnaires.
Annex 5 – Protocols for proposed and on-going studies in RMP part IV	No changes.
Annex 6 – Details of proposed additional risk minimisation measures (if applicable)	No changes.
Annex 7 – Other supporting data (including referenced material)	No changes.
Annex 8 – Summary of changes to the risk management plan over time	Updated to reflect the changes made to the RMP.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

RMP Version number: 1.2

Approved with procedure: EMEA/H/C/006058/IB/0003

Date of approval (opinion date): 18/08/2023

QPPV name[1]: Irina Güell

QPPV signature: The content of this RMP has been reviewed and approved by the marketing authorisation HIPRA's QPPV. The electronic signature is available on file.

04/03/2024

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ECDC	European Centre for Disease Control
EMA	European Medicines Agency
FIH	First-in-human
FOB	Functional Observation Battery
GLP	Good Laboratory Practice
HED	Human equivalent dose
ID50	50% inhibition dose
i.m.	Intramuscular
mRNA	messenger RNA
MPLA	Monophosphoryl lipid A
NHP	Non-human primate
PBS	Phosphate-buffered saline
RBD	Receptor binding domain
PHEIC	Public Health Emergency of International Concern
PSMF	Pharmacovigilance System Master File
SAE	Serious adverse event
S protein	Spike protein
VOC	Variant of concern
VOI	Variant of interest
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	COVID-19 Vaccine (recombinant, adjuvanted)
Pharmacotherapeutic group(s) (ATC Code)	Covid-19, protein subunit (J07BN04)
Marketing Authorisation Applicant	Hipra Human Health, S.L.U.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	BIMERVAX emulsion for injection
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Recombinant Protein Vaccine
	Summary of mode of action SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 variants, formulated in a phosphate-buffered saline (PBS) solution adjuvanted with SQBA adjuvant. The SQBA adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein RBD-specific immune response. The recombinant spike protein RBD domains of SARS-CoV-2 are recognised by immune cells as a foreign antigen and elicit neutralising antibody and cellular responses which may contribute to protection against COVID-19. Neutralizing antibodies against the RBD domain of SARS-CoV-2 prevent RBD binding to its cellular target ACE2, thus blocking membrane fusion and viral infection. Moreover, BIMERVAX vaccine induces antigen-specific CD4+ and CD8+ T cells, with a Th1 response.
	Important information about its composition One dose (0.5 mL) contains 40 µg of SARS-CoV-2 virus recombinant protein RBD (manufactured using a Chinese hamster ovary (CHO) suspension cell line stably transfected with a plasmid expressing the active substance antigen) in a phosphate-buffered (PBS) solution adjuvanted with 0.25 mL of SQBA. The SQBA adjuvant contains squalene as the internal oil phase, sodium citrate-citric acid buffer as the external aqueous phase and polysorbate 80 and sorbitan trioleate as emulsifiers.

Hyperlink to the Product Information	BIMERVAX emulsion for injection Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: BIMERVAX is a bivalent vaccine indicated as a booster for active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA vaccine COVID-19 vaccine
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: BIMERVAX is administered intramuscularly as a single dose of 0.5 mL at least 6 months after a previous COVID-19 vaccine. BIMERVAX may be given once as a booster dose to individuals 16 years of age and older who have received prior vaccination series with mRNA COVID-19 vaccines.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): Emulsion for injection in multidose vials of 10 doses. Each dose consists of 0.5 mL containing 40 µg of SARS-CoV-2 virus recombinant protein RBD in a phosphate-buffered (PBS) solution adjuvanted with 0.25 mL of SQBA. The emulsion is homogeneous white (pH: 6.0 – 7.5).
	Proposed (if applicable): Not applicable.
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(s) and target population(s)

Indication

Active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA vaccine COVID-19 vaccine. BIMERVAX is administered intramuscularly as a single dose of 0.5 mL at least 6 months after a previous COVID-19 vaccine. BIMERVAX may be given once as a booster dose to individuals 16 years of age and older who have received prior vaccination series with mRNA COVID-19 vaccines.

Incidence and prevalence

Coronavirus disease 2019 (COVID-19) was first identified in patients with severe respiratory disease in Wuhan, China in December 2019. Afterwards, the COVID-19 epidemic has spread all over the world (Sun *et al.*, 2020). The causative agent was a novel betacoronavirus scientifically named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). CoVs members belong to the subfamily *Coronovirinae* within the family *Coronaviridae* and the order *Nidovirales*. Based on their protein sequences and phylogenetic relationships, members of the *Coronavirinae* subfamily can be classified into four groups, *Alphacoronaviruses*, *Betacoronaviruses*, *Gammacoronaviruses*, and *Deltacoronaviruses*. The CoVs genome is a single-stranded positive-sense RNA (+ssRNA) molecule. The genome size ranges between 27–32 kbp, one of the largest known RNA viruses (Alanagreh *et al.*, 2020; Tegally *et al.*, 2020). Angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2. In the normal human lung, ACE2 is expressed on type I and II alveolar epithelial cells. Among them, 83% of the type II alveolar cells have ACE2 expression. The binding of SARS-CoV-2 on ACE2 causes an elevated expression of ACE2, which can lead to damages on alveolar cells. Damages to alveolar cells can, in turn, trigger a series of systemic reactions and even death (Zhao *et al.*, 2020).

COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO) on the 30 January 2020 (World Health Organization (WHO), 2020), and an end to this PHEIC was declared on 05 May 2023. However, COVID-19 remains an established and ongoing health issue, particularly in vulnerable populations (e.g., > 65 years of age, immunocompromised, pregnant women, and people with pre-existing medical conditions), as the virus is widely circulating and new variants are emerging (World Health Organization (WHO), 2023c).

The incidence and prevalence of COVID-19 is difficult to estimate as definitions of cases may have changed since the onset of the pandemic, testing availability and technology has changed, as have vaccination rates. In addition, there is the variable impact of different variants of concern (VOCs). As of 20 August 2023, COVID-19, has become a pandemic with more than 769 million confirmed cases and over 6.9 million deaths (World Health Organization (WHO), 2023b). In Europe, there have been more than 276 million confirmed cases of COVID-19 with more than 2 million deaths reported to WHO (Figure 1). During these months, several vaccines against SARS-CoV-2 have been developed. As of 19 February 2023 (week 7, 2023), over 976 million COVID-19 vaccine doses had been administered in the EU/EEA, with around 331 million people having received a complete primary vaccination course, 248 million having received a first booster dose, 63.9 million having received a second booster dose, and 5.9 million having received a third booster dose (ECDC, 2023b).

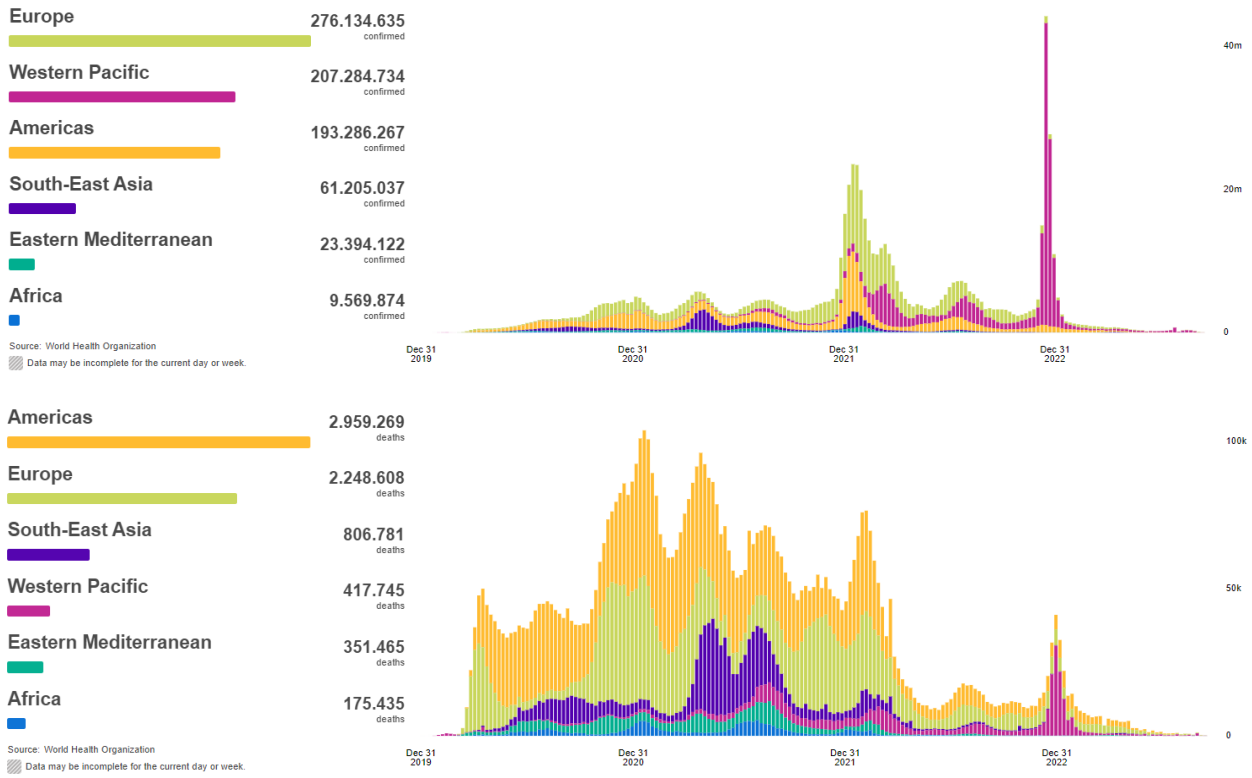

Figure 1. COVID-19 Cases Reported Weekly by WHO Region (top), and Global Deaths (bottom), as of 28 September 2023 (World Health Organization (WHO), 2023d)

Currently, reported cases do not accurately represent infection rates due to the reduction in testing and reporting globally. During the period from 24 July to 20 August 2023, 44% (103 of 234) of countries reported at least one case to WHO – a proportion that has been declining since mid-2022 (Figure 2). It is important to note that this statistic does not reflect the actual number of countries where cases exist. Additionally, data from previous weeks are continuously being updated to incorporate retrospective changes in reported COVID-19 cases and deaths made by countries.

At the regional level, the number of newly reported cases within a 28-day period has increased across three of the five WHO regions assessed: the European Region (+11%), the Western Pacific Region (+88%), and the Eastern Mediterranean Region (+112%); while case numbers decreased in two WHO regions: the African Region (-84%), and the South-East Asia Region (-45%). The number of newly reported deaths within a 28-day period has decreased across four regions: the African Region (-75%), the South-East Asia Region (-55%), the European Region (-49%), and the Western Pacific Region (-14%); while newly reported deaths increased in the Eastern Mediterranean Region (+70%).

At the country level, the highest numbers of new cases reported within the 28-day period were from the Republic of Korea (1 286 028 new cases; +117%), Australia (22,836 new cases; -53%), the United Kingdom (21,866 new cases; +92%), Italy (19,777 new cases; +32%), and Singapore (18,125 new cases; -40%). The highest numbers of new 28-day deaths were reported from the Republic of Korea (398 new deaths; +100%), the Russian Federation (166 new deaths; -51%), Italy (165 new deaths; -9%), Australia (148 new deaths; -58%), and the Philippines (136 new deaths; +386%) (World Health Organization (WHO), 2023b).

Among nine countries that reported at least 10 results from SARS-CoV-2 sequencing or genotyping for weeks 32–33 (7 August to 20 August 2023), the distribution of variants of concern (VOC) or of interest (VOI) was 56.4% (46.9–65.1% from nine countries) for XBB.1.5+F456L, 35.9% (27.7–53.1% from nine countries) for XBB.1.5, 2.6% (2.4–9.2% from five countries) for BA.2.75, and 1.9% (0.3–4.8% from three countries) for XBB. A precise estimate of the true variant distribution, as well as early detection of newly emerged variants is difficult due to reduced sequencing volumes and a low number of countries currently reporting data on SARS-CoV-2 sequencing or genotyping (ECDC, 2023a) .

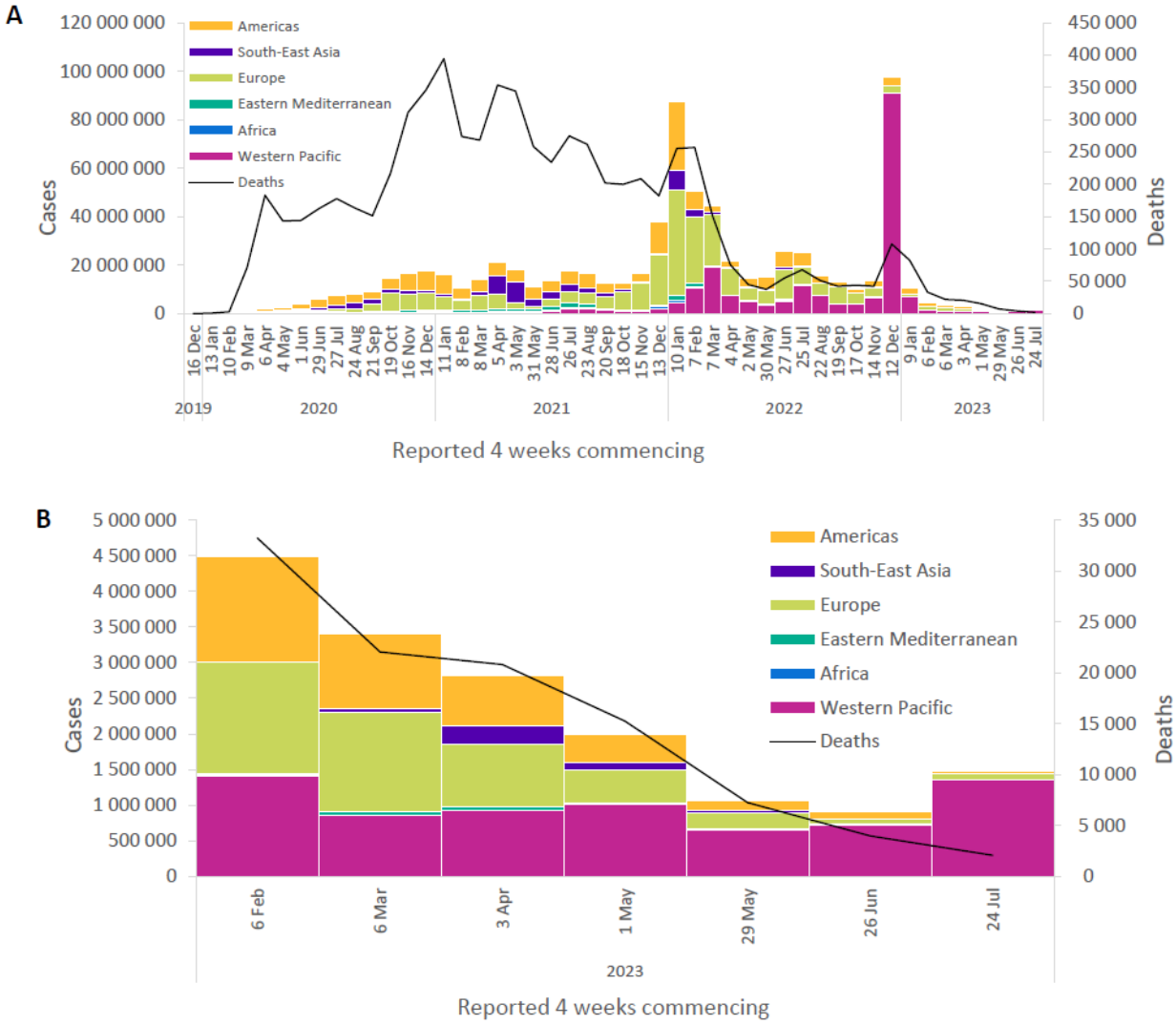

Figure 2. COVID-19 cases reported by WHO Region, and global deaths by 28-day intervals, as of 20 August 2023 (A); 6 February to 20 August 2023 (B) (World Health Organization (WHO), 2023b) .

By the end of week 34 (ending 27 August 2023), there was evidence of increasing transmission of COVID-19 in the EU/EEA, although levels of incidence seem to remain low with limited impact on severe disease to date. Current data availability, especially regarding severe disease, is limited, and the overall assessment of impact and severity of disease in the EU/EEA should therefore be interpreted with caution.

Among 21 countries that reported age-specific data on cases positive for COVID-19, 16 observed increases in case rates among people aged 80 years and above.

All 10 countries with data on hospital or ICU admissions/occupancy up to week 34 reported stable trends compared with the previous week. In total, 135 deaths were reported by 18 countries (compared to 52 deaths reported by 15 countries in the previous week), with two countries reporting increases in their death rates.

At the global level, during the period 17 July to 13 August 2023, 27 of 234 countries reported a total of 49,380 new hospitalizations, and 22 of 234 countries reported to WHO a total of 646 new intensive care unit (ICU) admissions (Figure 3). This represents a 21% increase and 44% decrease in hospitalizations and ICU admissions, respectively, compared to the previous 28 days (19 June to 16 July 2023). It is worth noting that the absence of reported data from other countries to the WHO does not imply that there are no COVID-19-related hospitalizations in those countries. The hospitalization data are preliminary and might change as new data become available. Furthermore, hospitalization data are subject to reporting delays. These data also likely include both hospitalizations with incidental cases of SARS-CoV-2 infection and those due to COVID-19 disease.

