BIMERVAX: Periodic safety update report assessment

30 March 2023 to 29 September 2023

This document consists of:

1. The PRAC assessment report of the Bimervax periodic safety update report (PSUR) covering the period 30 March 2023 to 29 September 2023, and;

2. The Bimervax PSUR itself.

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

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

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

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

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

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

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

EMA/PRAC/176523/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00011045/202309

Common name: COVID-19 Vaccine (recombinant, adjuvanted) (Bimervax)

Period covered by the PSUR: 30/03/2023 To: 29/09/2023

Centrally authorised Medicinal product(s): For presentations: See Annex A	**Marketing Authorisation Holder**
BIMERVAX	Hipra Human Health S.L.

Status of this report and steps taken for the assessment

Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	18 January 2024	18 January 2024
☐	PRAC Rapporteur's preliminary assessment report (AR)	18 March 2024	18 March 2024
☐	MS/PRAC members and MAH comments	17 April 2024	17 April 2024
☐	PRAC Rapporteur's updated assessment report following comments	2 May 2024	22 April 2024
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	16 May 2024	16 May 2024

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Table of contents

1. Background information on the procedure 5

2. Assessment conclusions and actions 5

3. Recommendations 6

4. PSUR frequency 6

Abbreviations

ACE	Angiotensin Converting Enzyme
ATC	Anatomical Therapeutic Chemical classification
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
DIBD	Development International Birth Date
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
EURD	European Union Reference Date
GMT	Geometric Mean Titres
GVP	Good Pharmacovigilance Practices
HLGT	High Level Group Term
IBD	International Birth Date
ICH	International Council on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
PHH-1V	COVID-19 Vaccine HIPRA (equivalent to BIMERVAX)
PBNA	Pseudovirion-Based Neutralisation Assay
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
RBD	Receptor Binding Protein
RMP	Risk Management Plan
RSI	Reference Safety Information
S	Spike
SAE	Severe Adverse Event
SAGE	Strategic Advisory Group on Immunization
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIIV	Seasonal Surface Antigen, Inactivated Adjuvanted Influenza Vaccine
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
Th	T helper cell type
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
WHO	World Health Organisation

1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for COVID-19 Vaccine (recombinant, adjuvanted) (Bimervax).

2. Assessment conclusions and actions

This is the 1st Periodic Safety Update Report (PSUR) for Bimervax emulsion for injection, (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus recombinant spike (S) protein Receptor Binding Domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains). This PSUR summarizes the safety information for Bimervax received by Hipra Human Health, S.L.U., Spain *(hereafter referred to as Hipra)* from the international birth date (IBD) 30 March 2023 through 29 September 2023, the data lock point (DLP) for this PSUR according to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs) is 29 March 2023.

BIMERVAX emulsion for injection (hereinafter referred to as BIMERVAX) contains 40 µg of SARS-CoV-2 virus recombinant S protein RBD fusion heterodimer – B.1.351-B.1.1.7 strains as active ingredient. BIMERVAX is presented as a multidose vial containing 10 doses of 0.5 mL each. A single intramuscular dose (0.5 mL) of BIMERVAX should be administered.

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.

During the period under review, no significant safety actions have been taken worldwide, related to either investigational uses or marketing experience.

During the period covered by this report, there were no safety-related changes to the RSI. Nonetheless, section 6.3 of the SmPC has been updated to extend the shelf life from 12 months to 15 months.

Cumulatively in clinical trials there have been 4,165 subjects exposed to Bimervax. During reporting interval there have been 137 patients vaccinated with Bimervax in the post-marketing setting.

A total of 141 SAEs have been reported in the studies HIPRA-HH-1, HIPRA-HH-2, HIPRAHH-4, HIPRA-HH-5, HIPRA-HH-10 and HAN-01. One hundred and forty (140) SAEs were considered non-related and 1 SAE (pericarditis) was considered as possibly related. Pericarditis is an important identified risk in the RMP and is listed in section 4.8 of the SmPC.

Cumulatively, no cases have been received for BIMERVAX from post-marketing sources.

4 clinical trials were completed during the current PSUR interval. Overall, no new significant safety information could be identified from 4 completed trials, that would require any regulatory action.

4 clinical trials were ongoing during the current PSUR reporting interval. There are no major findings in regard to safety at the DLP of this PSUR and no interim reports are available.

The following non-interventional studies are planned with BIMERVAX: *Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU* and *COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)*. The study protocols were submitted on 11 August 2023 for both studies. The final reports are estimated in 31 July 2026 and 31 July 2029.

There were no new nor ongoing signals during the current reporting interval.

The updated RMP version 1.3 (data lock point 30.08.2023) is currently being assessed in the scope of type II variation (Procedure No. EMEA/H/C/006058/II/0010). All safety concerns remain unchanged: Pericarditis as important identified risk, Myocarditis and Vaccine-associated enhanced disease (VAED), including

vaccine-associated enhanced respiratory disease (VAERD) as important potential risks. 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 and Long-term safety included in the list of safety concerns as a missing information.

Routine risk minimisation measures are considered sufficient.

No change to the PSUR submission frequency is deemed necessary. The current 6-month frequency for the submission of PSURs should remain unchanged.

Bimervax is under the additional monitoring list and no changes are warranted on that respect. The information regarding efficacy has not changed.

Based on the data presented in this PSUR, the overall risk/benefit balance for Bimervax in the approved indication remains unchanged.

3. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing COVID-19 Vaccine (recombinant, adjuvanted) (Bimervax) remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

4. PSUR frequency

☒No changes to the PSUR frequency

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

Annex: preliminary PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This is a 6-month Periodic Safety Update Report (PSUR) for *Hipra Human Health, S.L.U.*'s BIMERVAX emulsion for injection, containing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus recombinant spike (S) protein Receptor Binding Domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains – as active substance. This report summarises the safety data received from world-wide sources by Hipra Human Health, S.L.U. Pharmacovigilance's Unit from **30 March 2023 to 29 September 2023**.

The IBD for the product is the 30 March 2023.

BIMERVAX emulsion for injection (hereinafter referred to as BIMERVAX), is an emulsion for injection containing 40 µg of SARS-CoV-2 virus recombinant S protein RBD fusion heterodimer – B.1.351-B.1.1.7 strains as active ingredient per 0.5 mL. Route of administration - Intramuscular injection. BIMERVAX is a multidose vial containing 10 doses of 0.5 mL each. A single intramuscular dose (0.5 mL) of BIMERVAX should be administered.

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.

BIMERVAX belongs to the pharmacotherapeutic group: Vaccines, Covid-19 vaccines, Anatomical Therapeutic Chemical classification (ATC) code: J07BN.

1.2. Worldwide marketing authorisation status

BIMERVAX was first approved by the European Commission via centralised procedure on 30 March 2023. Therefore, BIMERVAX is valid in all European Economic Area (EEA) countries.

The product is currently approved in the above-mentioned countries and in the Great Britain.

Rapporteur assessment comment:

Information acknowledged.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

During the period under review, no significant safety actions have been taken worldwide, related to either investigational uses or marketing experience by Hipra Human Health, S.L.U. (Marketing Authorisation Holder [MAH] and sponsor of clinical trials), data monitoring committees, ethic committees or competent authorities, that had either a significant influence on the risk-benefit balance of the authorised medicinal product and/or an impact on the conduct of specific clinical trials or on the overall clinical development program.

Rapporteur assessment comment:

No actions were taken during the reporting period.

1.3.2. Changes to reference safety information

The current Summary of Product Characteristics (SmPC) for BIMERVAX (dated 29 June 2023) is used as the Reference Safety Information (RSI).

During the period covered by this report, there were no safety-related changes to the RSI. Nonetheless, section 6.3 of the SmPC has been updated to extend the shelf life from 12 months to 15 months.

Rapporteur assessment comment:

No safety-related changes were made to the RSI (SmPC).

1.3.3. Estimated exposure and use patterns

- *Cumulative Subject Exposure in Clinical Trials*

Approximately 4,165 subjects were exposed to BIMERVAX in 8 company-sponsored clinical trials cumulatively since the Development International Birth Date (DIBD). A cumulative total of 4,165 and 393 subjects were exposed to BIMERVAX and comparator treatments, respectively.

- *Cumulative and Interval Patient Exposure from Marketing Experience*

As of the DLP of this PSUR, BIMERVAX has only 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. A total of 3.2 million doses have been distributed to the Spanish Government up to the DLP of this report. On 25 September 2023, the Spanish Government through the Ministry of Health, confirmed to the MAH that 137 patients were vaccinated with BIMERVAX in Spain as of 19 September 2023.

Rapporteur assessment comment:

Cumulatively in clinical trials there have been 4,165 subjects exposed to Bimervax.

During reporting interval there have been 137 patients vaccinated with Bimervax.

1.3.4. Data in summary tabulations

Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 26.0) is used for coding adverse reactions described in case reports.