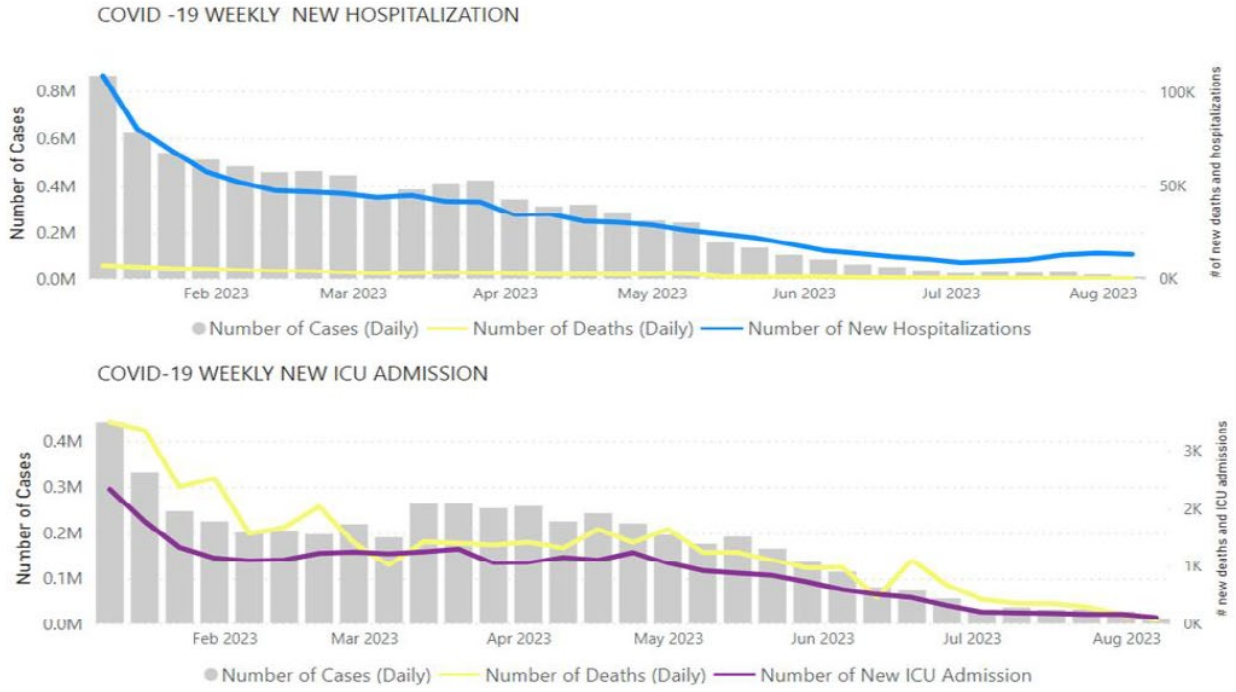

Figure 3. COVID-19 cases, deaths, hospitalizations, and ICU admissions reported weekly to WHO, as of 13 August 2023 (World Health Organization (WHO), 2023b)

Demographics of the population in the proposed indication and risk factors for COVID-19 in Europe

All age groups can acquire SARS-CoV-2 infection. During the first 3 months of the pandemic, the case notification rate was significantly higher among elderly populations however, currently the age distribution of the epidemic curve has begun to change because of vaccination programmes, with younger age groups (15-24 years old) now having the highest case notification rate, although cases of COVID-19 among individuals ≥ 65 years and older remain high. Figure 4 shows the case notification rates per 100,000 persons stratified by different age groups in the EU/EEA.

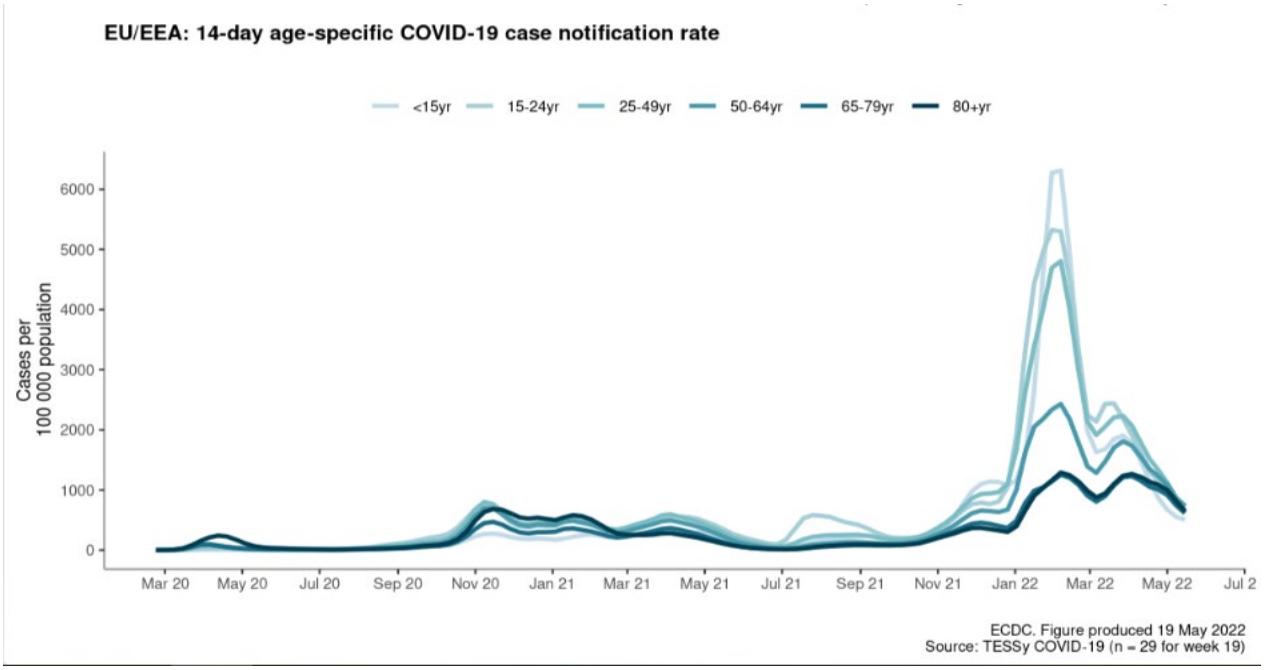

Figure 3. EU/EEA 14-Day Age-Specific COVID-19 Case Notification Rates (ECDC, 2022b)

Age is a very important predictor of severe COVID-19. The risk of severe outcomes increases sharply with increasing age, even after controlling for other potential confounding factors, including sex and underlying conditions (Bundle et al., 2021).

Individuals of both genders can acquire SARS-CoV-2 infection. Further sex-disaggregated data for COVID-19 in several European countries show a similar number of cases between the sexes, but more severe outcomes in aged men. Case fatality is highest in men with pre-existing cardiovascular conditions. The mechanisms accounting for the reduced case fatality rate in women are currently unclear (Gebhard *et al.*, 2020).

Important co-morbidities

Data pooled from 31 European countries and reported to The European Surveillance System (TESSy) have identified several underlying conditions that have a significant independent effect on severe COVID-19 outcomes. Severe disease is defined as admission to a hospital/intensive care unit (ICU), mechanical ventilation, or death. Severity of COVID-19 is associated with increased age, pre-existing medical conditions and the male sex. Underlying health conditions reported among adult patients with severe COVID-19 disease include diabetes, obesity, hypertension, history of heart failure, ischaemic heart disease, solid organ tumours, chronic obstructive pulmonary disease (COPD), chronic respiratory disease, chronic kidney disease, immune compromised status, cancer, neurological conditions, smoking, and pregnancy (ECDC, 2022c).

With regards to mortality among hospitalised COVID-19 cases, high-certainty evidence in age- and sex-adjusted analyses identified diabetes mellitus, renal disease and dementia as significant risk factors for mortality. Furthermore, there is moderate certainty evidence that ischaemic heart disease, stroke, solid organ tumours and obesity are also risk factors. Mortality among cases detected in the community setting is associated with a history of heart failure, stroke, diabetes, and end-stage renal disease. There is moderate to high certainty evidence of an association between hospitalisation for COVID-19 and diabetes, heart failure, COPD, renal disease, obesity, and ischaemic heart disease in the community setting (ECDC, 2022c).

Additionally, age is also an important effect modifier in the associations between certain underlying conditions and severe COVID-19 outcomes. While some pre-existing medical conditions are known risk factors for severe disease and ICU admission in all age groups, including children and adolescents, it is still not fully understood how these pre-existing conditions influence the course of COVID-19. The absolute probability of being hospitalised or dying increases with age, but findings indicate that a younger person with certain underlying conditions may have the same or even a higher probability of severe outcome than an older person without these conditions. Based on the analysis of 820,404 symptomatic paediatric cases reported by 10 EU Member States between August 2020 and October 2021, there is an increased risk of severe outcomes in cases with comorbidities such as cancer, diabetes, cardiac or lung disease. However, most (83.7%) hospitalised children had no reported comorbidity (Bundle *et al.*, 2021). This is relevant for age and risk-factor based prioritisation of vaccination, particularly among young people (ECDC, 2022c).

Vulnerable Groups

Residents of long-term care facilities are a medically and socially vulnerable group because of their increased age and the prevalence of underlying health conditions. Their social vulnerability can be exacerbated by non-pharmaceutical interventions against COVID-19 that limit physical personal interactions or affect access to health services, with consequences including feelings of abandonment and loneliness. All EU/EEA countries have experienced rapid increases in the incidence of outbreaks and fatal cases of COVID-19 in long-term care facilities. Outbreaks of COVID-19 among long-term care facilities residents have commonly spread rapidly, with high attack rates and high case fatality rates. This has been fuelled by the transmission dynamics of COVID-19, including the potential for asymptomatic transmission among and between staff and residents. Factors that have hampered the response to COVID-19 in long-term care facilities have included insufficient availability of personal protective equipment and of human resources; insufficient training in IPC, including use of personal protective equipment and case management, and reduced access to essential healthcare services (ECDC, 2022c).

The main existing treatment options

Approaches to dealing with the impact of the COVID-19 pandemic can be divided into two main approaches: (i) preventative measures designed to reduce transmission and/or severity by providing active immunity to infection and (ii) direct treatment measures to address the symptomology.

Preventative measures designed to reduce transmission and/or severity by providing active immunity to infection

During the 2021 European summer season, the incidence of SARS-CoV-2 declined in almost all EU/EEA countries and was at the lowest rate since September 2020. Some of the decline in SARS-CoV-2 incidence that has occurred since January 2021, combined with reductions in hospitalisations and deaths, particularly in older age groups, is attributed to COVID19 vaccines.

At the data lock point (DLP) of this risk management plan (RMP), seven vaccines have received approval by EMA (Table 1): Comirnaty (mRNA), Spikevax (mRNA), Jcovden (adenovirus), Vaxzevria (adenovirus), Nuvaxovid (recombinant protein, adjuvanted), COVID-19 Vaccine (inactivated, adjuvanted) Valneva and VidPrevtyn Beta (recombinant protein, adjuvanted). No further vaccines are currently under rolling review by the EMA.

Table 1. Approved COVID-19 vaccines

Vaccine	Description
Approved	
Comirnaty (developed by BioNTech and Pfizer)[2]	Single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.
Jcovden (previously COVID-19 Vaccine Janssen)[3]	Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein* (Ad26.COV2-S).
Spikevax (previously COVID-19 Vaccine Moderna)[4]	Single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.
Vaxzevria (previously COVID-19 Vaccine AstraZeneca)[5]	Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S).
Nuvaxovid (Novavax)[6]	SARS-CoV-2 spike protein (produced by recombinant DNA technology using a baculovirus expression system) adjuvanted with Matrix-M.
COVID-19 Vaccine (inactivated, adjuvanted) Valneva[7]	Inactivated SARS-CoV-2 virus, with two adjuvants.
VidPrevtyn Beta (Sanofi Pasteur)[8]	SARS-CoV-2 prefusion Spike delta TM protein, recombinant (B.1.351 strain).

[2] https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf
[3] https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf
[4] https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-epar-product-information_en.pdf
[5] https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf
[6] https://www.ema.europa.eu/en/documents/product-information/nuvaxovid-epar-product-information_en.pdf
[7] https://www.ema.europa.eu/en/news/ema-starts-rolling-review-valnevas-covid-19-vaccine-vla2001
[8] https://www.ema.europa.eu/en/documents/product-information/vidprevtyn-beta-epar-product-information_en.pdf

Importantly, evidence suggests that vaccine efficacy may wane over time (Gupta *et al.*, 2021; Keehner *et al.*, 2021; Naaber *et al.*, 2021; Thomas *et al.*, 2021) which may lead to a decline in immunity, which may occur at the level of the individual or at the population level, increasing the risk of serious disease, especially in vulnerable populations, as well as favouring the rise of breakthrough infections and the emergence of new VOCs (Dolgin, 2021; Juno *et al.*, 2021). This led to the proposal for a third "booster" dose for several of the approved vaccines as several studies supported the safety and immunogenicity of booster doses (Albach *et al.*, 2021; Bar-On *et al.*, 2021; Barda *et al.*, 2021; Mahase, 2021) (Figure 5). Initially a third dose was approved for the most vulnerable populations, but then was expanded to include all eligible adult individuals. In addition to this, several additional clinical studies have assessed heterologous vaccine approaches (i.e., mixing different vaccine brands or technology platforms in the primary sequence and/or as a booster to a different primary sequence) (Atmar *et al.*, 2021; Liu *et al.*, 2021; Nordstrom *et al.*, 2021; Sablerolles *et al.*, 2021).

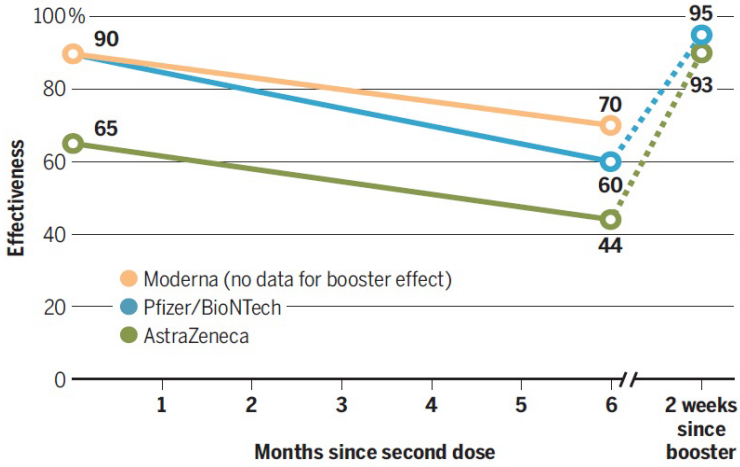

Figure 4. Vaccine effectiveness over time (Gupta *et al.*, 2021)
Two doses of messenger RNA (mRNA) or adenovirus vectored COVID-19 vaccines elicit high levels of protection from symptomatic disease, but this wanes over time. Emerging studies show that a third dose (booster) of the same type can restore effectiveness to >90%. Data are averages for Delta variant from multiple studies

As of 19 February 2023 (week 07, 2023), over 976 million vaccine doses have been administered in the EU/EEA, with around 331 million people having received a complete primary vaccination course, 248 million having received a first booster dose, 63.9 million having received a second booster dose and 5.9 million having already received a third booster dose. Since the start of COVID-19 vaccine deployment in December 2020 and as of 19 February 2023, the cumulative vaccine uptake in the total EU/EEA population has reached 73% (range: 30.0–86.4%) for the completed primary course and has been stable for several months, 54.7% for the first booster dose (range: 9.2–75.8%), 14.1% for the second booster dose (range: 0.2–33.6%) (pooled data from 30 reporting countries), and 1.7% (range: <0.1–9.5%) for the third booster dose (pooled data from 20 reporting countries). Among adults (aged 18 years and over) in the EU/EEA, the cumulative vaccine uptake has reached 82.4% (range: 35.2–96.4%) for the complete primary course, with no sign of further increase for several months, and 65.4% (range: 11.3–87.0%) for the first booster dose, increasing very slowly (pooled data from 30 reporting countries) (ECDC, 2023b).

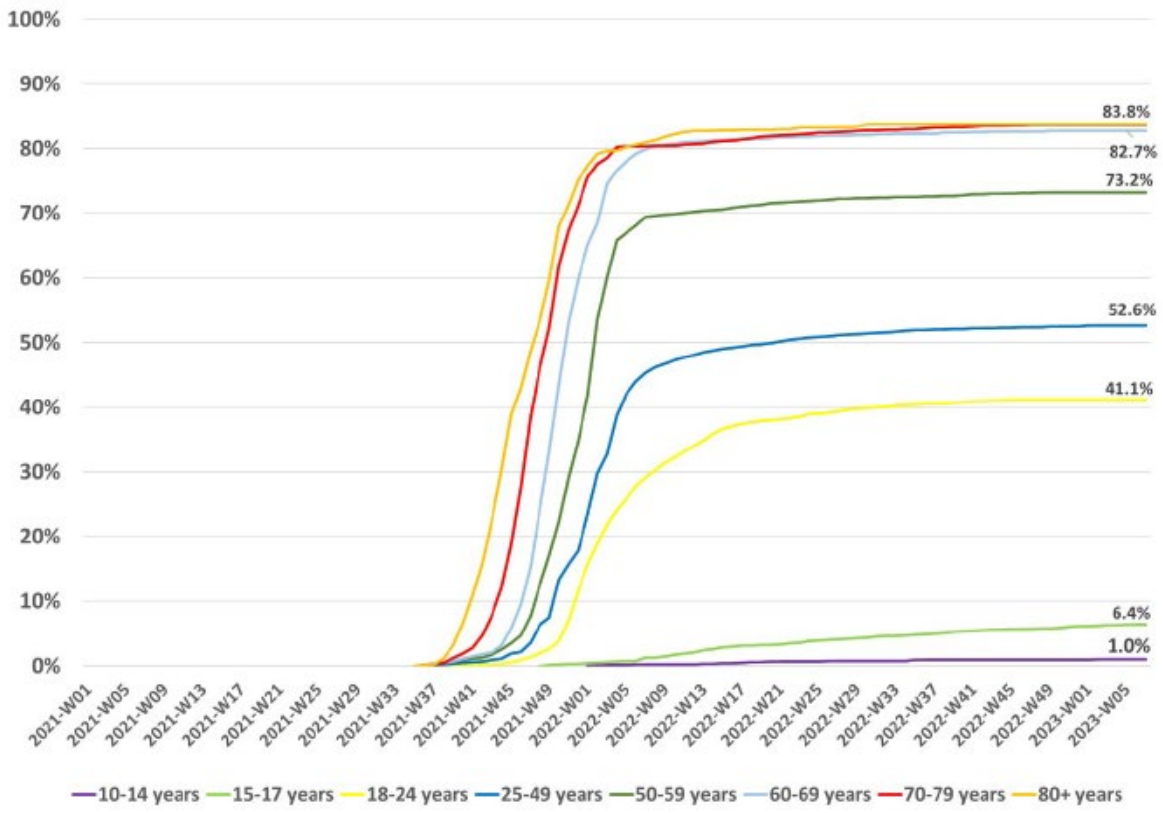

Figure 5. Median cumulative uptake of the first booster of COVID-19 vaccines by age group in the total population in the EU/EEA (as of 19 February 2023) (ECDC, 2023b)

Non-pharmaceutical interventions (NPI) are actions that people and communities take to help slowing down the spread of SARS-COV-2 (Flaxman *et al.*, 2020; Perra, 2021). Such community mitigation strategies range from individual actions such as good hand hygiene, appropriate use of face masks or physical distancing to more restrictive measures like limiting the size of gatherings or closure of schools and work offices. Contact tracing is a key tool for breaking transmission chains. Most NPI can have a negative impact on the general well-being of people, the functioning of society, and the economy (Muller *et al.*, 2021).

Direct treatment measures to address the symptomology

Treatment of confirmed SARS-CoV-2-positive individuals is based on severity of symptoms (Table 2). Coagulopathy is common in patients with severe COVID-19, and both venous and arterial thromboembolism have been reported (World Health Organization (WHO), 2023a).

Table 2. Recommended treatments for individuals with COVID-19 based on severity (World Health Organization (WHO), 2023a).

Severity	**Treatment**
Mild COVID-19	• Isolation to contain virus transmission. • Symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration. • Counselling of patients with mild COVID-19 about signs and symptoms of complications that should prompt urgent care. • Antibiotic therapy or prophylaxis should not be used
Moderate COVID-19	• Isolation to contain virus transmission. For patients at high risk for deterioration, isolation in hospital is preferred. • Use of pulse oximetry monitoring at home for symptomatic patients with COVID-19 and risk factors for progression to severe disease who are not hospitalised. • Antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection in patients with suspected or confirmed moderate COVID-19. • Close monitoring of patients with moderate COVID-19 for signs or symptoms of disease progression.
Severe COVID-19	• Immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target SpO_2 ≥ 94% and to any patient without emergency signs and hypoxaemia (i.e., stable hypoxaemic patient) to target SpO_2 > 90% or ≥ 92–95% in pregnant women. In adults, techniques such as positioning, e.g., high supported sitting, may help to optimize oxygenation, ease breathlessness and reduce energy expenditure. • Closely monitor patients for signs of clinical deterioration, such as rapidly progressive respiratory failure and shock. • Awake prone positioning of severely ill patients hospitalized with COVID-19 requiring supplemental oxygen (includes high flow nasal oxygen) or non-invasive ventilation. • Cautious fluid management in patients without tissue hypoperfusion and fluid responsiveness.

Severity	Treatment
Critical COVID-19: acute respiratory distress syndrome (ARDS)	• Prompt recognition of progressive acute hypoxemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy. • Equipment of health facilities with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces. • Endotracheal intubation performed by a trained and experienced provider using airborne precautions. • Implementation of mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 cmH_2O). In children, a lower level of plateau pressure (< 28 cmH_2O) is targeted, and a lower target of pH is permitted (7.15–7.30). Tidal volumes should be adapted to disease severity: 3–6 mL/kg PBW in the case of poor respiratory system compliance, and 5–8 mL/kg PBW with better preserved compliance. • Prone ventilation for 12–16 hours per day in adult patients with severe ARDS (PaO_2/FiO_2 < 150 mmHg). • Conservative fluid management strategy for ARDS patients without tissue hypoperfusion and fluid responsiveness. • In patients with moderate or severe ARDS, a trial of higher positive end-expiratory pressure (PEEP) instead of lower PEEP is suggested and requires consideration of benefits versus risks. • In patients with moderate-severe ARDS (PaO_2/FiO_2 < 150), neuromuscular blockade by continuous infusion should not be routinely used.
Critical COVID-19: septic shock	• Septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) ≥ 65 mmHg AND lactate is ≥ 2 mmol/L, in the absence of hypovolaemia. • Septic shock in children with any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or more of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnoea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia. • Resuscitation for septic shock in adults with 250–500 mL crystalloid fluid (including normal saline and Ringer's lactate) as rapid bolus in first 15–30 minutes. • Resuscitation for septic shock in children with 10–20 mL/kg crystalloid fluid as a bolus in the first 30–60 minutes. • Hypotonic crystalloids, starches or gelatins should not be used for resuscitation.

Severity	Treatment
	• Vasopressors are administered when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP ≥ 65 mmHg in adults and improvement of markers of perfusion. • In children, vasopressors are administered if signs of fluid overload are apparent or certain signs persist.

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

The transmission characteristics of SARS-CoV-2 are very similar to those of SARS-CoV and pandemic influenza (Viner *et al.*, 2020; Rahman *et al.*, 2021). SARS-CoV-2 presents a moderate to severe infectious threat with a mean R0 range of 2.24 to 3.58 (Rahman *et al.*, 2021). As a respiratory infectious disease, the virus is transmitted primarily by droplets, respiratory secretions, and direct contact although viral particles have been isolated from faecal swabs and blood. The incubation period on average is 1–14 days, however, is generally 3–7 days.

Presenting signs and symptoms of COVID-19 vary. Important factors for consideration include overall age of patient, comorbidities, vaccination status (including time after vaccination and waning immunity) and also the VOC responsible for the infection. Preliminary evidence suggests that infections with the Omicron VOC have a less severe clinical presentation than Delta VOC, for example, but more data are needed[9]. It is important to highlight that lower age, prior immunity from natural infection, vaccination including booster dose, and improved treatment options may contribute to observations of less severe outcomes and thus, the true risk of severe infection for the Omicron VOC may be underestimated.

According to a WHO summary (World Health Organization (WHO), 2023a), most adult persons experience fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), myalgias (11–35%). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported. Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported. Additional neurological manifestations reported include dizziness, agitation, weakness, seizures, or findings suggestive of stroke including trouble with speech or vision, sensory loss, or problems with balance in standing or walking. Older people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, confusion, and absence of fever.

In another European study published in September 2020, 1,420 patients with positive diagnosis of Covid-19 were recruited from 18 European hospitals. The most common symptoms were headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhoea (60.1%), gustatory dysfunction (54.2%) and sore throat (52.9%) and fever (45.4%) (Lechien *et al.*, 2020).

Patients with COVID-19 experience varying degrees of severity. Severity of COVID-19 based on WHO definitions is shown in Table 2. Some individuals may be asymptomatic, whereas around 80% of infected individuals have only mild infection (Viner *et al.*, 2020; Rahman *et al.*, 2021). In those patients that do become symptomatic, most people with COVID-19 develop only mild (40%) or moderate (40%) disease,

LINK https://www.ecdc.europa.eu/en/news-events/weekly-epidemiological-update-omicron-variant-concern-voc-week-2-data-20-january-2022 (Data as of January 20, 2022)

approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, ARDS, sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury (World Health Organization (WHO), 2023a). Importantly, asymptomatic subjects may have viral loads similar to those of symptomatic patients and are thus possible sources of infection. Of the remaining cases, approximately 15% develop severe disease characterised by dyspnoea, hypoxia, and lung changes on imaging, and 5% are critically ill. The critical ill often include elderly and those with underlying disorders who may experience acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and coagulation dysfunction, which may ultimately lead to multiple organ failure and even death. A small percentage of patients also manifest gastrointestinal symptoms, such as diarrhoea and vomiting. Overall, poor clinical outcomes among adult COVID-19 patients are associated with a higher comorbidity burden.

Based on early studies with the Wuhan strain, mild disease (no or mild pneumonia) was reported in 81% of cases, severe disease in 14%, critical disease in 5% with an overall case fatality rate of 2.3% with no deaths reported among noncritical cases (McKintosh, 2022). Among Omicron cases with known outcomes, 884 (1.14%) were hospitalised, 120 (0.16%) required ICU admission/respiratory support, and 48 (0.06%) died. The pattern of higher rates of hospitalisation, ICU admission, and death with increased age is apparent for Omicron cases, as it has been for Delta and previous variants[9]. Similarly, low hospital admission rates and case fatality for Omicron cases have been observed in some reports, whereas a shorter median length of hospital stay and/or significantly reduced need for respiratory support were also reported for Omicron, but more data are needed.

Post COVID-19 condition

In addition to the more "traditional" infection and symptom cycle described above, SARS-CoV-2 is also known to cause so-called "long COVID" or "post-COVID condition" which is generally defined as individuals with ongoing symptoms of COVID-19 that persist beyond four weeks from initial infection, last for at least 2 months and cannot be explained by an alternative diagnosis (Crook *et al.*, 2021; Davis *et al.*, 2021; World Health Organization (WHO), 2023a). Post-COVID-19 condition, has manifestations from multiple organ systems and its pathophysiology remains unclear and is most likely multifactorial. Fatigue, muscle or joint pain, breathlessness, and impaired sleep are common symptoms in adults and in children. Others include mental health effects including depression and anxiety, and neurological symptoms such as loss of smell and taste, headache, and difficulty in thinking or concentrating (also described as "brain fog"). These have considerable impact on patients' quality of life and well-being. Meta-analysis of 1.2 million records from 22 countries estimated that 6.2% of people with symptomatic SARS-CoV-2 infection developed post-COVID condition. Older age, female sex, being overweight or obese, smoking, pre-existing comorbidities, and severe COVID-19 including hospitalization or ICU admission are associated with increased risk of developing post-COVID condition, as per a systematic review and meta-analysis (World Health Organization (WHO), 2023a). SARS-CoV-2 vaccination was associated with a lower risk of post-COVID condition. The spectrum of presentation, pathophysiology, clinical course, diagnosis, and management of these conditions is under investigation. The following symptoms are considered to be the most common for long COVID: fatigue, dyspnoea, cough, sleep disturbances, anxiety, depression, cognitive impairment, and difficulty concentrating. Fatigue and concentration problems were noted to last beyond 12 weeks. The presence of post COVID-19 condition has been also reported in cohorts of children from several countries (ECDC, 2022a).

The prevalence of post-acute COVID-19 decreases over time since the acute presentation but it is not yet possible to determine how long the symptoms may persist (ECDC, 2022a).

SARS-CoV-2 Variants

Since the emergence of the pandemic situation, there are serious concerns about the emergence of new variants of the SARS-CoV-2 virus. Variants of concern (VOCs) were defined as those variants for which clear evidence is available indicating a significant impact on transmissibility, severity and/or immunity that is likely to have an impact on the epidemiological situation. Some of these variants have already been associated with higher transmissibility and decreased susceptibility to neutralisation by vaccine-induced antibodies compared to the parent strain, although the overall impact on vaccine effectiveness in preventing severe disease remains uncertain (Weisblum *et al.*, 2020; Gupta, 2021; Harvey *et al.*, 2021; Planas *et al.*, 2021).

As of March 2023, ECDC has de-escalated BA.2, BA.4 and BA.5 from its list of SARS-CoV-2 variants of concern (VOC), as these parental lineages are no longer circulating.

Variants of interest (VOI) are defined as those variants for which evidence is available on genomic properties, epidemiological evidence or in-vitro evidence that could imply a significant impact on transmissibility, severity and/or immunity, realistically having an impact on the epidemiological situation in the EU/EEA. However, the evidence is still preliminary or is associated with major uncertainty (Table 3). As of 10 August 2023, ECDC classified all XBB.1.5-like lineages with additional spike protein change F456L as variants of interest (VOI). This includes lineages EG.5, FL.1.5.1, XBB.1.16.6 and FE.1, among others. The reason for this classification is the rapid increase in proportion of these lineages in the EU/EEA, together with a slight increase in epidemiological indicators. These lineages are also increasing globally, with the World Health Organization (WHO) classifying EG.5, which is the most prevalent lineage within the group, as a VOI as of 9 August 2023, and the United Kingdom Health Security Agency (UKHSA) classifying EG.5.1 as a variant as of 31 July 2023. The reason ECDC is not singling out EG.5 within the group is that other 456L-lineages also exhibit elevated growth rates, and the likely source of the elevated growth rate is the F456L change itself.

Table 3. SARS-CoV2 variants of interest according to the European Centre for Disease Control (ECDC).

WHO label	Lineage + additional mutations	Country first detected	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	BA.2.75	India	(y)	May 2022	Unclear	Similar to Baseline	No evidence	Community
Omicron	XBB.1.5-like (a)	United States	N460KS486P F490S	n/a	Baseline	Baseline	Baseline	Dominant
Omicron	XBB.1.5-like + F456L (b) (e.g. EG.5, FL.1.5.1XBB. 1.16.6, and FE.1)	n/a	F456L N460KS486P F490S	n/a	Similar to Baseline	Increased	Similar to Baseline	Community

y: W152R, F157L, I210V, G257S, D339H, G446S, N460K, Q493 (reversion)

a: Monitoring an umbrella of SARS-CoV-2 lineages that have similar Spike protein profiles and characterised by a specific set of mutations (S:Q183E, S:F486P and S:F490S).

b: Monitoring an umbrella of SARS-CoV-2 lineages that have similar Spike protein profiles and characterised by a specific set of mutations (S:F456L, S:Q183E, S:F486P and S:F490S).

Based on https://www.ecdc.europa.eu/en/covid-19/variants-concern (access date 20/09/2023)

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

No risks have been identified in the non-clinical testing programme, and safety and toxicology data further support high tolerability and an excellent safety profile of the proposed dose and regimen for human use (i.e., 40 µg recombinant protein RBD fusion heterodimer / 0.5 mL dose).

At an initial stage of development, the antigen was a SARS-CoV-2 virus recombinant S protein RBD dimer with the sequence of the Wuhan strain. This antigen was also referred to as "RBD dimer". The vaccine containing the antigen **RBD dimer**-Wuhan strain, together with SBQA adjuvant was referred to as **PHH-1.** However, due to the quick spread of new variants around the world, HIPRA decided to develop a new antigen candidate (based on the same CHO cell platform technology) intended to confer protection against the new variants, and the PHH-1 vaccine was discontinued. The new antigen is the SARS-CoV-2 virus recombinant protein RBD fusion heterodimer - B.1.351-B.1.1.7 variants (beta and alpha variants), originally identified in South Africa and UK, respectively. Therefore, the vaccine containing the antigen **RBD fusion heterodimer** together with SBQA adjuvant corresponds to **PHH-1V**. Nonclinical studies used both types of antigens: initially RBD dimer (PHH-1), and later RBD fusion heterodimer (PHH-1V).

No single dose toxicology studies with PHH-1V vaccine have been performed or are planned. Instead, exposure obtained in the repeat-dose toxicity studies covers in excess the clinical posology for using BIMERVAX vaccine as a booster, as currently pursued, or as a prime-boost vaccine for naïve subjects.

The safety profile of PHH-1V vaccine was assessed by three GLP repeat dose toxicity studies: one with PHH-1 vaccine (same vaccine but with a Wuhan-strain antigen) in mice, and two with PHH-1V vaccine in rats and rabbits. These GLP studies evaluated the systemic toxicity of the vaccines when administered i.m. every two weeks for 29 days (Day 1, Day 15 Day 29), and included a recovery period of 4-weeks. The antigen dose tested in mice for PHH-1 vaccine was 50 µg, while in the studies with rats and rabbit with PHH-1V, the antigen dose was 40 µg. Additionally, the safety of PHH-1 and PHH-1V vaccines was preliminary assessed during the evaluation of the immunogenicity of these vaccine in mice, hamsters, pigs and NHPs, as well as in pilot non-GLP studies in mice and rabbits. These studies assessed different antigen doses up to 40 µg in the PHH-1V vaccine administered i.m. or SC. The main results of the GLP repeat dose toxicity studies are outlined below:

- The GLP toxicity study *AC25AA* in mice where PHH-1 vaccine was administered i.m. at an antigen dose of 50µg antigen in 0.1mL every two weeks for 29 days showed that PHH-1 vaccine caused local dermal reactions at the administration site for up to 24 hours and increased body temperature. There were no PHH-1-related effects on clinical signs, food consumption, body weight, functional observational battery (FOB) or clinical pathology. Histopathology analysis revealed slight test-item-induced effects in the lung, spleen, mesenteric lymph node, liver, and injection site, which were absent after the 4-week recovery period.
- A GLP repeat dose toxicity study in rats (*AC91AA*), where PHH-1V vaccine including 40 µg of antigen was administered i.m. to rats every two weeks for 29 days found that PHH-1V caused local dermal reactions at the administration site, which were mild and reversible. There were no effects on clinical signs, FOB, food consumption, body weight or clinical pathology. This study shows that PHH-1V is well tolerated in Sprague Dawley rats. There were no observations consistent with systemic toxicity, and local reactogenicity was of low magnitude.
- In the GLP toxicity study in rabbits, PHH-1V vaccine, including a dose of 40µg antigen, was administered every 2 weeks for 28 days. PHH-1V was locally and systemically well tolerated in

rabbits. As a general conclusion to the whole study, and based on general clinical signs, local reactions at the injection site, temperature, body weight, feed consumption, clinical haematology, biochemistry and coagulation data, macroscopic observation of tissues and microscopical findings, no adverse or toxicological effects have been identified in rabbits under the study conditions.

Specific studies assessing the toxicity of the SQBA adjuvant alone (without the antigen) were deemed not necessary considering the vast non-clinical and clinical data already available for this adjuvant. Moreover, nonclinical data for the SQBA adjuvant when combined with RBD dimer (PHH-1 vaccine) or RBD fusion heterodimer (PHH-1V vaccine) have been generated as part of the development of the final BIMERVAX vaccine. In this regard, the safety of the SQBA adjuvant is indeed supported by the good safety profile of the PHH-1 and PHH-1V vaccines in the above-described studies, including three GLP studies in mice, rats and rabbits.

Overall, these non-clinical studies support the high tolerability and an excellent safety profile of PHH-1V vaccine at antigen and adjuvant doses that are well above those to be used in human. Specifically, doses of antigens tested in mice, rat, rabbit and monkey are 176, 39, 10 and 4 times, respectively, higher than the proposed dose to be used in human, which is 40µg. Similarly, the adjuvant doses tested in mice, rat, rabbit and monkey are 28, 8, 10 and 4 times higher than the dose used in human, which is 250 µL. Moreover, the safety of PHH-1V was assessed in GLP studies after administration of 3 doses of vaccine at a frequency of one dose every 2 weeks. Both the number of doses and the frequency of administration are above those to be used in the clinical setting, where only one dose of PHH-1V, in the case of the intended booster indication, or 2 doses separated 21 days, in the case of a potential prime-boost indication, will be administered. In addition, no sex-dependent differences were observed in the safety profile of PHH-1 or PHH-1V vaccines.

No genotoxicity studies have been performed with BIMERVAX. No genotoxic potential is expected for the recombinant RBD fusion heterodimer antigen, as this type of substances would not interact directly with DNA or other chromosomal material. Also, the non-genotoxic potential of SQBA adjuvant has been demonstrated. Therefore, its genotoxicity is not expected, at least at the concentration used for BIMERVAX, which is the same as the concentration used in other currently approved vaccines.

No carcinogenicity studies have been conducted for BIMERVAX because the product is not to be administer chronically and the nature of its components raise no cause of concern.

The potential toxicity of PHH-1V on fertility and early embryonic development is being assessed in a GLP toxicology study (AE80AA) further evaluating the effect on embryofoetal and pre- and post-natal development in rats. This toxicology study is ongoing. Nevertheless, currently, an interim report is available providing fertility data of both males and females. Preliminary results included in this interim report demonstrate the good safety profile of PHH-1V as no mortalities have been detected and the body weight and local signs were similar between groups. No adverse effects on male and female fertility have been detected as the mating index is 100% and reproductive performance is equivalent between groups. No adverse effects of PHH-1V or its associated immune response were detected on embryofoetal or postnatal survival at the current date. Moreover, several aspects support the lack of concern regarding potential toxicity of BIMERVAX on fertility. Specifically, an assessment of male and female fertility by histopathological examination of the testis and ovaries in the GLP toxicity studies in mice (*AC25AA*), rat (*AC91AA*) and rabbit (*SEP-2021-011-PHH1V*) found no effect of PHH-1 or PHH-1V vaccines on these organs. Also, no effects on fertility have been described for the SQBA adjuvant at least at the dose to be used in BIMERVAX. Moreover, no effects on fertility have been associated to the development of

immunogenicity against SARS-CoV-2 during the development of other four COVID-19 vaccines currently approved (SmPC Comirnaty, 2021; SmPC COVID-19 Vaccine Janssen, 2021; SmPC Spikevax, 2021; SmPC Vaxzevria, 2021; SmPC Nuvaxovid, 2022).