- *From Clinical Trials*

A total of 141 SAEs have been reported in the studies HIPRA-HH-1, HIPRA-HH-2, HIPRAHH-4, HIPRA-HH-5, HIPRA-HH-10 and HAN-01. One hundred and forty (140) SAEs were considered non-related and 1 SAE was considered as possibly related.

- *From Post-marketing Data Sources*

Cumulatively, no cases have been received for BIMERVAX from post-marketing sources.

Rapporteur assessment comment:

No new important safety information is identified.

1.3.5. Findings from clinical trials and other sources

- ***Completed Clinical Trials***

The following 4 clinical trials were completed during the period covered by this report:

- **HIPRA-HH-1**. The purpose of this first-in-human Phase I/IIa completed clinical trial, HIPRA-HH-1, was the evaluation of the safety and immunogenicity of different dose levels of the recombinant protein in adult healthy volunteers. The study was conducted at various locations in Spain. Thirty (30) subjects were enrolled in this study divided into 3 Cohorts at different dose levels. Subjects at each Cohort were randomized 5:1 to receive COVID-19 Vaccine HIPRA (PHH-1V) or control with a commercial COVID-19 vaccine (Comirnaty). Individuals were treated as follows:
    - Cohort 1: 5 participants received 2 doses of COVID-19 Vaccine HIPRA 10 containing 10 µg of protein and 1 participant received 2 doses of Comirnaty;
    - Cohort 2: 10 participants received 2 doses of COVID-19 Vaccine HIPRA 20 containing 20 µg of protein and 2 participants received 2 doses of Comirnaty;
    - Cohort 3: 10 participants received 2 doses of PHH-1V containing 40 µg of protein and 2 participants received 2 doses of Comirnaty.

  Cumulatively, 2 non-product related SAEs were reported during the trial in the same patient.

- **HAN-01**. HAN-01 was a supportive phase IIb study conducted to evaluate safety and immunogenicity of recombinant protein RBD fusion dimer candidate vaccine against SARS-CoV-2 in healthy volunteers. The study was conducted in Vietnam. The dose (0.5 mL) was selected based on the results of Phase I/IIa study. Both vaccines, BIMERVAX and Comirnaty were administered by the intramuscular route. The treatment details for each arm were:
    - PHH-1V: 2 doses of PHH-1V containing 40 µg of protein separated by 21 days.
    - Comirnaty: 2 doses of Comirnaty separated by 21 days.

  A total of 629 participants were enrolled. Among them, 256 eligible participants were randomized into two groups: 128 received the first dose of PHH-1V and 128 subjects received the first dose of Comirnaty. However, not all subjects received the second vaccination. Therefore, 121 subjects received the second dose of BIMERVAX, and 124 subjects received the second dose of Comirnaty.

  Cumulatively, 4 non-product related SAEs were reported throughout the clinical trial.

- **HIPRA-HH-10**. The study HIPRA-HH-10 was a randomised, active controlled, double-blind, phase IIb, multicentre, noninferiority clinical study conducted 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. This clinical study was conducted at 7 sites located in Spain with a competitive enrolment. Only 4 centres enrolled subjects. Subjects were randomly assigned to the following two treatment arms in a BIMERVAX: Comirnaty, 2:1 ratio:
    - Cohort 1: single booster dose of BIMERVAX. Each dose consisted in a volume of 0.5 ml of BIMERVAX (40 µg of protein).
    - Cohort 2: single booster dose of Comirnaty.

  Both vaccines were administered by intramuscular route.

A total of 26 subjects were finally enrolled in the study (8 females and 18 males) due to the difficulties in finding participants with primary series with adenovirus vaccines and without having received a 3rd dose or having a previous infection at the time where this study was approved. Participants were ≥ 18 years old at Day 0. Eighteen (18) subjects received the BIMERVAX vaccine, and 8 received the Comirnaty vaccine.

Cumulatively, 1 non-product related SAE was reported throughout the duration of the study.

- **HIPRA-HH-5**. The study HIPRA-HH-5 was a phase III, open label, single arm, multi-centre trial conducted to assess the safety and immunogenicity of a booster vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2 in adults vaccinated against COVID-19. The investigational product was administered by the intramuscular route. Each dose consisted of a volume of 0.5 ml of PHH-1V (40 µg of protein).

  A total of 2,661 subjects were enrolled for the study, and 2,661 received the study treatment. The study group consisted of 1,272 females, 1,388 males and 1 participant of unspecified sex (the patient is transgender, and the site decided not to specify the sex of the participant).

  Cumulatively, 26 SAEs were reported throughout this study. Note that PTs were considered for SAEs calculation, and there were 4 events that were codified with two PTs. Overall, 22 cases were reported, but considering the explanation above, the final count results in 26 SAEs. Of the 26 SAEs, only 1 was considered related to study drug.

  Last visited patient in this study was on 03 March 2023. The final CSR was signed on 23 August 2023.

  In conclusion, according to the CSR dated 23 August 2023, no major findings were reported in regard to safety. The results of the study with regard to the safety showed that the vaccination with the PHH-1V vaccine 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.

Rapporteur assessment comment:

4 clinical trials were completed during the current PSUR interval:

HIPRA-HH-1 was the first-in-human Phase I/IIa completed clinical trial in which 2 non-product related SAEs were reported during the trial in the same patient.

HAN-01 was a supportive phase IIb study conducted to evaluate safety and immunogenicity of recombinant protein RBD fusion dimer candidate vaccine against SARS-CoV-2 in healthy volunteers and 4 non-product related SAEs were reported throughout the clinical trial.

HIPRA-HH-10 was a randomised, active controlled, double-blind, phase IIb, multicentre, noninferiority clinical study conducted 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. A total of 26 subjects were finally enrolled in the study and out of them 18 subjects received the BIMERVAX vaccine. Cumulatively, 1 non-product related SAE was reported throughout the duration of the study.

HIPRA-HH-5 was a phase III, open label, single arm, multi-centre trial conducted to assess the safety and immunogenicity of a booster vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2 in adults vaccinated against COVID-19. A total 2,661 subjects received investigational product. Out of the 26 SAEs reported from this trial, one case was considered related to study drug. No relevant differences in the safety profile were observed regardless of the primary vaccination

schedule received or a previous COVID-19 infection.

Overall, no new significant safety information could be identified from 4 completed trials, that would require any regulatory action.

- ***Ongoing Clinical Trials***

The clinical trials described below were either ongoing (HIPRA-HH-4, HIPRA-HH-3 and HIPRA-HH-11) or clinically completed but without an available CSR at the DLP of the present report, and thus considered ongoing (HIPRA-HH-2):

- **HIPRA-HH-2.** HIPRA-HH-2 was a Phase IIb, double-blind, randomised, active-controlled, multicentre, noninferiority, 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 SARSCoV-2 in adults fully vaccinated against COVID-19, followed by an extension period to study a fourth dose administration of PHH-1V. The study was composed of two parts: Part A and Part B. Part A aimed 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 Comirnaty vaccine. The objective of Part B was to determine and compare the changes in the immunogenicity measured by Pseudovirion-Based Neutralisation Assay (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 Cohorts 1 and 2.

Part A

In part A, a total of 862 patients were screened for this study, from which 765 eligible subjects were randomly assigned to the following two treatment arms in a PHH-1V: Comirnaty 2:1 ratio:

  - Cohort 1: single booster dose of PHH-1V containing 40 µg of antigen to be administered by intramuscular route (total of 513 subjects, including 325 females and 188 males).
  - Cohort 2: single booster dose of Comirnaty (total of 252 subjects, including 159 females and 93 males).

Additionally, randomisation was stratified by age group (18-64 vs ≥65 years old) with approximately 10% of the sample enrolled in the older age group.

  - In the Cohort 1 (PHH-1V) there was a total of 475 participants in the 18-64 years old age group (306 females and 169 males) and a total of 38 participants in the ≥65 years old age group (19 females and 19 males).
  - In the Cohort 2 (Comirnaty) there was a total of 234 participants in the 18-64 age group (149 females and 85 males) and total of 18 participants in the ≥65 years old age group (10 females and 8 males).

One (1) subject prematurely discontinued participation in the Comirnaty vaccine treatment arm. This subject withdrew consent for participation. Three (3) subjects prematurely discontinued study participation in the PHH-1V treatment arm. Two (2) subjects were lost to follow-up and 1 subject withdrew consent. No discontinuation was safety related.

Part B

In part B, a total of 301 patients were screened for this study, from which 288 were vaccinated with PHH-1V as dose 4. This study is an extension of the two Cohorts already present in Part A of the study:

- Cohort 1: 106 subjects with a primary vaccination of 2 Comirnaty doses + 1 booster dose of PHH1-V that received another booster dose with PHH-1V.
- Cohort 2: 182 subjects with a primary vaccination of 2 Comirnaty doses + 1 booster dose of Comirnaty that received another booster dose with PHH-1V.

- In Cohort 1, there were 94 subjects in the 18-64 age group and 12 subjects in the ≥65 age group. Overall, there were 42 male ad 64 females.
- In Cohort 2, there were 161 subjects in the 18-64 age group and 21 subjects in the ≥65 age group. Overall, there were 73 male, 107 females and 2 individuals of undifferentiated sex.

In Cohort 1, three (3) subjects prematurely discontinued (subjects' choice). One (1) participant prematurely discontinued (withdrew consent) the study in Cohort 2. None of such discontinuations were due to safety reasons.

Cumulatively, 18 non-related SAEs have occurred throughout this study.

The clinical trial was closed on 14 August 2023. According to the last version of the interim report, dated 26 April 2023, no major findings were reported with regard to safety. The final CSR is estimated to be available on 05 January 2024.

- **HIPRA-HH-4.** HIPRA-HH-4 is an ongoing 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 preexisting immunosuppressive conditions vaccinated against COVID-19 conducted at 6 sites located in Spain and Turkey. The aim of this study was the determination of the safety profile of PHH-1V in individuals with pre-existing immunosuppressive conditions.

  Participants in the study HIPRA-HH-4 must have any of the following underlying immunosuppressive conditions:

  - Confirmed Human Immunodeficiency Virus infection with persistent CD4 T cell counts <400 within last 6 months prior to Day 0 regardless of plasma Viral Load determination and Antiretroviral (ARV) treatment;
  - Primary Antibody Deficiency Disorders on immunoglobulin replacement therapy for at least 6 months prior to Day 0 (maintenance dose);
  - Kidney disease on dialysis program for at least 6 months prior to Day0;
  - Kidney transplant at least >1 year and with last anti-CD20/anti-CD3 biological treatment given at least >1 year prior to Day0 and on maintenance immunosuppressive therapy based on at least 3 drugs: tacrolimus, glucocorticoids and mycophenolate or everolimus/sirolimus;
  - Auto-immune disease on treatment with rituximab/ocrelizumab during within the last 6 months prior to Day 0.

In this study, a sample size of 400 participants has been proposed. As of the DLP of this report, a total of 240 participants have been enrolled. Among them, a total of 238 participants have been vaccinated: 231

participants (85 females and 146 males) have received the study treatment in Spain and 7 participants (6 males and 1 female) have received the study treatment in Turkey.

Cumulatively, 90 non-related SAEs were reported throughout this study until the DLP of this report.

There are no major findings in regard to safety at the DLP of this PSUR and no interim reports are available.

- **HIPRA-HH-3.** HIPRA-HH-3 is an ongoing phase IIb, open-label, multi-centre, non-Inferiority study of safety and immunogenicity of BIMERVAX as heterologous booster for the prevention of COVID-19 in adolescents from 12 years to less than 18 years of age conducted at 5 sites in Spain. It is aimed at determining and comparing the changes in immunogenicity measured by PBNA against Omicron BA.1 variant at Baseline and Day 14, after vaccination of adolescents with a heterologous booster dose of BIMERVAX versus post heterologous booster dose in young adults (aged 18 to 25 years) from the adult booster study (HIPRA-HH-2), as well as at assessing the safety and tolerability of BIMERVAX as a heterologous booster dose in adolescents primary vaccinated against COVID-19 with 2 doses of Comirnaty vaccine.

  Participants in this study must be adolescents from 12 to less than 18 years of age, primary vaccinated with 2 doses of Comirnaty, healthy or with stable chronic conditions (nonimmunocompromised).

  A sample size of 300 participants has been proposed. As of the DLP of this report, a total of 110 participants have been enrolled and 109 of them have been vaccinated. One (1) patient did not meet the inclusion criteria and was considered a screening failure.

  Cumulatively, no SAEs have been reported.

  There are no major findings in regard to safety at the DLP of this PSUR and no interim reports are available.

- **HIPRA-HH-11**. HIPRA-HH-11 is an ongoing phase II, randomized, double-blind, multi-centre trial to evaluate the safety and immunogenicity of BIMERVAX when co-administered with seasonal surface antigen, inactivated adjuvanted influenza vaccine (SIIV) in adults older than 64 years of age fully vaccinated against COVID-19. The study is being conducted at 8 sites in Spain and the main objective is to assess and compare the safety and tolerability of BIMERVAX coadministered with SIIV in adults with respect to each vaccine when administered alone.

  The proposed sample size is 300 adults aged 65 or older that will be enrolled and followed for 1 month after study treatment. The participants will be randomised 1:1:1 to one of the following three Cohorts:

  - Cohort 1: approximately 100 participants will receive one dose of SIIV in one arm + one dose of placebo in the other arm, at Day 0.
  - Cohort 2: approximately 100 participants will receive one dose of BIMERVAX in one arm + 1 dose of placebo in the other arm, at Day 0.
  - Cohort 3: approximately 100 participants will receive one dose SIIV in one arm + one dose of BIMERVAX in the other arm, at Day 0.

  Participants in this study must have received at least a primary scheme of an mRNA vaccine (2 doses). Booster doses or previous COVID-19 infections are allowed. Last dose must have been administered at least 6 months before Day 0. Additionally, participants must have a negative Rapid Antigen Test at Day 0 before vaccinations (history of COVID-19 infection is allowed if

occurred at least >30 days before Day 0) and be healthy or with stable chronic conditions (non-immunocompromised).

All participants will receive two administrations at Day 0 (each vaccine/placebo will be administered in a different arm, regardless the order) and will be followed for 1 month.

As of the DLP of this report, a total of 283 participants have been enrolled, 279 of these were randomized and 278 have received the study product.

There are no major findings in regard to safety at the DLP of this PSUR and no interim reports are available.

Rapporteur assessment comment:

4 clinical trials were ongoing during the current PSUR reporting interval.

HIPRA-HH-2 was a Phase IIb, double-blind, randomised, active-controlled, multicentre, noninferiority, 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 SARSCoV-2 in adults fully vaccinated against COVID-19, followed by an extension period to study a fourth dose administration of PHH-1V. The study was composed of two parts: Part A and Part B.

In part A, a total of 862 patients were screened for this study, from which 765 eligible subjects were randomly assigned to the following two treatment arms in a PHH-1V: Comirnaty 2:1 ratio. One (1) subject prematurely discontinued participatinn in the Comirnaty vaccine treatment arm. This subject withdrew consent for participation. Three (3) subjects prematurely discontinped study particippgtipn in tbe PHH-1V treatment arm. Two (2) subjects were lost to follow-up and 1 subject withdrew consent. No discontinuation was safety related.

In part B, a total of 301 patients were sereened for this study, from which 288 were vaccinated witb PHH-1V as dose 4. Cumulatively, 18 non-related SAEs have occurred throughout this study. The clinical trial was closed on 14 August 2023. Accprding tp the last version of the interim report, dated 26 April 2023, no major findings were reported with regard to safety. The final CSR is estimated to be available on 05 January 2024.

HIPRA-HH-4 is an ongoing phase IIb/III, epen 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 preexistiag immunosuppressive canditions yaccinated against COVID-19 conducted at 6 sites located in Spain and Turkey. In this study, a sample size of 400 participants has been proposed. As of the DLP of this report, a total of 240 participants have been enrolled. Among them, a total of 238 participants have been vaccinated: 231 participants (85 females and 146 males) have received the study treatment in Spain and 7 participapts (6 males and 1 female) have received the study treatment in Turkey. Cumulatively, 90 non-related SAEs were repprted throughout this study antil the DLP of this report.

HIPRA-HH-3 is an ongoing phase IIb, open-label, multi-centre, non-Inferiority study of safety and immunogenicity of BIMERVAX as heterologous booster for the prevention of COVID-19 in adolescents from 12 years to less than 18 years of age conducted at 5 sitas in Spaip. A sample size of 300 participants has been proposed. As of the DLP of this report, a total of 110 participants have been enrolled and 109 of them have been vaccinated. One (1) patient did not meet the inclusion criteria and was considered a screening failure. Cumulatively, no SAEs have been reported.

HIPRA-HH-11 is an ongoing phase II, randomized, double-blind, multi-centre trial to evgluate the safety and immunogenicity of BIMERVAX when co-administered with seasonal surface antigen, inactivated adjuvanted influenza vaccine (SIIV) in adults older than 64 years of age fully vaccinated against COVID-

19. As of the DLP of this report, a total of 283 participants have been enrolled, 279 of these were randomized and 278 have received the study product.

There are no major findings in regard to safety at the DLP of this PSUR and no interim reports are available.

- ***Findings from non-interventional studies***

Two (2) non-interventional studies are planned with BIMERVAX.

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

  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 compared with that of other COVID-19 vaccines authorised for the same indication; and a self-controlled risk interval study (a subtype of the self-controlled case series design) design to estimate the effect of the COVID-19 HIPRA vaccine booster on selected adverse events of special interest compared with no COVID-19 vaccination booster.