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies[a]	Relevance to Human Usage
Pharmacology	
Challenge studies • No evidence of vaccine-elicited disease enhancement at doses up to 40 µg.	• Suggests low risk of vaccine-enhanced disease in humans; being investigated in CTs. Nevertheless, vaccine-enhanced disease reactions have been identified as a potential risk (see Module SVII)
Toxicity	
Injection site reactions: • Local dermal reactions at the administration site and increased body temperature were common and reversible or showed signs of reversibility at the end of the recovery period in nonclinical studies.	• In common with other vaccines, BIMERVAX administration has the potential to generate injection site reactions such as oedema and erythema at the injection sites.
Inflammation and immune activation: • The death of two treated animals after the third administration and of one female after the second administration could have been caused by drug-induced anaphylactic reaction.	• Anaphylactic reaction could be more linked to a species (mice)-specific immunological response than to a toxicological response, a hypothesis confirmed by the histopathology report.
Developmental and Reproductive Toxicity • No effects on male and female fertility, embryofoetal or postnatal survival have been detected for the PHH-1V in the GLP toxicology study (AE80AA). Moreover, no effects have been observed in the histopathological examination of the testis and ovaries in the GLP toxicity studies with PHH 1V. • No effects on fertility have been described for the SQBA adjuvant.	• No effects are expected in WOCBP, pregnant women or their offspring.

Genotoxicity • No genotoxicity studies have been performed. • The non-genotoxic potential of the SQBA adjuvant has been demonstrated in analogous adjuvants widely used in humans.	• No genotoxic potential is expected for as this type of substances would not interact directly with DNA or other chromosomal material.

[a] Safety pharmacology, genotoxicity, and carcinogenicity studies were not conducted, in accordance with 2005 EMA and WHO vaccine guidelines, as they are generally not considered necessary to support development and licensure of vaccines for infectious diseases (EMEA/CHMP/VEG/134716/2004, 2005; World Health Organization (WHO), 2005).

Part II: Module SIII - Clinical trial exposure

At the DLP of this RMP, the clinical development plan includes two ongoing studies in Europe (HIPRA-HH-2 and HIPRA-HH-4), one completed supportive study in Asia (HAN-01) and three completed studies in Europe (HIPRA-HH-10, HIPRA-HH-5 and HIPRA-HH-1).

- The FIH clinical trial with BIMERVAX, already completed in Spain (Short Term Interim Analysis Report, 07-April-2022; Final CSR, 31-March-2023), was Phase I/IIa clinical study HIPRA-HH-1 (EudraCT: 2021-001411-82) approved in August 2021 by the Spanish national competent authority (NCA), AEMPS. It was a randomised, controlled, observer-blinded, dose-escalation, multicentre clinical trial to evaluate safety and immunogenicity of COVID-19 HIPRA vaccine in adult healthy volunteers. Results showed that HIPRA vaccine presented a very good safety and tolerability profile together with a high degree of immunogenicity in healthy adults when compared with a commercial vaccine. The risk-benefit assessment favoured the selection of the 40 µg dose level for its use in phase II trials.
- The Phase IIb clinical study HIPRA-HH-2 (EudraCT: 2021-005226-26) is an on-going (interim data are available; Interim Analysis Report, 18-May-2022; 6 months Interim Report, 28 Sep-2022, safety data not updated). It was approved in Spain in November 2021 and is a double-blind, randomised, active controlled, multi-centre, non-inferiority trial to assess immunogenicity and safety of a booster vaccination with BIMERVAX (PHH-1V) against SARS-CoV-2, in healthy adult volunteers fully vaccinated against COVID 19 followed by an extension period to study a fourth dose administration of PHH-1V.
- The Phase III study HIPRA-HH-5 (EudraCT: 2022-000074-25) is a completed study (interim data are available; Interim Analysis Report, 24 May 2022; CSR submission on 27 October 2023). It was approved in Spain in February 2022 and was an open-label trial, single-arm, multi-centre, international trial to assess the safety and immunogenicity of a booster vaccination with BIMERVAX against SARS-CoV-2, in adults vaccinated against COVID-19. Vaccination with BIMERVAX was overall well tolerated with a good safety profile. No relevant differences in the safety profile were observed regardless of the primary vaccination schedule received or a previous COVID-19 infection.
- The Phase IIb study HIPRA-HH-10 (EudraCT: 2022-000795-19) is also a completed study (Interim Analysis Report, 13-May-2022, CSR submitted on 28 July 2023). It was approved in Spain 8 March 2022 and was a double-blind, randomized, active controlled, multi-centre, non-inferiority trial to assess immunogenicity and safety of a booster vaccination with a recombinant protein RBD fusion dimer candidate (PHH-1V) against SARS-COV-2, in adults fully vaccinated

with adenovirus vaccine against COVID-19. BIMERVAX was well tolerated throughout the study and a good safety profile was observed.

- The Phase IIb/III study HIPRA-HH-4 (EudraCT: 2022-000785-18) is ongoing (no interim data available yet). It was approved in Spain 9 May 2022 and is an open label, single arm, multi-centre, trial to assess the immunogenicity and safety of an additional dose vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults with pre-existing immunosuppressive conditions vaccinated against COVID-19. In Turkey it was approved on 28 October 2022. Recruitment in Turkey is ongoing.
- The supportive study HAN-01 is a completed phase IIb clinical trial (Interim Analysis Report, 7-Apr-2022; CSR submitted on 14 July 2023). It was approved in Asia (Vietnam) in November 2021 and was a randomised, controlled, observer-blinded clinical trial to evaluate safety and immunogenicity of BIMERVAX compared with Pfizer–BioNTech (Comirnaty) vaccine in adult healthy volunteers. Overall, the observations demonstrated that BIMERVAX was well tolerated providing a good safety profile when two doses are administered 21 days apart.

Currently more than 3000 participants have been exposed to a single booster dose of 40 µg of PHH-1V after receiving a primary sequence of an approved COVID-19 vaccine 182 days previously. Overall extent of exposure of the CDP is provided in Table SIII.1.

This safety population represents the safety population as per the proposed clinical use and posology of PHH-1V as a booster vaccine.

This data in the intended clinical use population is supplemented by supporting data in 138 naïve individuals who received two doses of 40 µg as a primary sequence (i.e., the same clinical dose level, but with one administration more, and without underlying primary sequence vaccination received at least 182 days previously), as well as an additional 15 participants who received two administrations at lower dose levels without underlying primary vaccination (10 or 20 µg per dose).

Table SIII.1. Overall extent of exposure in the PHH-1V clinical development plan

Product and Dose level	# of doses	HIPRA-HH-1 Phase I/IIa	HIPRA-HH-2 Phase IIb	HIPRA-HH-5 Phase III	HIPRA-HH-10 Phase IIb	HAN-01 Phase IIb	HIPRA-HH-4 Phase IIb/III[2]	TOTAL
PHH-1V 10 µg	Two[1]	5	-	-	-	-	-	5
PHH-1V 20 µg	Two[1]	10	-	-	-	-	-	10
PHH-1V 40 µg	One (booster)	-	513	2661	18	-	400	3592
	Two[1]	10	-	-	-	128[3]	-	138
Comirnaty 30 µg mRNA	One (booster)	-	252	-	8	-	-	260
	Two[1]	5	-	-	-	128[4]	-	133

[1] Two doses administered as a homologous prime-boost sequence in naïve participants
[2] Planned exposure
[3] Out of the 128 participants that received a first dose, 121 received a second dose as a primary course vaccination
[4] Out of the 128 participants that received a first dose, 124 received a second dose as a primary course vaccination

Exposure of individual studies, where currently known. In the clinical trial Phase I/IIa (HIPRA-HH-1), there were 51 screened subjects and 30 randomised. All randomised subjects received the PHH-1V vaccine and are included in the Safety Population.

In the Phase IIb study (HIPRA-HH-2; Interim report HIPRA-HH-2) the safety analysis included 765 subjects that received a dose of the study vaccine: 513 subjects that received the PHH-1V vaccine and 252 that received the Comirnaty vaccine.

In the Phase III study clinical trial HIPRA-HH-5, 2661 participants received the booster dose of 40 µg of PHH-1V.

In the HAN-01 study there were 629 screened subjects and 256 randomized (128 in the vaccine group 1 [PHH-1V] and 128 in the vaccine group 2 [Comirnaty]). All selected subjects were included in the Safety population into one of the 2 groups. Finally, 121 participants received the second dose in Group 1 (PHH-1V) and 124 participants received the second dose in group 2 (Comirnaty).

Recruitment for HIPRA-HH-4 is ongoing and no exposure data for this study is currently available.

In the Phase IIb HIPRA-HH-10, recruitment was closed with 26 participants vaccinated. A total of 18 subjects received the PHH-1V vaccine, and 8 subjects received the Comirnaty vaccine.

Table SIII.2 presents the age group and gender information of the clinical trial population, and Table SIII.3 the race information. For individual studies, the treatment groups were well-matched for demographic characteristics with no relevant differences between treatment groups, except for the ethnicity, that includes different percentages of race sub-populations in each study based on where the study was conducted. Both male and female participants were included in approximately equal proportions.

Table SIII.2. Extent of exposure according age group and gender of the evaluated safety population from the clinical development plan of PHH-1V

Variable	Category	HIPRA-HH-1				HIPRA-HH-2		HAN-01		HIPRA-HH-5	HIPRA-HH-10	
		PHH-1V (10 µg)	PHH-1V (20 µg)	PHH-1V (40 µg)	Comirnaty (30 µg)	PHH-1V (40 µg)	Comirnaty (30 µg)	PHH-1V (40 µg)	Comirnaty (30 µg)	PHH-1V (40 µg)	PHH-1V (40 µg)	Comirnaty (30 µg)
n		5	10	10	5	513	252	128	128	2661	18	8
Age	Mean (SD)	30.20 (8.23)	27.90 (3.87)	26.00 (4.40)	28.40 (3.78)	42.1 (14.55)	41.6 (14.97)	45.6 (8.5)	45.6 (9.6)	34.4 (12.74)	44.5 (13.52)	47.6 (11.92)
	<18 years	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (1.35%)	0 (0.0%)	0 (0.0%)
	18 – <65 years	5 (100.0%)	10 (100.0%)	10 (100.0 %)	5 (100.0%)	475 (92.6%)	234 (92.9%)	128 (100.0%)	128 (100.0%)	2589 (97.85%)	17 (94.4%)	7 (87.5%)
	≥65 years	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	38 (7.4%)	18 (7.1%)	0 (0.0%)	0 (0.0%)	21 (0.79%)	1 (5.6%)	1 (12.5%)
Sex[1]	Male	4 (80.0%)	4 (40.0%)	6 (60.0%)	3 (60.0%)	188 (36.6%)	93 (36.9%)	49 (38.3%)	55 (43.0%)	1388 (52.2%)	14 (77.8%)	4 (50.0%)
	Female	1 (20.0%)	6 (60.0%)	4 (40.0%)	2 (40.0%)	325 (63.4%)	159 (63.1%)	79 (61.7%)	73 (57.0%)	1272 (47.8%)	4 (22.2%)	4 (50.0%)

Table shows values as mean (SD) for the continuous variables and n (%) for the categorical variables.
[1] In study HIPRA-HH-5, there was 1 participant with undifferentiated sex.

Table SIII.3. Extent of exposure according to race of the evaluated safety population from the clinical development plan of PHH-1V

Variable	Category	HIPRA-HH-1				HIPRA-HH-2		HAN-01		HIPRA-HH-5	HIPRA-HH-10	
		PHH-1V (10 µg)	PHH-1V (20 µg)	PHH-1V (40 µg)	Comirnaty (30 µg)	PHH-1V (40 µg)	Comirnaty (30 µg)	PHH-1V (40 µg)	Comirnaty (30 µg)	PHH-1V (40 µg)	PHH-1V (40 µg)	Comirnaty (30 µg)
n		5	10	10	5	513	252	128	128	2661	18	8
Race	Hispanic /Caucasian	5 (100.0%)	10 (100.0%)	9 (90.0%)	5 (100.0%)	505 (98.4%)	250 (99.%)	0 (0.0%)	0 (0.0%)	2633 (98.9%)	18 (100.0%)	8 (100.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.8%)	1 (0.4%)	128 (100.0%)	128 (100.0%)	2 (0.001%)	0 (0.0%)	0 (0.0%)
	American indian or alaska native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (0.3%)	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	2 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	19 (0.7%)	0 (0.0%)	0 (0.0%)

Table shows values as mean (SD) for the continuous variables and n (%) for the categorical variables.

Exposure to the Adjuvant

The SQBA adjuvant is an oil-in-water emulsion produced by HIPRA, and its qualitative and quantitative composition (9.75 mg squalene; 1.175 mg polysorbate-80; 1.175 mg sorbitan trioleate; 0.66 mg sodium citrate and 0.04 mg citric acid monohydrate) is identical to that used in other marketed vaccines in EU.

Overall, more than 30,000 individuals have participated in clinical trials of SQBA adjuvanted vaccines conducted by other MAH and more than 160 million doses of licensed vaccine have been administered using adjuvants with the same composition as SQBA. Safety and effectiveness data from clinical trials and observation studies attest to the safety of SQBA analogous adjuvants and to its ability to enhance the effectiveness of widely used vaccines in children and the elderly.

Therefore, based on the wide clinical experience using SQBA analogous adjuvants widely used in humans, in identical composition and concentration, no safety concerns are expected from its inclusion in the formulation of BIMERVAX.

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 inclusion and exclusion criteria for clinical studies are provided in the individual Clinical Study Reports (CSRs). The following exclusion criteria are based on the pivotal clinical studies whose results are available at the DLP of this RMP (HIPRA-HH-1, HIPRA-HH-2 and HIPRA-HH-5).

Table SIV.1: Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
Pregnant or lactating or intending to become pregnant or plans to breastfeed during the study.	Clinical development generally does not initially investigate benefit/risk in pregnant women.	Yes	Not applicable.
Any medical disease (acute, subacute, intermittent, or chronic) or condition that in the opinion of the Investigator compromises the subject's safety, preclude vaccination or compromises interpretation of the results.	Allowance of these conditions would confound assessment of safety	No	It is common medical practice to not administer vaccines in patients with disease or conditions that in the opinion of the investigator compromise the volunteer's safety, preclude vaccination or compromise interpretation of the results.
Ongoing serious psychiatric condition likely to affect participation in the study.	Participants with serious psychiatric condition are considered less likely to comply with study procedures and complete the long-term safety follow-up required by the study protocols.	No	Patients with ongoing severe depression, recent suicidal ideation, bipolar disorder, personality disorder, alcohol and drug dependency, severe eating disorder, psychosis, use of mood stabilisers or antipsychotic medication, are considered less likely to comply with the study requirements.
History of respiratory disease requiring daily medications currently or any treatment of respiratory disease exacerbations in the last 6 months.	Allowance of these conditions would confound assessment of safety.	Yes	Not applicable
History of significant cardiovascular disease or history of myocarditis or pericarditis as an adult.	Allowance of these conditions would confound assessment of safety.	Yes	Not applicable
History of neurological or neurodevelopmental conditions.	Allowance of these conditions would confound assessment of safety.	Yes	Not applicable
Ongoing malignancy or recent diagnosis of malignancy in the last five years.	Allowance of these conditions would confound assessment of efficacy.	No	It is common medical practice to not administer vaccines in patients with disease or conditions that in the opinion of the investigator compromise the volunteer's safety, preclude vaccination or compromise interpretation of the results.
Any confirmed or suspected autoimmune, immunosuppressive or immunodeficiency	Allowance of these conditions would	Yes	Not applicable

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
disease/condition (iatrogenic or congenital), including human immunodeficiency virus (HIV) infection, asplenia, or recurrent severe infections.	confound assessment of efficacy.		
History of hypersensitivity or severe allergic reactions, including anaphylaxis, generalised urticarial, angioedema and other significant reactions related to food, drugs, vaccines, or pharmaceutical agents, which are likely to be exacerbated by any component of the BIMERVAX.	Participants with medical history significant for allergic reactions are at increased risk for hypersensitivity reactions when receiving vaccines.	No	It is common medical practice to not administer a new vaccine in participants who have history of significant allergic reactions, including anaphylaxis, generalised urticarial, angioedema and other significant reactions related to food, drugs, vaccines, or pharmaceutical agents.
Use of any immunosuppressant, glucocorticoids, or other immune-modifying drugs within 2 months before Day 0; or anticipation of the need for immunosuppressive treatment within 182 days after vaccination (Day 0).	Allowance of these conditions would confound assessment of efficacy.	Yes	Not applicable
Received immunoglobulin, blood-derived products, or other immunosuppressant drugs within 90 days before vaccination (Day 0).	Allowance of these conditions would confound assessment of efficacy.	Yes	Not applicable
Known disturbance of coagulation; bleeding disorder (iatrogenic or congenital), blood dyscrasias, or prior history of significant bleeding or bruising following intramuscular (IM) injections or venepuncture.	Participants have a potential risk of hematoma due to the puncture of the deep tissues. Allowance of these conditions would confound assessment of safety.	No	It is common medical practice to not administer a product by the intramuscular route in participants with coagulopathy or bleeding disorders although the use of a needle with proper gauge can decreased the risk.
Suspected or known current alcohol abuse or any other substances abuse (except tobacco).	Participants with drug or alcohol abuse or drug addiction are considered less likely to comply with study procedures and complete the long-term safety follow-up required by the study protocols.	No	While these participants were to be excluded per protocol, participants are not always forthcoming regarding this aspect of their medical history, and it is assumed that a not inconsequential number were actually enrolled.

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
History of COVID-19 infection or close contact with anyone known to have SARS-CoV-2 infection within 15 days before Screening.	Allowance of this condition would confound assessment of safety and efficacy. Individuals with a history of non-severe COVID-19 infection were allowed in HIPRA-HH-5 if passed at least 30 days before study start.	No	Because these participants may have some degree of protection from subsequent infection by SARS-CoV-2 and therefore would confound the pivotal efficacy endpoint.
Paediatric population	Clinical development programmes generally investigate first the benefit risk in adults. In adults, the risk of symptomatic and severe COVID-19 usually is higher.	No	A paediatric investigation plan has been submitted on 21 February 2022 and is under ongoing review by the Agency.
Participant received or plans to receive other vaccines within 4 weeks before or after receiving any study vaccine.	Allowance of these conditions would confound assessment of safety and efficacy.	Yes	Interaction with other vaccines is included as missing information.
Subject has a life expectancy of less than 12 months	Allowance of these conditions would confound assessment of safety.	No	Not applicable. Long-term safety is included as missing information.