  The study protocol was submitted on 11 August 2023. A final report is planned for submission within 36 months after rollout of BIMERVAX booster vaccination campaigns in the first participating country (estimated date: 31 July 2026).

- ***COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)***

  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 foetus is lacking.

  The study protocol was submitted on 11 August 2023. A final report is planned for submission within 12 months after study completion (estimated date: 31 July 2029).

Rapporteur assessment comment:

The following non-interventional studies are planned with BIMERVAX: *Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU* and *COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER).* The study protocols were submitted on 11 August 2023 for both studies. The final reports are estimated in 31 July 2026 and 31 July 2029.

1.3.6. Lack of efficacy in controlled clinical trials

The results available from clinical trials do not indicate lack of efficacy that could reflect a significant risk to the treated population.

Rapporteur assessment comment:

Information acknowledged.

1.3.7. Late-breaking information

No important information concerning the efficacy/effectiveness or safety of BIMERVAX has been received since the data lock-point of this report.

Rapporteur assessment comment:

Information acknowledged.

2. Signal and risk evaluation

2.1. Summary of safety concerns

There is a Risk Management Plan (RMP) in place for BIMERVAX at the beginning of the reporting interval, which listed the following safety concerns:

Important identified risks	Pericarditis Myocarditis
Important potential risks	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

Rapporteur assessment comment:

The updated RMP version 1.3 (data lock point 30.08.2023) is currently being assessed in the scope of type II variation (Procedure No. EMEA/H/C/006058/II/0010). Currently all safety concerns remain unchanged.

2.2. Signal evaluation

Cumulatively, no signals as defined by the GVP Module VII corresponding with the term "validated signal" described in GVP Module IX have been detected.

Rapporteur assessment comment:

Information acknowledged.

2.3. Evaluation of risks and safety topics under monitoring

During the period covered by this report, no new important identified and potential risks have been identified. In addition, no new information relevant to previously recognised potential and identified risks and missing information has been identified.

Rapporteur assessment comment:

Taking into consideration the information provided by the MAH no further action is considered warranted at this stage.

2.4. Characterisation of risks

Important identified risk

Pericarditis (MedDRA PT: 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, 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 S protein that the mRNA encodes for, cross-react with structural similar host proteins in the heart, also known as molecular mimicry [Klamer, 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, 2022]. 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 S protein but have not been implicated in acquired myocarditis [Pillay, 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, 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, 2022].

Clinical Trial experience:

In the phase III study HIPRA-HH-5, of the 2,661 subjects included in the safety dataset, 1 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, 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, 2022].

Post-marketing experience:

No post-marketing data are yet available 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, 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 selflimiting. 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 (MedDRA PT: 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, 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 S protein that the mRNA encodes for, cross-react with structural similar host proteins in the heart, also known as molecular mimicry [Klamer, 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, 2022]. 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 has shown to be different depending on the type of vaccine/platform used. Vaccines using adenoviral vector-based platforms produce the S protein but have not been implicated in acquired myocarditis [Pillay, 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, 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, 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, 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 postauthorization surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than BIMERVAX vaccine [Twentyman, 2022].

Post-marketing experience:

No post-marketing data are yet available 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, 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 selflimiting. 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.

VAED, including VAERD (MedDRA PTs: Antibody-dependent enhancement and Enhanced respiratory disease)

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 middle east respiratory syndrome coronavirus (mice model) vaccines [Haynes, 2020; Lambert, 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, 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 and measles virus. It has been rarely encountered with existing vaccines or viral infections [Haynes, 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:

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).

Clinical Trial experience:

No events of VAED/VAERD have been reported in the current BIMERVAX clinical development programme.

Post-marketing experience:

No post-marketing data are yet available with BIMERVAX vaccine.

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.

Missing information

Use in pregnancy and while breastfeeding (MedDRA Standardised MedDRA Query (SMQ) Pregnancy and neonatal topics)

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 good laboratory practice 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 COVID-19 vaccines currently approved [SmPC Comirnaty, 2023; SmPC Jcovden, 2023; SmPC Nuvaxovid, 2023; SmPC Spikevax, 2023; SmPC Vaxzevria, 2023]. 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 (Medical history: MedDRA High Level Group Term (HLGT): Immunodeficiency syndromes; and/or Coded reaction: MedDRA SMQ: Opportunistic infection)

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., COPD), diabetes, chronic neurological disease, cardiovascular disorders) (patients with coded severe comorbidities in medical history)

Evidence source:

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 comorbidities may experience a different outcome than achieved in healthy individuals

administered vaccines.

16.4.3.4. Use in patients with autoimmune or inflammatory disorders (patients with coded autoimmune or inflammatory disorders in medical history)

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 (PT: Vaccine interaction)

Evidence source:

BIMERVAX is indicated as a booster in individuals vaccinated against COVID-19. The safety and immunogenicity of a booster vaccination with BIMERVAX 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 studies HIPRA-HH- 2 and HIPRA-HH10, and in the Phase III studies HIPRA-HH-5 and HIPRA-HH-4. A study 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 is currently being performed, phase II study HIPRA-HH-11.

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. 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 in the Phase IIb clinical study HIPRAHH- 2, up to 26 weeks in the Phase III study HIPRA-HH-5, up to 26 weeks in the Phase IIb HIPRA-HH-10 study, 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 of BIMERVAX is not fully known. 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 and planned post-authorisation studies.

16.5 Effectiveness of Risk Minimisation (if applicable)

Not applicable, since routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product and therefore, additional risk minimisation measures are not deemed necessary.

Rapporteur assessment comment:

The safety concerns remain unchanged.

3. Benefit evaluation

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.

Efficacy of BIMERVAX was inferred by immunobridging of immune responses to the previously authorised COVID-19 vaccine Comirnaty, for which vaccine efficacy had been established.

The immunogenicity of BIMERVAX was evaluated in one pivotal phase IIb double-blind clinical trial (HIPRA-HH-2) and in one phase III multi-centre clinical trial (HIPRA-HH-5). The other studies were considered supportive.

The results of the studies performed were considered indicative of a superior neutralizing immune response of BIMERVAX over the active comparator Comirnaty against Omicron BA.1 and Beta, as well as non-inferior neutralizing immune response against Delta, 14 days after booster administration. Additionally, long-term data indicated that antibodies may wane to a lesser degree after BIMERVAX administration than after Comirnaty administration for subjects above or below 65 years of age and irrespective of the virus strain [Bimervax. Public Assessment Report, 2023].

Clinical data demonstrate immunogenic activity of BIMERVAX, which is effective against the SARS-CoV-2 Wuhan strain and the different variants, including the Beta, Delta and Omicron variants. Clinical data demonstrates a more duration of the immune response against Wuhan, Beta, Delta and Omicron BA.1 for the booster with BIMERVAX compared to the Comirnaty vaccine, which is an important characteristic for a vaccine. A more sustained immune response against Wuhan, Beta, Delta and Omicron BA.1 is shown in individuals below 65 years old and in individuals 65 years old and older.

No severe COVID-19 infections were reported in the clinical studies, which supports that BIMERVAX provides protection to moderate, severe, life-threatening, and fatal forms of SARS-CoV-2 infections.

Rapporteur assessment comment:

There are no new data on efficacy during the current PSUR interval which are described in the approved product information.

4. Benefit-risk balance

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 clinical trials, BIMERVAX showed a good safety profile, with most common adverse reactions reported being injection site pain, headache, fatigue and myalgia. The median duration of local and systemic adverse reactions was 1 to 3 days. Most adverse reactions occurred within 3 days following vaccination and were mild to moderate in severity.

After its distribution to the market on 14 June 2023, a total of 137 patients have been administered with BIMERVAX, and no ICSRs have been received during the reporting period of the PSUR.

Pericarditis and myocarditis have been classified as important identified and potential risk for BIMERVAX, respectively. Most vaccine-associated pericarditis and myocarditis events have been mild and self-limiting. However, both events 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, their impact on the risk-balance of the vaccine is considered minimal. Only one case of a pericarditis event was detected in a clinical study using BIMERVAX, while no myocarditis events have been reported cumulatively. This single case of pericarditis was idiopathic, completely resolved with appropriate treatment, and was considered probably related to the vaccine due to temporal association.

VAED/VAERD has also been identified as an important potential risk for BIMERVAX. 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, 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. Up to the DLP of this report, no events of VAED or VAERD have been reported in clinical trials.

During the period covered by this PSUR, no signals were identified or evaluated.

During the period covered by this report, there has been no new or important data identified for the approved indication that could impact on the safety and efficacy specifications described in the current RSI.

Based on the data held on file by the MAH and the available scientific and medical literature, BIMERVAX remains an effective product for the approved indication when used as stated in the product reference information, and the benefits outweigh the risks to the patient by its administration.

Rapporteur assessment comment:

No new safety concerns or change in benefits have been identified in the assessment of the data presented in the current PSUR, thus, the benefit-risk balence for Bimerax remains unchanged.

No change to the PSUR submission frequency is deemed necessary. The current 6-month frequency for the submission of PSURs should remain unchanged. Bimervax is under the additional monitoring list and no any changes are warranted on that respect.

HIPRA

PERIODIC SAFETY UPDATE REPORT

for

ACTIVE SUBSTANCE: SARS-CoV-2 virus recombinant spike (S) protein Receptor Binding Domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains

ATC CODE: J07BN

MEDICINAL PRODUCT COVERED:

Invented Name of the Medicinal Product	Marketing Authorisation Numbers	Dates of Authorisation	Marketing Authorisation Holder
BIMERVAX®	EU/1/22/1709/001	30 March 2023	Hipra Human Health, S.L.U.
BIMERVAX®	PLGB 56346/0002	31 July 2023	Hipra Human Health, S.L.U.

AUTHORISATION PROCEDURE in the EU: Centralised procedure

INTERNATIONAL BIRTH DATE (IBD): 30 March 2023

INTERVAL COVERED BY THIS REPORT:

30 March 2023 to 29 September 2023

DATE OF THIS REPORT

20 November 2023

OTHER INFORMATION:

APPLICANT'S NAME AND ADDRESS:

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For communication and assessment of this report: [redacted]

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Executive Summary

Introduction

This is a 6-month Periodic Safety Update Report (PSUR) for Hipra Human Health, S.L.U.'s BIMERVAX emulsion for injection, containing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus recombinant spike (S) protein Receptor Binding Domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains – as active substance, compiled for the Regulatory Authorities in the format proposed in the Guideline on Good Pharmacovigilance Practices (GVP) (December 2013) module VII - and in the document International Council on Harmonisation (ICH) E2C-R2 (January 2013) aligned with the European Medicines Reference Dates (EURD) list submitting frequency. This report summarises the safety data received from world-wide sources by Hipra Human Health, S.L.U. Pharmacovigilance's Unit from 30 March 2023 to 29 September 2023.

Reporting interval

This executive summary provides a concise summary of the content and the most important information in the PSUR collected from 30 March 2023 to 29 September 2023.

Medicinal product

Name of the product	BIMERVAX emulsion for injection, hereinafter referred to as BIMERVAX.
Active substance	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus recombinant spike (S) protein Receptor Binding Domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains.
Pharmaceutical form	Emulsion for injection.
Indication	BIMERVAX is indicated as a booster for active immunisation to prevent Coronavirus Disease 2019 (COVID-19) in individuals 16 years of age and older who have previously received a messenger Ribonucleic Acid (mRNA) COVID-19 vaccine.
Regime of Dosage	A single intramuscular dose (0.5 mL) of BIMERVAX should be administered.

Number of countries in which the medicinal product is authorised

BIMERVAX was first approved by the European Commission via centralised procedure on 30 March 2023. Therefore, BIMERVAX is valid in all European Economic Area (EEA) countries.

The product is currently approved in the above-mentioned countries and in Great Britain.

Actions taken and proposed for safety reasons including significant changes to the investigator brochure and post-authorisation product information or other risk minimisation activities

None during this period.

Estimated cumulative clinical trials exposure

Approximately 4,165 subjects were exposed to BIMERVAX in 8 company-sponsored clinical trials cumulatively since the Development International Birth Date (DIBD). The estimates of the cumulative patient exposure are based upon exposure data from completed clinical trials, from ongoing clinical trials which are unblinded, and from the enrolment/randomisation schemes for those ongoing trials which are still blinded.

Estimated interval and cumulative exposure from marketing experience

One hundred and thirty-seven (137) doses of BIMERVAX have been administered during the period covered by this safety report and cumulatively until 19 September 2023 (equivalent to 137 patients vaccinated). Please, note that the data on cumulative exposure from marketing experience was provided by the Spanish Government through the Ministry of Health until 19 September 2023, and not until the DLP of the report.

Summary of the overall benefit-risk analysis evaluation

No new data on efficacy/effectiveness are available.

No relevant new information affecting the known safety profile of BIMERVAX has been identified. Therefore, the benefit-risk balance of the product remains positive.

Conclusions

In this PSUR (from 30 March 2023 to 29 September 2023), all available safety-relevant data obtained during the reporting period and all available cumulative data obtained since launch have been reviewed.

During the period under review:

- No new data on efficacy/effectiveness was identified,
- No case reports have been received,
- No other new information affecting the known safety profile of BIMERVAX has been found,
- No safety related actions or safety related investigations have been performed.

The evaluation of the collected information confirmed that the benefit-risk balance remains positive. Therefore, no changes to the Reference Safety Information (RSI) are required.

Table of Contents

0. ABBREVIATIONS 5
1. Introduction 6
2. World-wide marketing authorisation status 7
3. Actions taken in the reporting interval for safety reasons 8
4. Changes to reference safety information 8
5. Estimated exposure and use patterns 8
6. Data in summary tabulations 10
7. Summaries of significant findings from clinical trials during the reporting interval 11
8. Findings from non-interventional studies 17
9. Information from other clinical trials and sources 17
10. Non-clinical data 17
11. Literature 18
12. Other periodic reports 18
13. Lack of efficacy in controlled clinical trials 18
14. Late-breaking information 18
15. Overview of signals: new, ongoing or closed 18
16. Signal and risk evaluation 18
17. Benefit evaluation 25
18. Integrated benefit-risk analysis for authorised indications 27
19. Conclusions and actions 30
20. Appendices to the PSUR 31

0. ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ATC	Anatomical Therapeutic Chemical classification
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
DIBD	Development International Birth Date
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
EURD	European Union Reference Date
GMT	Geometric Mean Titres
GVP	Good Pharmacovigilance Practices
HLGT	High Level Group Term
IBD	International Birth Date
ICH	International Council on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
PHH-1V	COVID-19 Vaccine HIPRA (equivalent to BIMERVAX)
PBNA	Pseudovirion-Based Neutralisation Assay
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
RBD	Receptor Binding Protein
RMP	Risk Management Plan
RSI	Reference Safety Information
S	Spike
SAE	Severe Adverse Event
SAGE	Strategic Advisory Group on Immunization
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIIV	Seasonal Surface Antigen, Inactivated Adjuvanted Influenza Vaccine
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
Th	T helper cell type
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
WHO	World Health Organisation

1. Introduction

This is a 6-month Periodic Safety Update Report (PSUR) for Hipra Human Health, S.L.U.'s BIMERVAX emulsion for injection, containing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus recombinant spike (S) protein Receptor Binding Domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains – as active substance, compiled for the Regulatory Authorities in the format proposed in the Guideline on Good Pharmacovigilance Practices (GVP) (December 2013) module VII - and in the document International Council on Harmonisation (ICH) E2C-R2 (January 2013) aligned with the European Medicines Reference Dates (EURD) list submitting frequency. This report summarises the safety data received from world-wide sources by Hipra Human Health, S.L.U. Pharmacovigilance's Unit from 30 March 2023 to 29 September 2023.

1.1 International Birth Date (IBD)

The IBD for the product is the 30 March 2023.

1.2 Medicinal Product

BIMERVAX emulsion for injection (hereinafter referred to as BIMERVAX), is an emulsion for injection containing 40 µg of SARS-CoV-2 virus recombinant S protein RBD fusion heterodimer – B.1.351-B.1.1.7 strains as active ingredient per 0.5 mL.

BIMERVAX belongs to the pharmacotherapeutic group: Vaccines, Covid-19 vaccines, Anatomical Therapeutic Chemical classification (ATC) code: J07BN.

BIMERVAX is a recombinant protein vaccine whose active substance (antigen) is SARS-CoV-2 virus recombinant S protein RBD fusion heterodimer – B.1.351-B.1.1.7 strains. Following administration, an immune response is generated, both at a humoral and cellular level, against the SARS-CoV-2 RBD antigen. Neutralising antibodies against the RBD domain of SARS-CoV-2 prevent RBD binding to its cellular target Angiotensin Converting Enzyme 2 (ACE2), thus blocking membrane fusion and viral infection. Moreover, BIMERVAX induces antigen-specific T-cell immune response, which contributes to protection against COVID-19.

Authorised indication

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.

Pharmaceutical form

Emulsion for injection.

White homogeneous emulsion.

Route of administration, Dose

Intramuscular injection.

BIMERVAX is a multidose vial containing 10 doses of 0.5 mL each. A single intramuscular dose (0.5 mL) of BIMERVAX should be administered.

1.3 Populations being treated and studied

As mentioned above, BIMERVAX is indicated in individuals 16 years of age and older.

The safety and efficacy of BIMERVAX in children and adolescents less than 16 years of age have not been established yet. A clinical trial aiming to determine the safety and immunogenicity of BIMERVAX in adolescents from 12 years to less than 18 years of age, HIPRA-HH-3, is currently ongoing (please refer to section 7.2.4 of this report).