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

Rare Adverse Drug Reactions

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

BIMERVAX is intended as a booster for individuals previously vaccinated with mRNA vaccines. At the time of initiating Clinical Studies, there was limited exposure to COVID-19 mRNA vaccines in some special populations and no epidemiologic studies have been conducted in pregnant/breastfeeding women, paediatric participants (<18 years of age), and specific subpopulations that were excluded from the clinical development program. Limitations are based on the pivotal clinical studies whose results are available at the DLP of this RMP (HIPRA-HH-1, HIPRA-HH-2 and HIPRA-HH-5).

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Pregnant and breastfeeding women were excluded from the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients with hepatic, renal and cardiovascular or impairment were not specifically included in the clinical development programme. Immunocompromised patients safety and tolerability will be evaluated in the post authorisation HIPRA-HH-4 study.
Population with relevant different ethnic origin	Refer to Table SIII.3 for exposure information by ethnic origin from the studies
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Paediatric population	The safety and effectiveness in children and adolescents have not yet been established.
Elderly population	Participants over 65 years of age are included in the ongoing HIPRA-HH-2 study and the completed HIPRA-HH-5 and HIPRA-HH-10 studies. Refer to Table SIII.2 for exposure information by elderly population from the study.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

BIMERVAX is indicated as a booster for active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA COVID-19 vaccine. In March 2023, the European Commission granted Marketing Authorisation of BIMERVAX vaccine for use in the European Union. Later, on 31 July 2023, it was approved in United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA).

Post-authorisation exposure in the European Union from launch and up to 30 August 2023 is presented below.

SV.1.1 Method used to calculate exposure

BIMERVAX is to be procured and distributed through the Governments. Therefore, the estimate on the number of administered doses is based on information retrieved from official governmental websites.

Post-marketing data by age group or gender is not available. For this reason, BIMERVAX exposure described in this section is an estimation with some uncertainties regarding the lack of exposure information publicly available.

SV.1.2 Exposure

As of DLP of this RMP, 3.2 million doses have been distributed to the Spanish Government, no more doses have been distributed in any other country. The first units of BIMERVAX were distributed to the Spanish territory on 14 June 2023

According to the Ministry of Health of the Spanish government (https://www.sanidad.gob.es/areas/alertasEmergenciasSanitarias/alertasActuales/nCov/pbiVacunacion.htm; accessed on 06 September 2023), as of date 30 June 2023, there were 26,566,506 people with booster doses in Spain. No most up-to-date data were publicly available. As of date 28 April 2023, there were 26,553,194 people with booster doses in Spain, which results in 13,312 doses administered throughout this period and an average of 6,656 booster doses of COVID-19 vaccines being administered per month. Considering that the vaccination rate with BIMERVAX during this period is estimated to be very low and that the first units of BIMERVAX were distributed to the Spanish territory on 14 June 2023, until the DLP of this RMP (30 August 2023), it is estimated that a total of 165 doses of BIMERVAX might have been administered.

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

Potential for misuse for illegal purposes

COVID-19 vaccines do not have characteristics that would make it attractive for misuse or for illegal purposes. Therefore, the potential for misuse and/or counterfeit of COVID-19 vaccines is considered unlikely.

Part II: Module SVII - Identified and potential risks

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

All safety data available from the BIMERVAX clinical development programme have been evaluated in order to formulate the important safety concerns described within this RMP.

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

Not all adverse reactions for the vaccine are considered to meet the level of importance/severity compared to the condition to be prevented necessitating inclusion in the list of safety concerns in the RMP.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- Risks with minimal and temporary clinical impact on patients (in relation to the severity of the disease prevented):
  - Injection site local sensitivity, injection site pain and tenderness, injection site erythema or redness, and injection site induration or swelling.
  - Fever
  - Fatigue or tiredness
  - Headache
  - Myalgia or muscle pain
  - Nausea
  - Diarrhoea

Further considerations for COVID-19 vaccines

Reactogenicity (local and systemic)

In accordance with the European Medicines Agency (EMA) requirements (coreRMP19 guidance), the reactogenicity profile of COVID-19 vaccine (adjuvanted) HIPRA, available from the BIMERVAX vaccine clinical development, is described below for local and systemic reactions. Further analysis including observed differences between ages (younger and older groups) and after the first and second injections are still ongoing.

Phase I/IIa clinical study HIPRA-HH-1

All of solicited local adverse reactions (ADRs) were considered risks with minimal and temporary clinical impact (Grade 1 and 2 severity) on the participants. There were no solicited adverse events with grade 3 or 4 during the Phase I/IIa clinical study HIPRA-HH-1 (Phase I/IIa HIPRA-HH-1 study is still ongoing, only Short Term report safety results are available at the DLP of this RMP). The ADRs identified during the clinical development program include solicited local ADRs at the injection site including pain, local sensitivity, erythema or redness, induration or swelling. Systemic ADRs reported included fever, vomiting or nausea, diarrhoea, headache, fatigue or tiredness, myalgia or muscle pain.

Local Adverse Reactions: The most frequent solicited local AEs after the first and second dose of either vaccine were pain at the injection site (70% subjects dosed with 40 µg PHH-1V versus 100% subjects dosed with Comirnaty), local sensitivity (80% both in subjects dosed with 40 µg PHH-1V and Comirnaty), erythema/redness (10% subjects dosed with 40 µg PHH-1V versus 0% subjects dosed with Comirnaty) and induration/swelling (10% of subjects dosed with 40 µg PHH-1V versus 0% subjects dosed with Comirnaty). All these local AEs were of low intensity (Grade 1 or 2, mild to moderate) and a clear antigen dose-effect was not observed.

Systemic Adverse Reactions:

The most frequent solicited systemic AEs were headache (50% subjects dosed with 40 µg PHH-1V versus 60% subjects dosed with Comirnaty), fatigue (40% subjects dosed with 40 µg PHH-1V versus 40% subjects dosed with Comirnaty), myalgia (10% subjects dosed with 40 µg PHH-1V versus 40% subjects dosed with Comirnaty), and diarrhoea (10% subjects dosed with 40 µg PHH-1V versus 0% subjects dosed with Comirnaty). All were of mild intensity, except headache which was moderate in one subject dosed with 40 µg PHH-1V. Other systemic AEs appeared at a lower frequency. Fever was observed in 3 out of 5 (60%) of subjects vaccinated with Comirnaty after the administration of the second dose, however it was not observed in any of the subjects vaccinated with BIMERVAX. Grade 2 headache, fatigue and myalgia appeared with a lower frequency in subjects vaccinated with BIMERVAX at any tested antigen dose than in subjects vaccinated with Comirnaty.

Overall, in terms of frequency of systemic AEs, BIMERVAX has demonstrated a safety profile. A lower grade of systemic AEs was observed with BIMERVAX compared to Comirnaty.

Phase IIb clinical study HIPRA-HH-2

Most (89%) of solicited local adverse reactions (ADRs) were considered risks with minimal and temporary clinical impact (Grade 1 and 2 severity) on the participants. The ADRs identified during the clinical development program include solicited local ADRs at the injection site including pain, local sensitivity, erythema or redness, induration or swelling. Systemic ADRs reported included fever, vomiting or nausea, diarrhoea, headache, fatigue or tiredness, myalgia or muscle pain.

Local Adverse Reactions: the most frequent solicited local AEs were pain and tenderness, with 75.2% of subjects experiencing pain and 65.1% of subjects experiencing tenderness on Day 0, 12 hours and decreasing to 1.2% and 1.4%, respectively, on Day 7. The percentage of subjects who reported solicited local reactions of pain and tenderness from Day 0, 12 hours to Day 7 were higher in the Comirnaty vaccine arm compared to the PHH-1V vaccine arm. This is shown predominantly on Day 1 when 69.8% of subjects reported pain and 63.5% of subjects reported tenderness in the Comirnaty vaccine arm, however, only 51.1% of subjects reported pain and 48.5% of subjects reported tenderness in the PHH-1V vaccine arm.

Systemic Adverse Reactions: the most frequent solicited systemic AEs were fatigue (16.9% on Day 0, 12 hours, 22.4% on Day 1, 9.4% on Day 2, 5.5% on Day 3, 3.8% on Day 4, 3.0% on Day 5, 2.5% on Day 6, Day 1.6% on Day 7). Fatigue was reported more frequently in the Comirnaty vaccine arm on Day 0, 12 hours (18.7%), Day 1 (35.3%), and Day 2 (13.1%) compared to the PHH-1V vaccine arm (16.0%, 16.0%, and 7.6%, respectively). Other frequently reported solicited systemic adverse events included headache and muscle pain. Overall, both events increased in frequency from Day 0, 12 hours (headache: 15.7%, muscle pain: 12.4%) to Day 1 (headache: 18.7%, muscle pain: 17.5%) then decreased on Day 2 (headache: 8.2%, muscle pain: 7.7%) through to Day 7 (headache: 3.4%, muscle pain: 1.0%). In general, the frequency of solicited systemic adverse events were similar in the PHH-1V vaccine arm and Comirnaty vaccine arm up to 7 days post vaccination. However, in the first days after vaccination the frequency was higher in the Comirnaty arm.

Phase III clinical study HIPRA-HH-5

Most (84%) of solicited local adverse reactions (ADRs) were considered risks with minimal and temporary clinical impact (Grade 1 and 2 severity) on the participants. The most frequently reported types of ADRs were injection site pain (82%) and fatigue (31.25%). Other frequently reported ADRs were headache (30.88%), diarrhoea (7.75%) and vomiting (5.93%).

Local Adverse Reactions: The most frequently reported solicited local reactions from Day 0 to Day 7 were pain and tenderness, with 63.64% of subjects experiencing pain and 56.92% of subjects experiencing tenderness on Day 0 and decreasing to 1.25% and 1.40%, respectively, on Day 7.

Systemic Adverse Reactions: The most frequently reported solicited systemic event from Day 0 through to Day 7 was fatigue. Overall, the percentage of subjects who reported experiencing fatigue was 17.27% on Day 0, 19.58% on Day 1, 10.70% on Day 2, 6.08% on Day 3, 4.65% on Day 4, 4.57% on Day 5, 3.82% on Day 6, and 2.87% on Day 7. Other frequently reported solicited systemic events from Day 0 through to Day 7 included headache and muscle pain. Overall, both events increased in frequency from Day 0 (headache: 14.10%, muscle pain: 11.00%) to Day 1 (headache: 17.35%, muscle pain: 13.23%) then decreased on Day 2 (headache: 8.69%, muscle pain: 7.26%) through to Day 7 (headache: 2.87%, muscle pain: 1.89%).

Aspects of the formulation

SQBA adjuvant:

BIMERVAX with SQBA adjuvant is currently being evaluated in 5 ongoing clinical trials. The SQBA adjuvant is an oil-in-water emulsion produced by HIPRA and its qualitative and quantitative composition (9.75 mg squalene; 1.175 mg polysorbate-80; 1.175 mg sorbitan trioleate; 0.66 mg sodium citrate and 0.04 mg citric acid monohydrate) is identical to that used in other currently marketed vaccines in EU. Adjuvant fraction in BIMERVAX represents about a 50 % v/v of its final composition.

More than 30,000 individuals have participated in clinical trials of analogous SQBA adjuvanted vaccines conducted by other MAHs and more than 160 million doses of licensed vaccine have been administered.

Therefore, based on the wide clinical experience using the SQBA adjuvant in identical composition and concentration, no safety concerns are expected from its inclusion in the formulation of BIMERVAX. Additionally, analogous adjuvants have shown excellent compatibility with a variety of subunits antigens, all of which have been formulated by a simple mixing of antigen with the adjuvant. So, no significant interaction between the adjuvant and the antigen is expected.

In conclusion, based on the wide clinical available experience using analogous adjuvants, in identical composition and concentration, no safety concerns can be expected from its inclusion in the formulation of BIMERVAX.

Adverse Events of Special Interest

The HIPRA List of AESI is drawn from efforts by regulatory authorities, internationally recognized collaborations, and the scientific literature to identify AESI for vaccinations, and COVID-19 vaccinations specifically. BIMERVAX list of AESIs is provided in Annex 7.

Relevance of long-term follow-up

Given the expedited nature of the BIMERVAX clinical development programme in response to the global COVID-19 pandemic, understanding of the long-term safety profile of BIMERVAX is currently limited. Consequently, while there is no scientific evidence to suspect an adverse long-term safety profile, it is recognised that further follow-up for all vaccines developed in response to the COVID-19 pandemic is required.

In the ongoing clinical studies, it is planned to follow all participants contributing to safety pool for up to 48 weeks in Phase I/IIa clinical study HIPRA-HH-1, up to 52 weeks after booster vaccination of Day 0 in the Phase IIb clinical study HIPRA-HH-2 and up to 26 weeks for the fourth dose, up to 52 weeks in the Phase IIb/III study HIPRA-HH-4 and up to 24 weeks in the supportive Phase IIb study HAN-01.

Risks of vaccination errors in the context of mass vaccination campaigns

As BIMERVAX may be administered in large-scale vaccination programmes, there may be a potential for vaccination errors. Vaccination errors may relate to administration, vaccination scheme, storage conditions, or errors associated with multidose vials. These potential vaccination errors are mitigated through a number of strategies:

- SmPC section 6.6 contains instructions on handling and administration conditions for COVID-19 vaccine (adjuvanted) HIPRA. Instructions on storage are provided in SmPC section 6.4. Instructions on vaccination scheme are provided in SmPC section 4.2.
- Vaccination reminder cards and stickers with batch/lot numbers will be available to member states, if requested, for use by member state vaccinators.
- A website (www.hipracovid19.com) will be available for more information.

Furthermore, as other COVID-19 vaccines are also available, there is the potential for confusion or interchangeability with other COVID-19 vaccines. The above mechanisms are in place to facilitate safe use and avoidance of vaccination errors.

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

Important Identified Risks

Pericarditis

Risk-benefit impact: Most vaccine-associated pericarditis events have been mild and self-limiting. However, pericarditis is an event which may be serious, and although generally mild may be potentially life-threatening. Balanced with the risk of death and illness seen with COVID-19 itself, the impact on the risk-balance of the vaccine is considered minimal.

Important Potential Risks:

Myocarditis

Risk-benefit impact: Most vaccine-associated myocarditis events have been mild and self-limiting. However, myocarditis is an event which may be serious, and although generally mild may be potentially life-threatening. Balanced with the risk of death and illness seen with COVID-19 itself, the impact on the risk-balance of the vaccine is considered minimal.

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

Risk-benefit impact: Vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes. There is a theoretical risk, mostly based on non-clinical beta-coronavirus data, of VAED occurring either before the full vaccine regimen is administered or in vaccinees who have waning immunity over time (Agrawal *et al.*, 2016). VAERD refers to the predominantly lower respiratory tract presentation of VAED. VAED/VAERD may be serious or life-threatening, and requires early detection, careful monitoring, and timely medical intervention. Consequently, if VAED were to be identified as a risk, it could potentially impact the benefit risk.

Missing information

Use in pregnancy and while breastfeeding

Risk-benefit impact: The target indication for BIMERVAX is adults ≥ 16 year of age thus will include women of childbearing potential. Pregnant and breastfeeding women are typically excluded from initial clinical trials. There is no experience with use of BIMERVAX in pregnant women. Studies to assess the potential toxicity on fertility are ongoing. Nevertheless, an assessment of male and female fertility by histopathological examination of the testis and ovaries in the GLP toxicity studies in mice (AC25AA), rat (AC91AA) and rabbit (SEP-2021-011-PHH1V) found no effect of PHH-1 or PHH-1V vaccines on these organs. Also, no effects on fertility have been described in the literature for the SQBA adjuvant, at least at the dose to be used in BIMERVAX. Moreover, no effects on fertility have been associated to the development of immunogenicity against SARS-CoV-2 during the development of other four COVID-19 vaccines currently approved (SmPC Comirnaty, 2021; SmPC COVID-19 Vaccine Janssen, 2021; SmPC Spikevax, 2021; SmPC Vaxzevria, 2021; SmPC Nuvaxovid, 2022). Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development. It is unknown whether BIMERVAX is excreted in human milk. 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 can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy.

Use in immunocompromised patients

Risk-benefit impact: In the clinical development program, subjects with immunosuppressive conditions or medications were to be excluded from the study. However, a study to assess the use of BIMERVAX in immunocompromised patients is currently on-going. In general, immunocompromised individuals are at greater risk of morbidity and mortality from vaccine-preventable disease. In addition, the efficacy of the vaccine may be lower in immunocompromised individuals, thus decreasing their protection from COVID-19. Even though there is no evidence that the safety profile of this population receiving BIMERVAX will be different to that of the general population, the possibility cannot be excluded. Additionally, a post

authorization study in immunocompromised patients will be conducted to assess the safety and tolerability of BIMERVAX as a booster dose in adult subjects.

Use in frail patients with comorbidities (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 individuals with co-morbidities who are potentially at higher risk of severe COVID-19. Although there is no evidence that the safety profile of this population receiving BIMERVAX will be different to that of the general population, the possibility cannot be excluded.

Use in patients with autoimmune or inflammatory disorders

Risk-benefit impact: There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease. Although there is no evidence that the safety profile of this population receiving BIMERVAX will be different to that of the general population, the possibility cannot be excluded.

Interaction with other vaccines

Risk-benefit impact: BIMERVAX is indicated as a booster in individuals vaccinated against COVID 19. The safety and immunogenicity of a booster vaccination with BIMERVAX (PHH-1V) against SARS-CoV-2 in healthy adult volunteers fully vaccinated against COVID 19 (Vaxzevria, Spikevax, Janssen and Comirnaty), is being evaluated in the Phase IIb clinical study HIPRA-HH-2 and Phase III study HIPRA-HH-5. Studies to determine if co-administration of BIMERVAX with other vaccines (i.e., with seasonal illness vaccines [such as the influenza vaccines]) may affect the efficacy or safety of either vaccine have not been performed.

Long-term safety

Risk-benefit impact: The long-term safety of BIMERVAX is unknown at present, however further safety data are being collected in ongoing clinical trials. The clinical development program has a safety follow up period of 48 weeks in Phase I/IIa clinical study HIPRA-HH-1, up to 52 weeks after booster vaccination of Day 0 in the Phase IIb clinical study HIPRA-HH-2up to 52 weeks in the Phase IIb/III study HIPRA-HH-4 and up to 24 weeks in the supportive Phase IIb study HAN-01.

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. Presentation of important identified risks and important potential risks

Important Identified Risks

Pericarditis

Potential mechanisms: Viruses are the primary cause of pericarditis, including amongst others adeno- and enteroviruses. SARS-CoV-2 has been associated with pericarditis as well, and multiple cases have been described since the outbreak of the COVID-19 pandemic (Klamer *et al.*, 2022).