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. A clinical trial aiming to determine the immunogenicity and safety of BIMERVAX in adults with pre-existing immunosuppressive conditions vaccinated against COVID-19 (HIPRA-HH-4) is currently ongoing (please refer to section 7.2.3 of this report).

There is no experience with the use of BIMERVAX in pregnant women and it is unknown whether BIMERVAX is excreted in human milk.

BIMERVAX is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients contained in the product.

2. World-wide marketing authorisation status

BIMERVAX was first approved by the European Commission via centralised procedure on 30 March 2023. Therefore, BIMERVAX is valid in all European Economic Area (EEA) countries.

The product is currently approved in the above-mentioned countries and in the Great Britain.

Details of worldwide marketing authorisation status are presented in the following table:

Table 1: Worldwide Marketing Authorisation Status

Country	Invented Name of the Medicinal Product	Marketing Authorisation Number	Date of Authorisation	Approved dose	Indication
EEA	BIMERVAX emulsion for injection	EU/1/22/1709/001	30 March 2023	0.5 mL containing 40 µg of SARS-CoV-2 virus recombinant S protein RBD fusion heterodimer (B.1.351 and B.1.17 strains)	BIMERVAX is indicated as a booster for active immunisation to prevent COVD-19 in individuals 16 years of age and older who have previously received a mRNA COVID-19 vaccine.
Great Britain	BIMERVAX emulsion for injection	PLGB 56346/0002	31 July 2023	0.5 mL containing 40 micrograms of SARS-CoV-2 virus recombinant	BIMERVAX is indicated as a booster for active immunisation to prevent COVD-19 in

Country	Invented Name of the Medicinal Product	Marketing Authorisation Number	Date of Authorisation	Approved dose	Indication
				S protein RBD fusion heterodimer (B.1.351 and B.1.17 strains)	individuals 16 years of age and older who have previously received a mRNA COVID-19 vaccine.

3. Actions taken in the reporting interval for safety reasons

During the period under review, no significant safety actions have been taken worldwide, related to either investigational uses or marketing experience by Hipra Human Health, S.L.U. (Marketing Authorisation Holder [MAH] and sponsor of clinical trials), data monitoring committees, ethic committees or competent authorities, that had either a significant influence on the risk-benefit balance of the authorised medicinal product and/or an impact on the conduct of specific clinical trials or on the overall clinical development program.

4. Changes to reference safety information

The current Summary of Product Characteristics (SmPC) for BIMERVAX (dated 29 June 2023) is used as the Reference Safety Information (RSI) and is presented in Appendix 1.

During the period covered by this report, there were no safety-related changes to the RSI. Nonetheless, section 6.3 of the SmPC has been updated to extend the shelf life from 12 months to 15 months.

5. Estimated exposure and use patterns

5.1 Cumulative Subject Exposure in Clinical Trials

Approximately 4,165 subjects were exposed to BIMERVAX in 8 company-sponsored clinical trials cumulatively since the Development International Birth Date (DIBD).

Four (4) company-sponsored clinical trials had been completed prior to the Data Lock Point (DLP) of this PSUR (HIPRA-HH-1, HAN-01, HIPRA-HH-10 and HIPRA-HH-5). Furthermore, 4 clinical trials are ongoing: 1 clinical trial which is clinically completed but without an available Clinical Study Report (CSR) at the DLP of this report (HIPRA-HH-2) and 3 clinical trials which are not clinically completed (HIPRA-HH-4, HIPRA-HH-3 and HIPRA-HH-11).

The estimates of the cumulative patient exposure are based upon exposure data from completed clinical trials, from ongoing clinical trials which are unblinded, and from the enrolment/randomisation schemes for those ongoing trials which are still blinded.

In the above-mentioned clinical trials, a cumulative total of 4,165 and 393 subjects were exposed to BIMERVAX and comparator treatments, respectively.

Estimates of the cumulative patient exposure are provided in the tables below.

Table 2: Estimated cumulative subject exposure from clinical trials

Treatment	Number of Subjects
Medicinal Product*	4,165
Comparator	393
Placebo	0

**Please note that study HIPRA-HH-11 is still blinded. BIMERVAX patient exposure from this trial is estimated based on its enrolment/randomisation schemes.*

The age and sex distribution of patients treated in clinical trials is summarised in Table 3 and Table 4.

Table 3: Cumulative subject exposure to investigational drug from clinical trials by age

Age range	Total
<18	145
18-64	3,679
>=65	341
Total	**4,165**

Table 4: Cumulative subject exposure to investigational drug from clinical trials by sex

Sex	Total
Male	2,077
Female	2,085
Undifferentiated	3
Total	**4,165**

The race distribution of patients treated in clinical trials is summarised in Table 5.

Table 5: Cumulative subject exposure to investigational drug from clinical trials by racial group

Racial group	Number of Subjects
White	3,958
Hispanic/Caucasian	24
American Indian or Alaska Native	13
Black or African American	11
Asian	137
Other	22
Total	**4,165**

5.2 Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1. Post-authorisation (non-clinical trial) exposure

BIMERVAX is to be procured and distributed through the Governments; therefore, information on post-authorisation (non-clinical trial exposure) will be requested to the Government of each country in which BIMERVAX has been distributed. Should the Governments not provide these data, an estimation based on sold doses and vaccination trends will be made.

As of the DLP of this PSUR, BIMERVAX has only 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. A total of 3.2 million doses have been distributed to the Spanish Government up to the DLP of this report.

On 25 September 2023, the Spanish Government through the Ministry of Health, confirmed to the MAH that 137 patients were vaccinated with BIMERVAX in Spain as of 19 September 2023.

Patient exposure is shown in the following table:

Table 6: Interval and cumulative sales data from 30 March 2023* to 29 September 2023

Country	Brand name	Patients vaccinated
Spain	BIMERVAX	137
	Total	**137**

*First units of BIMERVAX were distributed to the Spanish territory on 14 June 2023.

Therefore, 137 doses of BIMERVAX have been administered during the period covered by this safety report and cumulatively until 19 September 2023 (equivalent to 137 patients vaccinated).

5.2.2. Post-authorisation use in special populations

Post-authorisation exposure data regarding to sex, age, racial/ethnic group, particular doses, indications, off-label use or use in special populations has not been provided.

Therefore, it is unknown whether during the period covered by this report, there was post-authorisation use in special populations.

5.2.3. Pattern of use of the medicinal product

No patterns of use different to those described in the RSI of the product have been identified with the available data.

6. Data in summary tabulations

6.1 Reference Information

Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 26.0) is used for coding adverse reactions described in case reports.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Cumulative summary tabulations of all Serious Adverse Events (SAEs) reported in clinical trials, from the DIBD to the DLP of this PSUR are provided in Appendix 2.1. SAEs are organised by System Organ Class (SOC) and Preferred Term (PT), and divided by product name (investigational medicinal product treatments, blinded, comparator treatments and placebo), as applicable.

A total of 141 SAEs have been reported in the studies HIPRA-HH-1, HIPRA-HH-2, HIPRA-HH-4, HIPRA-HH-5, HIPRA-HH-10 and HAN-01. One hundred and forty (140) SAEs were considered non-related and 1 SAE was considered as possibly related.

6.3 Cumulative and Interval Summary Tabulations from Post-marketing Data Sources

Cumulative and interval summary tabulations of adverse reactions from post-marketing data sources are provided in Appendix 2.2. These adverse reactions are derived from spontaneous Individual Case Safety Report (ICSRs), including world-wide reports from

healthcare professionals, consumers, scientific literature, and competent authorities and from solicited ICSRs including those from non-interventional studies. Serious and non-serious adverse reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources are presented in a single table, with interval and cumulative data presented side-by-side. The table is organised by MedDRA SOC.

Cumulatively, no cases have been received for BIMERVAX from post-marketing sources. Therefore, no tabulated information is provided in Appendix 2.2.

7. Summaries of significant findings from clinical trials during the reporting interval

A total of 8 clinical trials were either ongoing or completed during the current reporting period. Specifically, 4 of them were completed and the remaining 4 are ongoing.

A listing of all the sponsored post-authorisation interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval is available in Appendix 4.

7.1 Completed Clinical Trials

The following 4 clinical trials were completed during the period covered by this report, which are described below.

No clinically important emerging efficacy and safety findings were obtained from clinical trials completed during the reporting interval.

7.1.1 HIPRA-HH-1

The purpose of this first-in-human Phase I/IIa completed clinical trial, HIPRA-HH-1, was the evaluation of the safety and immunogenicity of different dose levels of the recombinant protein in adult healthy volunteers. The study was conducted at various locations in Spain. Thirty (30) subjects were enrolled in this study divided into 3 Cohorts at different dose levels. Subjects at each Cohort were randomized 5:1 to receive COVID-19 Vaccine HIPRA (PHH-1V) or control with a commercial COVID-19 vaccine (Comirnaty). Individuals were treated as follows:

- Cohort 1: 5 participants received 2 doses of COVID-19 Vaccine HIPRA 10 containing 10 µg of protein and 1 participant received 2 doses of Comirnaty;
- Cohort 2: 10 participants received 2 doses of COVID-19 Vaccine HIPRA 20 containing 20 µg of protein and 2 participants received 2 doses of Comirnaty;
- Cohort 3: 10 participants received 2 doses of PHH-1V containing 40 µg of protein and 2 participants received 2 doses of Comirnaty.