Pericarditis has been identified as a possible rare side effect of mRNA vaccines. The pathophysiological mechanisms behind the development of myocarditis and pericarditis after a COVID-19 vaccination are currently not completely understood. One hypothesis is that the immune system detects the mRNA molecules as antigens, triggering an immune reaction in certain individuals. Another mechanism that has been proposed is that antibodies against a part of the SARS-CoV-2's spike protein that the mRNA encodes for, cross-react with structural similar host proteins in the heart, also known as molecular mimicry (Klamer *et al.*, 2022).

A mechanism of action by which a vaccine could cause pericarditis has not been established.

Evidence source(s) and strength of evidence: The most important published cohort studies demonstrate that pericarditis is a very rare side effect after COVID-19 mRNA vaccination, with an incidence of approximately 1-4 cases per 100,000 vaccinated subjects. Young males 16-29 appear to be at highest risk, predominantly after receiving the second dose (Klamer *et al.*, 2022). The risk of pericarditis is higher in persons who were infected with the SARS-CoV-2 than in those who received the vaccine. Most patients fully recover with rest and an adequate treatment.

The risk of pericarditis has shown to be different depending on the type of vaccine/platform used. Vaccines using adenoviral vector-based platforms produce the spike protein but have not been implicated in acquired myocarditis (Pillay *et al.*, 2022). Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than BIMERVAX vaccine (Twentyman *et al.*, 2022)

Only one case of a pericarditis event was detected in a clinical study using BIMERVAX.

Characterisation of the risk:

Pericarditis is a rare disease with an estimated annual incidence prior to COVID-19 vaccine pandemic of 16 per 100 000 persons in the general population. The true incidence may be higher, as signs and symptoms vary, and it therefore can be challenging to make the diagnosis (Klamer *et al.*, 2022).

Clinical Trial experience:

In the phase III study HIPRA-HH-5, of the 2646 subjects included in the safety dataset, one case of pericarditis was reported. The event was considered product related because it could not be discarded due to temporal association. In the absence of alternative aetiologies, a causal association with the vaccine could not be excluded in this case.

The most important published cohort studies demonstrate that pericarditis is a very rare side effect after COVID-19 mRNA vaccination, with an incidence of approximately 1-4 cases per 100,000 vaccinated subjects. Young males 16-29 appear to be at highest risk, predominantly after receiving the second dose (Klamer *et al.*, 2022).The risk of pericarditis is higher in persons who were infected with the SARS-CoV-2 than in those who received the vaccine.

Pericarditis events have also been detected in clinical studies and post-authorization surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than BIMERVAX vaccine (Twentyman *et al.*, 2022).

Post-marketing experience:

No post-marketing cases have been received with BIMERVAX vaccine.

Risk factors and risk groups: Adolescent and young adult males following the second dose of vaccine may be at higher risk (Gargano *et al.*, 2021).

Preventability: Considering that a mechanism of action by which a vaccine could cause pericarditis has not been established, preventative measures cannot be defined at this time.

Impact on the risk-benefit balance of the product:

The rate of vaccine-associated pericarditis is low, and the events have been mild and self-limiting. In consideration of the fact that the risk of death and illness (including myocarditis) seen with SARS-CoV-2 itself, the impact on the risk-benefit balance of the vaccine is considered as minimal.

Public health impact:
The public health impact of the potential risk of pericarditis is expected to be low as pericarditis are very rare side effects after COVID-19 vaccination and events have been mild and self-limiting.

Important potential risks

Myocarditis

Potential mechanisms: Viruses are the primary cause of myocarditis, including amongst others adeno- and enteroviruses. SARS-CoV-2 has been associated with myocarditis as well, and multiple cases have been described since the outbreak of the COVID-19 pandemic (Klamer *et al.*, 2022).

Myocarditis has been identified as possible rare side effects of mRNA vaccines. The pathophysiological mechanisms behind the development of myocarditis and pericarditis after a COVID-19 vaccination are currently not completely understood. One hypothesis is that the immune system detects the mRNA molecules as antigens, triggering an immune reaction in certain individuals. Another mechanism that has been proposed is that antibodies against a part of the SARS-CoV-2's spike protein that the mRNA encodes for, cross-react with structural similar host proteins in the heart, also known as molecular mimicry (Klamer *et al.*, 2022).

A mechanism of action by which a vaccine could cause myocarditis has not been established.

Evidence source(s) and strength of evidence: The most important published cohort studies demonstrate that myocarditis is a very rare side effect after COVID-19 mRNA vaccination, with an incidence of approximately 1-4 cases per 100,000 vaccinated subjects. Young males 16-29 appear to be at highest risk, predominantly after receiving the second dose (Klamer *et al.*, 2022). The risk of myocarditis is higher in persons who were infected with the SARS-CoV-2 than in those who received the vaccine. Most patients fully recover with rest and an adequate treatment.

The risk of myocarditis has shown to be different depending on the type of vaccine/platform used. Vaccines using adenoviral vector-based platforms produce the spike protein but have not been implicated in acquired myocarditis (Pillay *et al.*, 2022) Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than BIMERVAX vaccine (Twentyman *et al.*, 2022)

Considering limited safety data, the available evidence is not sufficient to rule out myocarditis as a safety concern. Thus, it is added as an important potential risk.

Characterisation of the risk:

Myocarditis is a rare disease with an estimated annual incidence prior to COVID-19 vaccine pandemic of 16 per 100 000 persons in the general population. The true incidence may be higher, as signs and symptoms vary, and it therefore can be challenging to make the diagnosis (Klamer *et al.*, 2022).

Clinical Trial experience:

No case of myocarditis has been observed in the clinical trials of BIMERVAX vaccine.

The most important published cohort studies demonstrate that myocarditis is a very rare side effect after COVID-19 mRNA vaccination, with an incidence of approximately 1-4 cases per 100,000 vaccinated subjects. Young males 16-29 appear to be at highest risk, predominantly after receiving the second dose (Klamer *et al.*, 2022).The risk of myocarditis is higher in persons who were infected with the SARS-CoV-2 than in those who received the vaccine.

Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than BIMERVAX vaccine (Twentyman *et al.*, 2022).

Post-marketing experience:

No post-marketing cases have been received with BIMERVAX vaccine.

Risk factors and risk groups: Adolescent and young adult males following the second dose of vaccine may be at higher risk (Gargano *et al.*, 2021).

Preventability: Considering that a mechanism of action by which a vaccine could cause myocarditis has not been established, preventative measures cannot be defined at this time.

Impact on the risk-benefit balance of the product:

The rate of vaccine-associated myocarditis is low, and the events have been mild and self-limiting. In consideration of the fact that the risk of death and illness (including myocarditis) seen with SARS-CoV-2 itself, the impact on the risk-benefit balance of the vaccine is considered as minimal.

Public health impact:

The public health impact of the potential risk of myocarditis is expected to be low as myocarditis is very rare side effect after COVID-19 vaccination and events have been mild and self-limiting.

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

Potential mechanisms: The pathogenesis of VAED in the context of SARS-CoV-2 is unclear. Although animal models of SARS-CoV-2 infection have not shown evidence of VAED after immunisation, 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. (Haynes *et al.*, 2020; Lambert *et al.*, 2020). VAERD refers to the predominantly lower respiratory tract presentation of VAED. The mechanism of the pathogenesis of VAERD 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). Less severe cases of SARS were associated with accelerated induction of a Th1 cell response; whereas, Th2 cell responses have been associated with enhancement of lung disease following infection in hosts parenterally vaccinated with inactivated SARS-CoV vaccines (Lambert *et al.*, 2020).

Evidence source(s) and strength of evidence: This potential risk is theoretical because it has not been described in association with the BIMERVAX vaccine or it has not been reported from any other late phase clinical trial of other human vaccine. As mentioned above, this potential risk has been included based on these animal data with these related betacoronaviruses. VAERD refers to the predominantly lower respiratory tract presentation of VAED. Evidence sources have been collected from literature on viral vaccines, safety information of other SARS-CoV-2 vaccines and clinical trials. VAED was observed in children given formalin-inactivated whole-virus vaccines against respiratory syncytial virus (RSV) and measles virus. It has been rarely encountered with existing vaccines or viral infections (Haynes *et al.*, 2020). Although, no events of VAED/VAERD have been reported in the current BIMERVAX clinical development programme, there is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes, which would manifest as VAED/VAERD (Graham, 2020).

Characterisation of the risk: No events of VAED/VAERD have been reported in the current BIMERVAX clinical development programme or in the post-marketing experience. Currently, VAED/VAERD has not been reported in other COVID-19 vaccines. If it would occur in vaccinated individuals, VAED/VAERD will manifest as a modified and/or more severe clinical presentation of SARS-CoV-2 viral infection upon subsequent natural infection. This may result having higher rates of unfavourable outcomes, especially in individuals at known risk for severe COVID-19 (e.g., older or immunocompromised).

Risk factors and risk groups: No risks groups or risks factors have been identified. Nevertheless, 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).

Preventability: Information about the prevention of VAED/VAERD in the context of SARS-COV-2 is currently unknown as the risk is theoretical.

Impact on the risk-benefit balance of the product:

VAED (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: The potential risk of VAED/VAERD could have a public health impact if large populations of individuals are affected. As this safety concern is currently theoretical and has not been observed in the ongoing BIMERVAX vaccine clinical trials, there is no public health impact at this time.

SVII.3.2. Presentation of the missing information

Missing information

Use in pregnancy and while breastfeeding

Evidence source: There is no experience with use of BIMERVAX vaccine in pregnant women. Nevertheless, an assessment of male and female fertility by histopathological examination of the testis and ovaries in the GLP toxicity studies in mice (AC25AA), rat (AC91AA) and rabbit (SEP-2021-011-PHH1V) found no effect of PHH-1 or PHH-1V vaccines on these organs. Also, no effects on fertility have been described for the SQBA adjuvant, according to analogous adjuvants, at least at the dose to be used in BIMERVAX. Moreover, no effects on fertility have been associated to the development of immunogenicity against SARS-CoV-2 during the development of other four COVID-19 vaccines currently approved (SmPC Comirnaty, 2021; SmPC COVID-19 Vaccine Janssen, 2021; SmPC Spikevax, 2021; SmPC Vaxzevria, 2021; SmPC Nuvaxovid, 2022). Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development. Administration of BIMERVAX vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. It is unknown whether BIMERVAX vaccine is excreted in human milk.

Anticipated risk/consequence of the missing information: Targeted populations of the indication will include women of childbearing potential, thus, the use of BIMERVAX in pregnant and/or breastfeeding women will occur.

Use in immunocompromised patients

Evidence source: Subjects with immunosuppressive conditions or medications were to be excluded from the study in the BIMERVAX clinical development program. Studies to assess the use of BIMERVAX in immunocompromised patients are ongoing. There is no evidence that the safety profile of this population receiving BIMERVAX will be different to that of the general population, but given the paucity of data, the possibility cannot be ruled out.

Anticipated risk/consequence of the missing information: As the vaccinees weakened immune system may not reach a sufficient response, vaccines may be less effective in individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressants.

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

Evidence source: The BIMERVAX has not been studied in frail individuals with severe comorbidities that may compromise immune function due to the condition or treatment of the condition. Frail patients with comorbidities (e.g., COPD, diabetes mellitus, chronic neurological disease, cardiovascular disorders) are potentially at risk of developing a more severe manifestation of COVID-19. There is no evidence that the

safety profile of this population receiving BIMERVAX will be different to that of the general population, but given the scarcity of data, the possibility cannot be ruled out.

Anticipated risk/consequence of the missing information: In general, there is a potential that frail participants with unstable health conditions and co-morbidities may experience a different outcome than achieved in healthy individuals administered vaccines.

Use in patients with autoimmune or inflammatory disorders

Evidence source: There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders. Although there is no evidence that the safety profile of this population receiving BIMERVAX will be different to that of the general population, the possibility cannot be excluded.

Anticipated risk/consequence of the missing information: In general, individuals with autoimmune or inflammatory disorders may experience a different outcome than achieved in healthy individuals administered vaccines.

Interaction with other vaccines

Evidence source: BIMERVAX is indicated as a booster in individuals vaccinated against COVID-19. The safety and immunogenicity of a booster vaccination with BIMERVAX (PHH-1V) against SARS-CoV-2 in healthy adult volunteers fully vaccinated with Vaxzevria, Spikevax, Janssen and Comirnaty vaccines against COVID-19, is being evaluated in the Phase IIb clinical study HIPRA-HH-2, and in the Phase IIb/III study HIPRA-HH-4. Studies to determine if co-administration of BIMERVAX with other vaccines (i.e., with seasonal illness vaccines [such as the influenza vaccines]) may affect the efficacy or safety of either vaccine have not been performed.

Population in need of further characterisation: Subjects fully vaccinated against COVID-19 after immunisation with BIMERVAX.

Anticipated risk/consequence of the missing information: There is the theoretical question as whether vaccines may interact with each other and change the immune response to either vaccine or induce safety concerns. It is common medical practice to administer vaccines concurrently. Participants receiving BIMERVAX may be administered seasonal flu vaccines during the vaccination period of the pandemic.

Long-term safety

Evidence source: Understanding of the long-term safety profile of BIMERVAX is currently limited but complete safety data up to 1 year is available for the Phase III study HIPRA-HH-5. Nevertheless, per protocols, the clinical development program has a safety follow up period of 48 weeks in Phase I/IIa clinical study HIPRA-HH-1, up to 52 weeks after booster vaccination of Day 0 in the Phase IIb clinical study HIPRA-HH-2, up to 52 weeks in the Phase IIb/III study HIPRA-HH-4 and up to 24 weeks in the supportive Phase IIb study HAN-01.

Anticipated risk/consequence of the missing information: At the time of vaccine availability, the long-term safety data of BIMERVAX is available in the CSR of the Phase III study HIPRA-HH-5. Although there are currently no known risks with a potentially late onset, given the limited data, the possibility cannot be excluded. Data will continue to be collected from participants in ongoing studies.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Pericarditis
Important potential risks	Myocarditis
	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breastfeeding
	Use in immunocompromised patients
	Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance (PV) activities for the lifecycle of a product are critical components to the detection, assessment, and understanding of risks. Objectives of routine pharmacovigilance include having processes in place to assure the ongoing and timely collection, processing, follow-up, and analysis of individual AE reports and aggregate data globally, following global safety Standard Operating Procedures and regulatory guidance. Activities include the collection, processing and analysis of individual case safety reports, the review and reporting on aggregate data, and a signal detection system.

HIPRA 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.

Routine PV activities are consistent with the EMA Guidelines on Good Pharmacovigilance Practices (GVP). A comprehensive description of all aspects of the PV system is provided in the Pharmacovigilance System Master File (PSMF), which is available upon request.

- *Signal detection and management*

HIPRA has a safety surveillance and reporting system in place to organize the collection, data entry in the company global safety database and evaluation of any AEs or other safety information reported to HIPRA and an established signal management process including signal detection, validation and evaluation of spontaneous reports from all sources. Potential signal detection data sources include safety data from MAH-sponsored clinical trials and non-interventional studies; spontaneous AE reports; specific review of AEs consistent with the AESI list provided in Annex 7, which considers relevant sources such as Brighton Collaboration SPEAC list, ACCESS Project AESI and cases definitions, CBER Surveillance Program – list of AESI; non-clinical studies; quality and manufacturing reports; published literature; and communications from external sources, including regulatory agencies, and (if applicable) business partners. The detection of signals described in the BIMERVAX Signal Detection System plan involves qualitative and quantitative pharmacovigilance methods. In addition, observed versus expected analyses will be conducted periodically as part of routine signal management activity and will use appropriate lists of AESI and background rates from ACCESS, CONSIGN and ConcePTION. The primary data sources for signal detection and the minimum frequency of review are outlined below.

Activity/Data Source		Frequency of Review
Qualitative Data Review	ICSR (Individual Case Safety Report) medical review of serious cases	Each business day
	Review of signal notifications	Each business day
	Literature review of PubMed including Medline and an additional data source (Embase, Scopus or Web of Science)	Weekly
	Line listing review of adverse event reports from HIPRA safety database which includes both clinical trial SAEs and post-marketing ICSRs, including revision of AESIs (Annex 7), and quality and manufacturing reports.	Weekly
	Standardised MedDRA [Medical Dictionary tor Regulatory Activities] queries and targeted PT searches	Weekly
	Review of BIMERVAX Safety Database, including all spontaneous and solicited ICSRs, Medicines and Healthcare products Regulatory Agency (MHRA), Eudravigilance Data Analysis System (EVDAS), and other regulatory databases, as required	Bi-weekly
	Batch trend analysis	Monthly
	Review of Pharmacovigilance Risk Assessment Committee (PRAC) recommendations on signals and relevant safety information from regulatory agencies.	Monthly
Quantitative Data Review	Trends over time/frequency analysis of AESIs (Annex 7)	Monthly
	Disproportionality analysis using EVDAS	Bi-weekly
	Observed versus expected (O/E) analysis of AESIs (Annex 7)	Monthly
	Time-to-onset analysis	Monthly
	Cluster analysis	When applicable

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific AE follow-up questionnaire for the following safety concern:**
    - Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD).
    - Myocarditis/pericarditis

Please find this questionnaire in Annex 4.

Other forms of routine pharmacovigilance activities

- *Summary Safety Reports (SSRs)*

In addition to routine 6-monthly PSUR production, SSRs are compiled to support timely and continuous benefit risk evaluations. Given the current COVID-19 vaccination patterns, the initiation of summary safety reports submission requirement for new vaccines should only be triggered by the start of mass vaccination using the product in any EU Member State. The need and periodicity of continuing the submission of the summary safety reports will be initiated by the rapporteur and re-evaluated based on the available post-marketing evidence for each vaccine, and at the request of the MAH, as soon as the safety data enables a decision to be made. Topics covered by SSR include:

- Interval and cumulative number of reports, overall and stratified by age groups and in special populations (e.g., pregnant women), by report type, (medically confirmed vs. non-medically confirmed) and by seriousness;
- Interval and cumulative number of reports per HLT and SOC;
- Reports per EU country;
- Exposure data based on administered doses rather than distributed doses whenever possible, stratified by region (country within the EU), by age groups, gender and by dose number (when applicable);
- Safety-related changes to the reference safety information and actions taken in the interval
- List of ongoing and closed signals in the interval, including a summary of their evaluation; reviews of signals identified during the period or of safety topics identified by EMA and requested to be addressed in the SSR;
- Summaries of reported cases of selected AESIs considered relevant for periodically review with the SSR submission and RMP safety concerns: report numbers and relevant cases, including observed versus expected (O/E) analysis using appropriate lists of AESI and background rates from ACCESS, CONSIGN and ConcePTION, an adequate risk window and, when appropriate, stratified by age groups or presented per region/EU country (e.g. if background rates vary), and complemented with a sensitivity analysis.
- Discussion if any unusual pattern of fatal reports (considering co-morbidities and frailty) is observed during initial post-marketing use;
- Data on medication errors, if a pattern of errors leading to harm is identified and/or risk minimisation activities are considered warranted;
- Details of the search strategy, case definitions for all provided reviews and methodology for O/E analyses including source of background rates, risk windows, etc.;
- Risk/benefit considerations.

- *Traceability*

The SmPC includes instructions for healthcare professionals to record the name and batch number of the administered vaccine to improve traceability (section 4.4) and to report any suspected adverse reactions including batch/Lot number if available (section 4.8).

HIPRA has available vaccination reminder cards (Annex 7) to member states, that may be completed at the time of vaccination when necessary for individual members states. The card will be also accessible electronically and through a QR code, on the applicant's website.

The Traceability and Vaccination Reminder cards contain the following elements:

- Placeholder space for name of vaccinee;
- Vaccine brand name and manufacturer name;
- Placeholder space for date of vaccination;
- Placeholder space for the batch number;
- Reminder to retain the card "Make sure you keep this card";
- QR code that links to a website with additional information on product use; and
- Adverse event reporting information.

In addition, two traceability stickers per dose, containing both printed and a 2D-code encoding brand name and batch/lot number will be made available to support documentation of the batch/lot traceability. We also acknowledge that some EU member states may require utilisation of nationally mandated vaccination cards or electronic systems to document batch/lot number; therefore, the available traceability and vaccination reminder cards and/or stickers with printed lot/batch information may not be utilised in all member states.

III.2 Additional pharmacovigilance activities

The MAH intends to address general safety through continuation of safety surveillance from ongoing interventional clinical trials, two non-interventional post-authorisation safety studies and one non-interventional effectiveness study.

Ongoing clinical trials

Study short name and title: **HIPRA-HH-2; A Phase IIb, double-blind, randomised, active-controlled, multi-centre, non-inferiority trial followed by a Phase III, single-arm, open-label trial, to assess immunogenicity and safety of a booster vaccination with a recombinant protein RBD fusion dimer candidate (PHH-1V) against SARS-CoV-2, in adults fully vaccinated against COVID-19 followed by an extension period to study a fourth dose administration of PHH-1V.**

Rationale and study objectives:

- Primary objectives:

Part A: To determine and compare the changes of the immunogenicity measured by pseudovirus neutralisation against Wuhan strain (also known as L strain); To assess the safety and tolerability of PHH-1V as a booster dose in healthy adult subjects fully vaccinated against COVID-19 with the Pfizer–BioNTech (Comirnaty) vaccine.

Part B: To determine and compare the changes in the immunogenicity measured by PBNA against omicron BA.1 subvariant, at Day 14 post-dose 4 of PHH-1V in cohort 2 versus post-dose 3 in cohort 2. To assess the safety and tolerability of PHH-1V as a fourth dose in adult subjects in **cohort 1 and 2**.

- Secondary objectives:

Part A: To determine and compare the changes of the immunogenicity measured by SARS-CoV-2 PBNA against the Variants of Concern (VOC); To determine and compare the changes in immunogenicity measured by wild type SARS-CoV-2 neutralisation test (VNA); To evaluate the immunogenicity measured by enzyme-linked immunosorbent assay (ELISA) to the SARS-CoV-2 spike glycoprotein; To evaluate T-cell mediated responses against the SARS-CoV-2 S glycoprotein; To assess Th-1/Th-2 T-cell mediated responses against the SARS-CoV-2 S glycoprotein.

Part B: To determine and compare the changes in the immunogenicity measured by PBNA against omicron BA.1 subvariant, at Days 98 and 182 post-dose 4 of PHH-1V in cohort 2 versus post-dose 3 in cohort 2. To determine and compare the changes in the immunogenicity measured by PBNA against omicron BA4/5 subvariant and other VOCs, at Days 14, 98 and 182 post-dose 4 of PHH-1V in cohort 2 versus post-dose 3 in **cohort 2.** To determine and compare the changes in immunogenicity measured by PBNA against omicron BA.1, BA4/5 subvariant and other VOC at Days 14, 98 and 182 post-dose 4 of PHH-1V in **cohort 1** versus post-dose 3 in cohort 2.

Study design:

Part A: This is a randomised, active controlled, Phase IIb, multi-centre, non-inferiority clinical study. Subjects will be followed for 1 year after the administration of the booster dose with HIPRA COVID-19 vaccine. Ten hospitals from Spain participate in the trial. Subjects will be followed for 52 weeks after the booster vaccination and the study duration (for each subject) will be up to 56 weeks. Interventional study.

Part B: is a Phase IIb, open-label extension, to determine the immunogenicity, reactogenicity, safety, and tolerability of a fourth dose vaccine against COVID-19. Subjects will be followed for 6 months after the administration of the fourth dose with HIPRA COVID-19 vaccine. Interventional study.

Study population:

Part A: 602 adults aged above 18 years old, approximately a 10% of them aged above 65 years old, randomised 2:1 to either HIPRA's boosting vaccine (PHH-1V) or Pfizer–BioNTech (Comirnaty) boosting vaccine.

Part B: Approximately 100 adults aged above 18 years old, with a primary vaccination with 2 doses of Comirnaty + 1 Booster dose of PHH-1V (Cohort 1) and approximately 100 adults aged above 18 years old, with a primary vaccination with 2 doses of Comirnaty + 1 Booster dose of Comirnaty (Cohort 2). Both cohorts will receive a fourth dose with HIPRA's PHH-1V between 6 and 12 months after the third dose.

Milestones: Study HIPRA-HH-2 is on-going (submitted to the Ethics Committee and Competent Authorities on the 28 October 2021, approved on the 15 November 2021 and initiated on 16 November 2021). The interim clinical study report (CSR) was available on 18 May 2022. A 6 months Interim Report was available on 29 September 2022 (safety data not updated). An extension of this study is currently ongoing to assess the administration of a fourth dose of PHH-1V (submitted as a protocol amendment to the Ethics Committee and Competent Authorities on the 12th of July 2022, approved on the 4th August 2022 and initiated on 12th September 2022). Therefore, the final CSR is estimated on 05 January 2024. First participant was enrolled on 16 November 2021 and due to extension, last participant was enrolled on 2 December 2022.

Study short name and title: **HIPRA-HH-4: A Phase IIb/III, open label, single arm, multi-centre, trial to assess the immunogenicity and safety of an additional dose vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults with pre-existing immunosupressive conditions vaccinated against COVID-19**.

Rationale and study objectives:

- Primary objective: to determine and compare the changes of the immunogenicity measured by pseudovirus (or live virus for the HIV cohort) neutralization against Omicron, Beta and Delta any other relevant Variants of Concern (VOC) in the epidemiologic moment, after administration of HIPRA's vaccine (PHH-1V).
- Secondary objectives: to determine and compare the changes of the immunogenicity measured by pseudovirus (or live virus for the HIV cohort) neutralization against Omicron, Beta and Delta and any other relevant Variants of Concern (VOC) in the epidemiologic moment at long term after administration of HIPRA's vaccine (PHH-1V). To evaluate the immunogenicity measured by means of total antibody against Receptor Binding Domain of the Spike protein of SARS-CoV-2 quantification, measured by an electrochemiluminescence immunoassay (ECLIA) after administration of HIPRA's vaccine (PHH-1V). To assess the safety and tolerability of PHH-1V as an additional dose in adult individuals with pre-existing immunosuppressive conditions.

Study design: Phase IIb/III Open label, single arm, multi-centre clinical trial. Subjects will be followed for 52 weeks post-vaccination. Interventional study.

Study population: Approximately 400 adults aged above 18 years old will be enrolled in 6 sites from Turkey and Spain.

Milestones: Study HIPRA-HH-4 is on-going (Spain: submitted to the Ethics Committee and Competent Authorities on 24 March 2022, approved on 9 May 2022 and initiated on 12 May 2022; Turkey: submitted to the Ethics Committee and Competent Authorities on 29 April, approved on 28 October 2022). Final CSR is estimated on 13 September 2024. First participant was enrolled in Spain on 12 May 2022 and recruitment is closed with 231 participants vaccinated. Recruitment in Turkey is ongoing.

Planned post-authorisation studies

To further characterise the BIMERVAX safety and effectiveness profile, the following three (3) non-interventional studies will be conducted:

Study name and title: **Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU**

Rationale and study objectives: This study consists of two components—a vaccine utilisation study and a comparative safety study—. The vaccine utilisation study will characterise the individuals receiving the BIMERVAX vaccine. The comparative safety study uses two different designs: a cohort design to estimate the effect of BIMERVAX vaccine on adverse events of special interest (AESIs) compared with that of other COVID-19 vaccines authorised for the same indication; and a self-controlled risk interval (SCRI) study (a subtype of the self-controlled case series design) design to estimate the effect of the COVID-19 HIPRA vaccine booster on selected AESIs compared with no COVID-19 vaccination booster.

The study objectives are:

1. The objective of the vaccine utilisation study will be to characterise recipients BIMERVAX in relation to demographics and clinical characteristics at the time of vaccination, including the following: pregnancy status, age of childbearing potential, immunocompromised status, comorbidities, presence of autoimmune and inflammatory disorders, and interaction with other vaccines (influenza).
2. The objective of the comparative study:
    a. Using a cohort design will be to estimate the effect of BIMERVAX on adverse events of special interest (AESIs)—as described in a protocol for the vACCine covid-19 monitoring readinESS (ACCESS) project (Dodd et al., 2020)—compared with that of other COVID-19 vaccines authorised for the booster indication.
    b. Using a SCRI design will be to estimate the effect of BIMERVAX booster on selected AESIs (those that can be studied under a self-controlled design as specified in ACCESS) compared with no COVID-19 vaccine as a booster.

Study design: The vaccine utilisation study will be descriptive and will characterise eligible individuals at the time of vaccination. The comparative safety component will follow ACCESS specifications for vaccine safety studies, for both the cohort and SCRI studies. The SCRI design was chosen over a SCCS because the SCRI design uses a post-exposure control period to minimise the probability of violating the assumption that the outcome does not influence the exposure. The study period will be from the date of availability of BIMERVAX in each participant country to 2-3 years past that date, pending the timing and potential seasonality of booster administration campaigns.

Study population: The eligible population for the vaccine utilisation study will be all individuals actively enrolled in each of the selected European health data sources for at least 12 months before vaccination with BIMERVAX who receive a dose of BIMERVAX within the study period.

The general eligibility criteria for the cohort comparative safety study will be as follows:

- Receipt of a full primary vaccination course with an mRNA and/or an adenovirus COVID-19 vaccine.
- Receipt of a dose of the COVID-19 HIPRA vaccine or another COVID-19 vaccine with the same indication. The date of this vaccination will be the cohort entry date.
- For each AESI, a previous diagnosis of that AESI will exclude an individual from participation.

The general eligibility criteria for the SCRI comparative safety study will be as follows:

- Receipt of a full primary vaccination course with an mRNA and/or an adenovirus COVID-19 vaccine.
- Receipt of a dose of the COVID-19 HIPRA vaccine. The date of this vaccination will be time zero, i.e., the anchor to define the risk and control intervals.
- Having experienced the AESI of interest in either the risk or control interval.

Milestones: The study protocol was submitted following receipt of first regulatory authorisation in the EEA (at the next regulatory opportunity as of 31 July 2023). One progress report is planned for submission 3 months after protocol endorsement. Two interim reports are planned to be submitted at 12 and 24 months following rollout of BIMERVAX booster vaccination campaigns in the first participating country. A final study report is planned for submission at 36 months after rollout of BIMERVAX booster vaccination campaigns in the first participating country, and 48 months in the case of pregnancy outcomes.

Study name and title: **COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)**

Rationale and study objectives: BIMERVAX emulsion for injection Covid-19 Vaccine (recombinant, adjuvanted) will be used in pregnant populations. Scientific evidence regarding its safety for pregnant women and the developing fetus is lacking.

The study objective is:

- To estimate the risk of obstetric outcomes (spontaneous abortion, antenatal bleeding, gestational diabetes, gestational hypertension, intrauterine growth restriction, postpartum hemorrhage, fetal distress, uterine rupture, placenta previa, chorioamnionitis, Caesarean delivery, COVID-19), neonatal outcomes (major congenital malformations, low birth weight, neonatal death, neonatal encephalopathy, neonatal infections, neonatal acute kidney injury, preterm birth, respiratory distress in the newborn, small for gestational age, stillbirth, COVID-19), and infant outcomes (developmental milestones [motor, cognitive, language, social-emotional, and mental health skills], height, weight, failure to thrive, medical conditions during the first 12 months of life, COVID-19) among pregnant women exposed to single (homologous) or mixed (heterologous) BIMERVAX series from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched reference group who received no COVID-19 vaccines during pregnancy.

Study design: The C-VIPER is an international, non-interventional, post-marketing cohort study designed to collect prospective safety data among women vaccinated with BIMERVAX during pregnancy or within 30 days prior to the first day of the LMP.

Study population: The study population will include 2 cohorts of pregnant women 18 years of age and older matched by country and gestational age (±2 weeks):

- Cohort 1: pregnant women exposed from 30 days prior to the first day of the LMP to end of pregnancy to at least one dose of BIMERVAX. These participants are enrolled as part of the C-VIPER.
- Cohort 2: pregnant women unexposed to a COVID-19 vaccine during pregnancy. These participants are enrolled through the Pregistry International Exposure Registry (PIPER) with the same methods as those in Cohort 1. Women vaccinated before 30 days prior to the first day of the LMP are eligible for inclusion.

Registration and participation via a website especially developed for the C-VIPER will be voluntary. Eligible women can enrol at any time during pregnancy.

Milestones: The total duration of the study will be 5 years. Obstetric, neonatal, and infant outcomes will be assessed on an ongoing basis as data become available. Data on pregnancy, neonatal and infant outcomes will be included in the interim reports as soon as available. The first two years will include, primarily, enrolment of pregnancies; the third and fourth years will involve follow-up of pregnancies and newborns; and, the final year, will be for data analyses and publications. Results on pregnancy and neonatal outcomes, even preliminary, are expected within the first year of the study. The study protocol was submitted following receipt of first regulatory authorisation in the EEA (at the next regulatory opportunity as of 31 July 2023). A final report is planned for submission within 12 months after study completion (estimated date: 31 July 2029).

Study name and title: **Post-authorisation effectiveness study of BIMERVAX emulsion for injection in Europe in VAC4EU**

Rationale and study objectives: This study will evaluate the risk of COVID-related outcomes due to the use of BIMERVAX vaccine compared with use of other COVID-19 vaccines with the same indication.

The study objective is:

1. To estimate the effect of the BIMERVAX on COVID-19–related outcomes—i.e., COVID-19 infection, COVID-19–related hospitalisations or emergency department visits—compared with other COVID-19 vaccines authorised for the booster indication.

Study design: This will be a cohort study following the vaccine covid-19 monitoring readinESS (ACCESS) project specifications for vaccine effectiveness studies. The study period will be from the date of availability of the BIMERVAX in each participant country to 2-3 years past that date pending timing and potential seasonality of booster administration campaigns. Non-interventional study.

Study population: The general eligibility criteria for the comparative effectiveness study will be as follows:

- Received a full primary vaccination course with an mRNA and/or an adenovirus COVID-19 vaccine.
- Received a dose of the BIMERVAX or of another COVID-19 vaccine with the same approved indication. The date of this vaccination will be the cohort entry date.

Milestones: The study protocol was submitted following receipt of first regulatory authorisation in the EEA (at the next regulatory opportunity as of 31 August 2023). One progress report is planned for submission 3 months after protocol endorsement. An interim report is planned to be submitted at 12 months following rollout of BIMERVAX booster vaccination campaigns in the first participating country. A final study report is planned for submission at 24-36 months after rollout of BIMERVAX booster vaccination campaigns in the first participating country. Schedule is dependent on protocol endorsement date, uptake of the COVID-19 vaccine (adjuvanted) HIPRA, approvals for data extraction and contracts with research team and occurrence of COVID-19 waves.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation.				
Not applicable.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances.				
Not applicable.				

Category 3 - Required additional pharmacovigilance activities				
HIPRA-HH-2 *On-going*	Assess immunogenicity and safety of a booster vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults fully vaccinated against COVID-19 with the Comirnaty vaccine	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis/Pericarditis Long-term safety	Protocol submission	28 October 2021
			Final CSR	05 January 2024
HIPRA-HH-4 *On-going*	To determine and compare the changes of the immunogenicity measured by pseudovirus (or live virus for the HIV cohort*) neutralization against Omicron, Beta and Delta any other relevant Variants of Concern (VOC) in the epidemiologic moment, at Baseline and at Day 14 after administration of HIPRA's vaccine (PHH-1V). To determine and compare the changes of the immunogenicity measured by pseudovirus (or live virus for the HIV cohort) neutralization against Omicron, Beta and Delta and any other relevant Variants of Concern (VOC) in the epidemiologic moment at Days, 91, 182 and 365, after administration of HIPRA's vaccine (PHH-1V). To evaluate the immunogenicity measured by means of total antibody against Receptor Binding Domain of the Spike protein of SARS-CoV-2 quantification, measured by an electrochemiluminescence immunoassay (ECLIA) at Baseline and at Days 14, 91, 182 and 365 after administration of HIPRA's vaccine (PHH-1V). To assess the safety and tolerability of PHH-1V as an additional dose in adult individuals with pre-existing immunosuppressive conditions	Use in immunocompromised patients Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis/Pericarditis Long-term safety	Protocol submission	24 March 2022
			Final CSR	13 September 2024

Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU *Planned*	Vaccine utilisation study: To characterise recipients of the BIMERVAX in relation to demographics and clinical characteristics at the time of vaccination, including the following: pregnancy status, age of childbearing potential, immunocompromised status, comorbidities, presence of autoimmune and inflammatory disorders, and interactions with other vaccines (influenza). Comparative safety study: 1. Cohort design: To estimate the effect of BIMERVAX on adverse events of special interest (AESIs)—as described in a protocol for the vACCine covid-19 monitoring readinESS (ACCESS) compared with that of other COVID-19 vaccines authorised for the booster indication. 2. SCRI design: To estimate the effect of the BIMERVAX booster on selected AESIs (those that can be studied under a self-controlled design as specified in ACCESS) compared with no COVID-19 vaccine as a booster.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Myocarditis/Pericarditis Long-term safety	Protocol submission	31 July 2023
			Final study report	*31 July 2026
Post-authorisation safety study of the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) *Planned*	To evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with a COVID-19 vaccine.	Use in pregnancy and in breast feeding	Protocol submission	31 July 2023
			Final study report	31 July 2029

*36 months after rollout of BIMERVAX booster vaccination campaigns in the first participating country

Table Part III.3.2: Planned post authorisation effectiveness studies

Study **Status**	**Summary of objectives**	**Effectiveness uncertainties addressed**	**Milestones**	**Due dates**
Post-authorisation effectiveness study of BIMERVAX emulsion for injection in Europe in VAC4EU *Planned*	To estimate the effect of the BIMERVAX on COVID-19–related outcomes—i.e., COVID-19 infection, COVID-19–related hospitalisations or emergency department visits—compared with other COVID-19 vaccines authorised for the booster indication.	COVID-19 vaccine effectiveness in real-world setting	Protocol submission	31 August 2023
			Final study report	*31 August 2025/ 31 August 2026

* 24-36 months after rollout of BIMERVAX vaccine booster vaccination campaigns in the first participating country. Pending timelines and potential seasonality of booster campaigns. Once actual timelines are known, a second interim report may be needed

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Pericarditis	Routine risk communication: SmPC section 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Important potential risks	
Myocarditis	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
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 breastfeeding	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 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 PL section 2 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 comorbidities (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 4.4 PL section 2 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 PL section 2 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	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

Routine risk minimisation activities as described in Part V.1. are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Pericarditis	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 05 January 2024. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.