Cumulatively, 2 non-product related SAEs were reported during the trial in the same patient.

In conclusion, the results from the study in terms of safety and tolerability suggested that the HIPRA vaccine at all doses tested was well tolerated, with mild and self-limited local reactogenicity being comparable to that of a commercial vaccine and suggesting less systemic AEs (especially fever) than the comparator. There were no changes in laboratory parameters or vital signs suggestive of vaccine-induced toxicity.

7.1.2 HAN-01

HAN-01 was a supportive phase IIb study conducted to evaluate safety and immunogenicity of recombinant protein RBD fusion dimer candidate vaccine against SARS-CoV-2 in healthy volunteers. The study was conducted in Vietnam. The dose (0.5 mL) was selected based on the results of Phase I/IIa study.

Both vaccines, BIMERVAX and Comirnaty were administered by the intramuscular route.

The treatment details for each arm were:

- PHH-1V: 2 doses of PHH-1V containing 40 µg of protein separated by 21 days.
- Comirnaty: 2 doses of Comirnaty separated by 21 days.

A total of 629 participants were enrolled. Among them, 256 eligible participants were randomized into two groups: 128 received the first dose of PHH-1V and 128 subjects received the first dose of Comirnaty. However, not all subjects received the second vaccination. Therefore, 121 subjects received the second dose of BIMERVAX, and 124 subjects received the second dose of Comirnaty.

Cumulatively, 4 non-product related SAEs were reported throughout the clinical trial.

In conclusion, the results from the study proved the safety, tolerability and high immunogenic potential of the COVID-19 Vaccine HIPRA (PHH-1V) against relevant variants of concern when administered in a primary vaccination schedule.

7.1.3 HIPRA-HH-10

The study HIPRA-HH-10 was a randomised, active controlled, double-blind, phase IIb, multi-centre, noninferiority clinical study conducted 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. This clinical study was conducted at 7 sites located in Spain with a competitive enrolment. Only 4 centres enrolled subjects.

Subjects were randomly assigned to the following two treatment arms in a BIMERVAX: Comirnaty, 2:1 ratio:

- Cohort 1: single booster dose of BIMERVAX. Each dose consisted in a volume of 0.5 ml of BIMERVAX (40 µg of protein).
- Cohort 2: single booster dose of Comirnaty.

Both vaccines were administered by intramuscular route.

A total of 26 subjects were finally enrolled in the study (8 females and 18 males) due to the difficulties in finding participants with primary series with adenovirus vaccines and without having received a 3rd dose or having a previous infection at the time where this study was approved. Participants were ≥ 18 years old at Day 0. Eighteen (18) subjects received the BIMERVAX vaccine, and 8 received the Comirnaty vaccine.

Cumulatively, 1 non-product related SAE was reported throughout the duration of the study.

In conclusion, the results of the study in terms of safety showed that vaccination with BIMERVAX and Comirnaty vaccines were overall well tolerated.

7.1.4 HIPRA-HH-5

The study HIPRA-HH-5 was a phase III, open label, single arm, multi-centre trial conducted to assess the safety and immunogenicity of a booster vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2 in adults vaccinated

against COVID-19. The investigational product was administered by the intramuscular route. Each dose consisted of a volume of 0.5 ml of PHH-1V (40 µg of protein).

A total of 2,661 subjects were enrolled for the study, and 2,661 received the study treatment. The study group consisted of 1,272 females, 1,388 males and 1 participant of unspecified sex (the patient is transgender, and the site decided not to specify the sex of the participant).

Cumulatively, 26 SAEs were reported throughout this study. Note that PTs were considered for SAEs calculation, and there were 4 events that were codified with two PTs. Overall, 22 cases were reported, but considering the explanation above, the final count results in 26 SAEs. Of the 26 SAEs, only 1 was considered related to study drug.

Last visited patient in this study was on 03 March 2023. The final CSR was signed on 23 August 2023.

In conclusion, according to the CSR dated 23 August 2023, no major findings were reported in regard to safety. The results of the study with regard to the safety showed that the vaccination with the PHH-1V vaccine 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.

7.2 Ongoing Clinical Trials

The clinical trials described below were either ongoing (HIPRA-HH-4, HIPRA-HH-3 and HIPRA-HH-11) or clinically completed but without an available CSR at the DLP of the present report, and thus considered ongoing (HIPRA-HH-2).

The MAH is not aware of clinically important information that has arisen from ongoing clinical trials.

7.2.1 HIPRA-HH-2

HIPRA-HH-2 was a Phase IIb, double-blind, randomised, active-controlled, multicentre, non-inferiority, 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.

The study was composed of two parts: Part A and Part B.

Part A aimed 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 Comirnaty vaccine.

The objective of Part B was to determine and compare the changes in the immunogenicity measured by Pseudovirion-Based Neutralisation Assay (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 Cohorts 1 and 2.

Part A

In part A, a total of 862 patients were screened for this study, from which 765 eligible subjects were randomly assigned to the following two treatment arms in a PHH-1V: Comirnaty 2:1 ratio:

- Cohort 1: single booster dose of PHH-1V containing 40 µg of antigen to be administered by intramuscular route (total of 513 subjects, including 325 females and 188 males).
- Cohort 2: single booster dose of Comirnaty (total of 252 subjects, including 159 females and 93 males).

Additionally, randomisation was stratified by age group (18-64 vs ≥65 years old) with approximately 10% of the sample enrolled in the older age group.

- In the Cohort 1 (PHH-1V) there was a total of 475 participants in the 18-64 years old age group (306 females and 169 males) and a total of 38 participants in the ≥65 years old age group (19 females and 19 males).
- In the Cohort 2 (Comirnaty) there was a total of 234 participants in the 18-64 age group (149 females and 85 males) and total of 18 participants in the ≥65 years old age group (10 females and 8 males).

One (1) subject prematurely discontinued participation in the Comirnaty vaccine treatment arm. This subject withdrew consent for participation. Three (3) subjects prematurely discontinued study participation in the PHH-1V treatment arm. Two (2) subjects were lost to follow-up and 1 subject withdrew consent. No discontinuation was safety related.

Part B

In part B, a total of 301 patients were screened for this study, from which 288 were vaccinated with PHH-1V as dose 4. This study is an extension of the two Cohorts already present in Part A of the study:

- Cohort 1: 106 subjects with a primary vaccination of 2 Comirnaty doses + 1 booster dose of PHH1-V that received another booster dose with PHH-1V.
- Cohort 2: 182 subjects with a primary vaccination of 2 Comirnaty doses + 1 booster dose of Comirnaty that received another booster dose with PHH-1V.

- In Cohort 1, there were 94 subjects in the 18-64 age group and 12 subjects in the ≥65 age group. Overall, there were 42 male ad 64 females.
- In Cohort 2, there were 161 subjects in the 18-64 age group and 21 subjects in the ≥65 age group. Overall, there were 73 male, 107 females and 2 individuals of undifferentiated sex.

In Cohort 1, three (3) subjects prematurely discontinued (subjects' choice). One (1) participant prematurely discontinued (withdrew consent) the study in Cohort 2. None of such discontinuations were due to safety reasons.

Cumulatively, 18 non-related SAEs have occurred throughout this study.

The clinical trial was closed on 14 August 2023. According to the last version of the interim report, dated 26 April 2023, no major findings were reported with regard to safety. The final CSR is estimated to be available on 05 January 2024.

7.2.2 HIPRA-HH-4

HIPRA-HH-4 is an ongoing 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 immunosuppressive conditions vaccinated against COVID-19 conducted at 6 sites located in Spain and Turkey. The aim of this study was the determination of the safety profile of PHH-1V in individuals with pre-existing immunosuppressive conditions.

Participants in the study HIPRA-HH-4 must have any of the following underlying immunosuppressive conditions:

- Confirmed Human Immunodeficiency Virus infection with persistent CD4 T cell counts <400 within last 6 months prior to Day 0 regardless of plasma Viral Load determination and Antiretroviral (ARV) treatment;
- Primary Antibody Deficiency Disorders on immunoglobulin replacement therapy for at least 6 months prior to Day 0 (maintenance dose);
- Kidney disease on dialysis program for at least 6 months prior to Day0;
- Kidney transplant at least >1 year and with last anti-CD20/anti-CD3 biological treatment given at least >1 year prior to Day0 and on maintenance immunosuppressive therapy based on at least 3 drugs: tacrolimus, glucocorticoids and mycophenolate or everolimus/sirolimus;
- Auto-immune disease on treatment with rituximab/ocrelizumab during within the last 6 months prior to Day 0.