Important potential risks		
Myocarditis	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 05 January 2024. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 05 January 2024. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Missing information		
Use in pregnancy and while breastfeeding	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None*

Important potential risks		
	<u>specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond the Product Information:</u> None	<u>Additional pharmacovigilance activities:</u> **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026. • Post-authorisation safety study of the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER); protocol submission on 31 July 2023; final study report 31 July 2029.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in immunocompromised patients	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Use in frail patients with comorbidities (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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Use in patients with autoimmune or inflammatory disorders	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine 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 study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Interaction with other vaccines	Routine risk communication: SmPC section 4.5 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine 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 study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Long-term safety	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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 05 January 2024. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.

Part VI: Summary of the risk management plan

Summary of risk management plan for BIMERVAX emulsion for injection

This is a summary of the risk management plan (RMP) for BIMERVAX emulsion for injection. The RMP details important risks of BIMERVAX, how these risks can be minimised, and how more information will be obtained about BIMERVAX's risks and uncertainties (missing information).

BIMERVAX 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how BIMERVAX should be used.

This summary of the RMP for BIMERVAX should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BIMERVAX's RMP.

I. The medicine and what it is used for

BIMERVAX is a bivalent vaccine indicated as a booster for active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA vaccine COVID-19 vaccine (see SmPC for the full indication). It contains COVID-19 Vaccine (recombinant, adjuvanted) as the active substance and it is given by intramuscular injection

Further information about the evaluation of BIMERVAX vaccine benefits can be found in the corresponding EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

Important risks of BIMERVAX, together with measures to minimise such risks and the proposed studies for learning more about BIMERVAX 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.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment and MSSRs so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of BIMERVAX is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of BIMERVAX 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 BIMERVAX. 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);

List of important risks and missing information	
Important identified risks	Pericarditis
Important potential risks	Myocarditis
	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breastfeeding
	Use in immunocompromised patients
	Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety

II.B Summary of important risks

Important identified risk: Pericarditis	
Evidence for linking the risk to the medicine	The most important published cohort studies demonstrate that pericarditis is a very rare side effect after COVID-19 mRNA vaccination, with an incidence of approximately 1-4 cases per 100,000 vaccinated subjects. Young males 16-29 appear to be at highest risk, predominantly after receiving the second dose. The risk of pericarditis is higher in people who were infected with the SARS-CoV-2 than in those who received the vaccine. Most patients fully recover with rest and an adequate treatment. The risk of pericarditis has shown to be different depending on the type of vaccine/platform used. Vaccines using adenoviral vector-based platforms produce the spike protein but have not been implicated in acquired myocarditis. Pericarditis events have also been detected in clinical studies and post-authorization surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than BIMERVAX vaccine. Only one case of a pericarditis event was detected in a clinical study using BIMERVAX.
Risk factors and risk groups	Adolescent and young adult males following the second dose of COVID-19 vaccine may be at higher risk.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.8. PL Section 4. <u>Additional risk minimisation measures:</u> None

Additional pharmacovigilance activities	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection</u> *Specific adverse reaction follow-up questionnaire* <u>Additional pharmacovigilance activities:</u> **Ongoing clinical trials** • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 05 January 2024. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU. Protocol submission on 31 July 2023; final estimated date 31 July 2026.

Important potential risk: Myocarditis	
Evidence for linking the risk to the medicine	The most important published cohort studies demonstrate that myocarditis is a very rare side effect after COVID-19 mRNA vaccination, with an incidence of approximately 1-4 cases per 100,000 vaccinated subjects. Young males 16-29 appear to be at highest risk, predominantly after receiving the second dose. The risk of myocarditis is higher in people who were infected with the SARS-CoV-2 than in those who received the vaccine. Most patients fully recover with rest and an adequate treatment. The risk of myocarditis and pericarditis has shown to be different depending on the type of vaccine/platform used. Vaccines using adenoviral vector-based platforms produce the spike protein but have not been implicated in acquired myocarditis. Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than BIMERVAX vaccine. No case of myocarditis has been observed in the clinical studies of BIMERVAX vaccine.
Risk factors and risk groups	Adolescent and young adult males following the second dose of COVID-19 vaccine may be at higher risk.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> None <u>Additional risk minimisation measures:</u> None

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 05 January 2024. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU. Protocol submission on 31 July 2023; final estimated date 31 July 2026.

Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	
Evidence for linking the risk to the medicine	This potential risk is theoretical because it has not been described in association with the BIMERVAX vaccine or it has not been reported from any other late phase clinical trial of other human vaccine. As mentioned above, this potential risk has been included based on animal data with related betacoronaviruses. VAERD refers to the predominantly lower respiratory tract presentation of VAED. Evidence sources have been collected from literature on viral vaccines, safety information of other SARS-CoV-2 vaccines and clinical trials. VAED was observed in children given formalin-inactivated whole-virus vaccines against respiratory syncytial virus (RSV) and measles virus. It has been rarely encountered with existing vaccines or viral infections (Haynes *et al.*, 2020). Although, no events of VAED/VAERD have been reported in the current BIMERVAX clinical development programme, there is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes, which would manifest as VAED/VAERD (Graham, 2020).
Risk factors and risk groups	No risks groups or risks factors have been identified. Nevertheless, 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).
Risk minimisation measures	<u>Routine risk minimisation measures:</u> None <u>Additional risk minimisation measures:</u> None

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 05 January 2024. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection vaccine in Europe in VAC4EU: protocol submission on 31 July 2023; final study report estimated date 31 July 2026.

Missing information: Use in pregnancy and while breastfeeding	
Evidence for linking the risk to the medicine	There is no experience with use of BIMERVAX vaccine in pregnant women. Nevertheless, an assessment of male and female fertility by histopathological examination of the testis and ovaries in the GLP toxicity studies in mice (AC25AA), rat (AC91AA) and rabbit (SEP-2021-011-PHH1V) found no effect of PHH-1 or PHH-1V vaccines on these organs. Also, no effects on fertility have been described for the SQBA adjuvant, using an analogous adjuvant, at least at the dose to be used in BIMERVAX vaccine. Moreover, no effects on fertility have been associated to the development of immunogenicity against SARS-CoV-2 during the development of other four COVID-19 vaccines currently approved (SmPC Comirnaty, 2021; SmPC COVID-19 Vaccine Janssen, 2021; SmPC Spikevax, 2021; SmPC Vaxzevria, 2021; SmPC Nuvaxovid, 2022). Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development. Administration of BIMERVAX vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. It is unknown whether BIMERVAX vaccine is excreted in human milk.
Anticipated risk/consequence of the missing information	Targeted populations of the indication will include women of childbearing potential, thus, the use of BIMERVAX in pregnant and/or breastfeeding women will occur.
Risk minimisation measures	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX vaccine in Europe in VAC4EU: protocol submission on 31 July 2023; final study report estimated date 31 July 2026. • Post-authorisation safety study of the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER). Protocol submission on 31 July 2023. Final estimated date 31 July 2029.

Missing information: Use in immunocompromised patients	
Evidence for linking the risk to the medicine	Subjects with immunosuppressive conditions or medications were to be excluded from the study in the BIMERVAX clinical development program. There is no evidence that the safety profile of this population receiving BIMERVAX will be different to that of the general population, but given the paucity of data, the possibility cannot be ruled out.
Anticipated risk/consequence of the missing information	As the vaccines weakened immune system may not reach a sufficient response, vaccines may be less effective in individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressants.
Risk minimisation measures	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024 **Post-authorisation safety study** • Post-authorisation safety study of BIMRVAX emulsion for injection vaccine in Europe in VAC4EU: protocol submission on 31 July 2023; final study report estimated date 31 July 2026.

Missing information: Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	
Evidence for linking the risk to the medicine	BIMERVAX has not been studied in frail individuals with severe comorbidities that may compromise immune function due to the condition or treatment of the condition. Frail patients with comorbidities (e.g., COPD, diabetes mellitus, chronic neurological disease, cardiovascular disorders) are potentially at risk of developing a more severe manifestation of COVID-19. There is no evidence that the safety profile of this population receiving BIMERVAX will be different to that of the general population, but given the scarcity of data, the possibility cannot be ruled out.
Anticipated risk/consequence of the missing information	In general, there is a potential that frail participants with unstable health conditions and co-morbidities may experience a different outcome than achieved in healthy individuals administered vaccines.
Risk minimisation measures	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
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Post-authorisation safety study** • Post-authorisation safety study of the BIMERVAX emulsion for injection in Europe in VAC4EU: protocol submission on 31 July 2023; final study report estimated date 31 July 2026.

Missing information: Use in patients with autoimmune or inflammatory disorders	
Evidence for linking the risk to the medicine	There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders. Although there is no evidence that the safety profile of this population receiving BIMERVAX will be different to that of the general population, the possibility cannot be excluded.
Anticipated risk/consequence of the missing information	In general, individuals with autoimmune or inflammatory disorders may experience a different outcome than achieved in healthy individuals administered vaccines.
Risk minimisation measures	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU: protocol submission on 31 July 2023; final study report estimated date 31 July 2026.

Missing information: Interaction with other vaccines	
Evidence for linking the risk to the medicine	BIMERVAX is indicated as a booster in individuals vaccinated against COVID 19 with mRNA vaccines. The safety and immunogenicity of a booster vaccination with BIMERVAX against SARS-CoV-2 in healthy adult volunteers fully vaccinated against COVID 19, is being evaluated in the Phase IIb clinical study HIPRA-HH-2 and Phase III study HIPRA-HH-5. Studies to determine if co-administration of BIMERVAX with other vaccines (i.e., with seasonal illness vaccines [such as the influenza vaccines]) may affect the efficacy or safety of either vaccine have not been performed.
Anticipated risk/consequence of the missing information	There is the theoretical question as whether vaccines may interact with each other and change the immune response to either vaccine or induce safety concerns. It is common medical practice to administer vaccines concurrently. Participants receiving BIMERVAX may be administered seasonal flu vaccines during the vaccination period of the pandemic.
Risk minimisation measures	Routine risk communication: SmPC section 4.5 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU: protocol submission on 31 July 2023; final study report estimated date 31 July 2026.

Missing information: Long-term safety	
Evidence for linking the risk to the medicine	Understanding of the long-term safety profile of BIMERVAX is currently limited but complete safety data up to 1 year is available for the Phase III study HIPRA-HH-5. Nevertheless, per protocols, the clinical development program has a safety follow up period up to 52 weeks after booster vaccination in the Phase IIb clinical study HIPRA-HH-2 and up to 52 weeks in the Phase IIb/III study HIPRA-HH-4.
Anticipated risk/consequence of the missing information	At the time of vaccine availability, the long-term safety data of BIMERVAX is available in the CSR of the Phase III study HIPRA-HH-5. Although there are currently no known risks with a potentially late onset, given the limited data, the possibility cannot be excluded. Data will continue to be collected from participants in ongoing studies.
Risk minimisation measures	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
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 05 January 2024. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 13 September 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection vaccine in Europe in VAC4EU: protocol submission on 31 July 2023; final study report estimated date 31 July 2026.

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 BIMERVAX.

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

Study: **HIPRA-HH-2**

Purpose of the study:

Part A: The primary objectives of this study are to determine and compare the changes of the immunogenicity measured by pseudovirus neutralisation against Wuhan strain (also known as L strain) at Baseline and Day 14, after HIPRA's vaccine (PHH-1V) versus subjects who have received complete vaccination, including homologous booster, with the Comirnaty vaccine at least 182 days and with a maximum of 365 days before booster vaccination, and to assess the safety and tolerability of PHH-1V as a booster dose in healthy adult subjects fully vaccinated against COVID-19 with the Comirnaty vaccine.

Part B: The primary objectives of this study are to determine and compare the changes in the immunogenicity measured by PBNA against omicron BA.1 subvariant, at Day 14 post-dose 4 of PHH-1V in cohort 2 versus post-dose 3 in cohort 2, and to assess the safety and tolerability of PHH-1V as a fourth dose in adult subjects in cohort 1 and 2.

Study: **HIPRA-HH-4**

Purpose of the study: The primary objective of this study to determine and compare the changes of the immunogenicity measured by pseudovirus (or live virus for the HIV cohort) neutralization against Omicron, Beta and Delta any other relevant Variants of Concern (VOC) in the epidemiologic moment, after administration of HIPRA's vaccine (PHH-1V). The secondary objectives are to determine and compare the changes of the immunogenicity measured by pseudovirus (or live virus for the HIV cohort) neutralization against Omicron, Beta and Delta and any other relevant Variants of Concern (VOC) in the epidemiologic moment at long term after administration of HIPRA's vaccine (PHH-1V). To evaluate the immunogenicity measured by means of total antibody against Receptor Binding Domain of the Spike protein of SARS-CoV-2 quantification, measured by an electrochemiluminescence immunoassay (ECLIA) after administration of HIPRA's vaccine (PHH-1V). To assess the safety and tolerability of PHH-1V as an additional dose in adult individuals with pre-existing immunosuppressive conditions.

Study: **Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU**

Purpose of the study: This study consists of two components—a vaccine utilisation study and a comparative safety study—. The vaccine utilisation study will characterise the individuals receiving the BIMERVAX vaccine. The comparative safety study uses two different designs: a cohort design to estimate the effect of BIMERVAX vaccine on adverse events of special interest (AESIs) compared with that of other COVID-19 vaccines authorised for the booster indication; and a self-controlled risk interval (SCRI) study (a subtype of the self-controlled case series design) design to estimate the effect of the COVID-19 HIPRA vaccine booster on selected AESIs compared with no COVID-19 vaccine as a booster.

Study: **Post-authorisation safety study of the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)**

Purpose of the study: This study aims to estimate the risk of obstetric outcomes (spontaneous abortion, antenatal bleeding, gestational diabetes, gestational hypertension, intrauterine growth restriction, postpartum hemorrhage, fetal distress, uterine rupture, placenta previa, chorioamnionitis, Caesarean delivery, COVID-19), neonatal outcomes (major congenital malformations, low birth weight, neonatal death, neonatal encephalopathy, neonatal infections, neonatal acute kidney injury, preterm birth, respiratory distress in the newborn, small for gestational age, stillbirth, COVID-19), and infant outcomes (developmental milestones [motor, cognitive, language, social-emotional, and mental health skills], height, weight, failure to thrive, medical conditions during the first 12 months of life, COVID-19) among pregnant women exposed to single (homologous) or mixed (heterologous) BIMERVAX series from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched reference group who received no COVID-19 vaccines during pregnancy.

Study: **Post-authorisation effectiveness study of BIMERVAX emulsion for injection in Europe in VAC4EU**

Purpose of the study: this study will estimate the effect of the BIMERVAX on COVID-19–related outcomes—i.e., COVID-19 infection, COVID-19–related hospitalisations or emergency department visits—compared with other COVID-19 vaccines authorised for the booster indication.

Part VII: Annexes

Table of contents of the Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

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The following specific adverse reaction follow-up questionnaire* will be used to collect further information on important identified and potential risks:

4A. Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) questionnaire

4B. Myocarditis/pericarditis questionnaire

*Subject to national health authority agreement

VACCINE ASSOCIATED ENHANCED DISEASE QUESTIONNAIRE

Instructions for use:
This Data Capture Aid (DCA) is intended to enable the retrieval of clinical details about potential vaccine associated enhanced disease experienced by an individual following administration of BIMERVAX. Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

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 ☐ Other_____ ☐ Refused or Unknown

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Other_____ ☐ Unknown

3. BIMERVAX:

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-19illness (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:*

PCR test result:

Variant type if known:

Viral load (including Cycle Threshold):

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

MYOCARDITIS/PERICARDITIS QUESTIONNAIRE

Instructions for use:
This Data Capture Aid (DCA) is intended to enable the retrieval of clinical details about potential myocarditis/pericarditis experienced by an individual following administration of BIMERVAX. Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

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 ☐ Other_____ ☐ Refused or Unknown

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Other_____ ☐ Unknown

3. BIMERVAX:

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**	
☐ Myocarditis			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown
☐ Pericarditis			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown

Were clinical cardiac symptoms present? (If yes, please circle what is relevant)
Acute chest pain or pressure - Palpitations - Dyspnea after exercise - Dyspnea at rest or lying down – Diaphoresis (excessive sweating)

Were Non-Specific Symptoms present? (If yes, please circle what is relevant)
Fatigue - Abdominal pain - Dizziness/Syncope - Edema - Cough - Weakness - Nausea/Vomiting - Diarrhea - Shoulder/Upper back pain - Cyanosis - Low grade intermittent fever - Altered Mental Status

In Infants and Young Children: Irritability - Vomiting - Poor feeding - Tachypnea – Lethargy
Other: please specify _____

In the event of death, please provide the date and cause of death: _____

Was an autopsy performed? ☐ Yes (if yes please attach the autopsy report) ☐No
Was the patient hospitalized for the adverse event(s)? ☐ Yes (if yes, provide date of hospitalization) _____ ☐ No
Is a discharge report available? ☐Yes (if yes, please attach the report) ☐No

5. Patient treatment

Drug name	Start Date *(DD/MM/YY)*	Route	Stop Date *(DD/MM/YY)*	Daily dose/ Any additional information

6. Relevant Medical History/Concurrent Diseases

Medical History (please, specify all relevant medical conditions)	Start date	Stop date	Is the patient treated for this condition?

7. 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

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

Lab test /Diagn. procedure	Date and Results	Normal Reference Range
Troponin T ☐ Yes ☐ No		
Troponin I ☐ Yes ☐ No		
Creatine Kinasa Myocardial ☐ Yes ☐ No		
C-reactive protein ☐ Yes ☐ No		

Erythrocyte sedimentation rate ☐ Yes ☐ No		
D-Dimer ☐ Yes ☐ No		
Cardiac Magnetic Resonance Imaging Study ☐ Yes ☐ No		
Echocardiogram ☐ Yes ☐ No		
EKG ☐ Yes ☐ No		
Radiography ☐ Yes ☐ No		
Myocardial Tissue Histopathology/ Endomyocardial biopsy ☐ Yes ☐ No		
CT-Scan ☐ Yes ☐ No		
Diagnostic tests for infectious etiologies, including but not limited to COVID-19 ☐ Yes ☐ No		
Other, *pls specify:*		

Thank you for completing this form.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.