In this study, a sample size of 400 participants has been proposed. As of the DLP of this report, a total of 240 participants have been enrolled. Among them, a total of 238 participants have been vaccinated: 231 participants (85 females and 146 males) have received the study treatment in Spain and 7 participants (6 males and 1 female) have received the study treatment in Turkey.

Cumulatively, 90 non-related SAEs were reported throughout this study until the DLP of this report.

There are no major findings in regard to safety at the DLP of this PSUR and no interim reports are available.

7.2.3 HIPRA-HH-3

HIPRA-HH-3 is an ongoing phase IIb, open-label, multi-centre, non-Inferiority study of safety and immunogenicity of BIMERVAX as heterologous booster for the prevention of COVID-19 in adolescents from 12 years to less than 18 years of age conducted at 5 sites in Spain. It is aimed at determining and comparing the changes in immunogenicity measured by PBNA against Omicron BA.1 variant at Baseline and Day 14, after vaccination of adolescents with a heterologous booster dose of BIMERVAX versus post heterologous booster dose in young adults (aged 18 to 25 years) from the adult booster study (HIPRA-HH-2), as well as at assessing the safety and tolerability of BIMERVAX as a heterologous booster dose in adolescents primary vaccinated against COVID-19 with 2 doses of Comirnaty vaccine.

Participants in this study must be adolescents from 12 to less than 18 years of age, primary vaccinated with 2 doses of Comirnaty, healthy or with stable chronic conditions (non-immunocompromised).

A sample size of 300 participants has been proposed. As of the DLP of this report, a total of 110 participants have been enrolled and 109 of them have been vaccinated. One (1) patient did not meet the inclusion criteria and was considered a screening failure.

Cumulatively, no SAEs have been reported.

There are no major findings in regard to safety at the DLP of this PSUR and no interim reports are available.

7.2.4 HIPRA-HH-11

HIPRA-HH-11 is an ongoing phase II, randomized, double-blind, multi-centre trial to evaluate the safety and immunogenicity of BIMERVAX when co-administered with seasonal surface antigen, inactivated adjuvanted influenza vaccine (SIIV) in adults older than 64 years of age fully vaccinated against COVID-19. The study is being conducted at 8 sites in Spain and the main objective is to assess and compare the safety and tolerability of BIMERVAX co-administered with SIIV in adults with respect to each vaccine when administered alone.

The proposed sample size is 300 adults aged 65 or older that will be enrolled and followed for 1 month after study treatment. The participants will be randomised 1:1:1 to one of the following three Cohorts:

- Cohort 1: approximately 100 participants will receive one dose of SIIV in one arm + one dose of placebo in the other arm, at Day 0.
- Cohort 2: approximately 100 participants will receive one dose of BIMERVAX in one arm + 1 dose of placebo in the other arm, at Day 0.
- Cohort 3: approximately 100 participants will receive one dose SIIV in one arm + one dose of BIMERVAX in the other arm, at Day 0.

Participants in this study must have received at least a primary scheme of an mRNA vaccine (2 doses). Booster doses or previous COVID-19 infections are allowed. Last dose must have been administered at least 6 months before Day 0. Additionally, participants must have a negative Rapid Antigen Test at Day 0 before vaccinations (history of COVID-19 infection is allowed if occurred at least >30 days before Day 0) and be healthy or with stable chronic conditions (non-immunocompromised).

All participants will receive two administrations at Day 0 (each vaccine/placebo will be administered in a different arm, regardless the order) and will be followed for 1 month.

As of the DLP of this report, a total of 283 participants have been enrolled, 279 of these were randomized and 278 have received the study product.

There are no major findings in regard to safety at the DLP of this PSUR and no interim reports are available.

7.3 Long-term Follow-up

Not applicable.

7.4 Other Therapeutic Use of Medicinal Product

Not applicable.

7.5 New Safety Data Related to Fixed Combination Therapies

Not applicable.

8. Findings from non-interventional studies

Two (2) non-interventional studies are planned with BIMERVAX. Tabulated information is provided in Appendix 5.

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

  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 compared with that of other COVID-19 vaccines authorised for the same indication; and a self-controlled risk interval study (a subtype of the self-controlled case series design) design to estimate the effect of the COVID-19 HIPRA vaccine booster on selected adverse events of special interest compared with no COVID-19 vaccination booster.

  The study protocol was submitted on 11 August 2023. A final report is planned for submission within 36 months after rollout of BIMERVAX booster vaccination campaigns in the first participating country (estimated date: 31 July 2026).

- **COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)**

  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 foetus is lacking.

  The study protocol was submitted on 11 August 2023. A final report is planned for submission within 12 months after study completion (estimated date: 31 July 2029).

9. Information from other clinical trials and sources

9.1 Other Clinical Trials

HIPRA is not aware of any initiated, ongoing or completed Investigator-Initiated Trial or other clinicals trials/study sources conducted with BIMERVAX.

9.2 Medication Errors

No cases reporting medication errors have been collected from post-marketing sources, since no case reports from such sources have been received cumulatively.

10. Non-clinical data

During the reporting period, no non-clinical studies were conducted.

11. Literature

From 30 March 2023 to 29 September 2023, a weekly literature search has been performed in order to identify new or relevant information evaluating the safety of the active substance contained in BIMERVAX (SARS-CoV-2 virus recombinant S protein RBD fusion heterodimer – B.1.351-B.1.1.7 strains). This information has been retrieved using specific search criteria in Medline and Embase.

No relevant information that could have a significant impact on the benefit/risk balance of the product has been detected in the scientific literature reviewed.

12. Other periodic reports

There are no other periodic reports for BIMERVAX presented for the period under review separate from this PSUR.

13. Lack of efficacy in controlled clinical trials

The results available from clinical trials do not indicate lack of efficacy that could reflect a significant risk to the treated population.

14. Late-breaking information

No important information concerning the efficacy/effectiveness or safety of BIMERVAX has been received since the data lock-point of this report.

15. Overview of signals: new, ongoing or closed

Cumulatively, no signals as defined by the GVP Module VII corresponding with the term "validated signal" described in GVP Module IX have been detected. Therefore, Appendix 3 contains no data.

16. Signal and risk evaluation

16.1 Summary of Safety Concerns

There is a Risk Management Plan (RMP) in place for BIMERVAX at the beginning of the reporting interval, which listed the following safety concerns:

Summary of safety concerns	
Important identified risks	Pericarditis Myocarditis
Important potential risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Summary of safety concerns	
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

16.2 Signal Evaluation

No safety signals were closed during the reporting interval.

16.3 Evaluation of Risks and New Information

During the period covered by this report, no new important identified and potential risks have been identified. In addition, no new information relevant to previously recognised potential and identified risks and missing information has been identified.

16.4 Characterisation of Risks

The frequency of safety concerns is expressed in reporting rates. The reporting rates are based on the number of cases reported from post-marketing sources and the estimate of patient exposure. Since patient exposure are only available to the MAH since 14 June 2023, the reporting rates can only be estimated from this date.

16.4.1. Important identified risks

16.4.1.1. Pericarditis *(MedDRA PT: 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, 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 S protein that the mRNA encodes for, cross-react with structural similar host proteins in the heart, also known as molecular mimicry [Klamer, 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, 2022]. 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 S protein but have not been implicated in acquired myocarditis [Pillay, 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, 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, 2022].

Clinical Trial experience:

In the phase III study HIPRA-HH-5, of the 2,661 subjects included in the safety dataset, 1 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, 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, 2022].

Post-marketing experience:

No post-marketing data are yet available 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, 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.

16.4.2. Important potential risks

16.4.2.1. Myocarditis *(MedDRA PT: 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, 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 S protein that the mRNA encodes for, cross-react with structural similar host proteins in the heart, also known as molecular mimicry [Klamer, 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, 2022]. 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 has shown to be different depending on the type of vaccine/platform used. Vaccines using adenoviral vector-based platforms produce the S protein but have not been implicated in acquired myocarditis [Pillay, 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, 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, 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, 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, 2022].

Post-marketing experience:

No post-marketing data are yet available 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, 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.

16.4.2.2. VAED, including VAERD *(MedDRA PTs: Antibody-dependent enhancement and Enhanced respiratory disease)*

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 middle east respiratory syndrome coronavirus (mice model) vaccines [Haynes, 2020; Lambert, 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, 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 and measles virus. It has been rarely encountered with existing vaccines or viral infections [Haynes, 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:

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).

Clinical Trial experience:

No events of VAED/VAERD have been reported in the current BIMERVAX clinical development programme.

Post-marketing experience:

No post-marketing data are yet available with BIMERVAX vaccine.

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.

16.4.3. Missing information

16.4.3.1. Use in pregnancy and while breastfeeding *(MedDRA Standardised MedDRA Query (SMQ) Pregnancy and neonatal topics)*

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 good laboratory practice 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 COVID-19 vaccines currently approved [SmPC Comirnaty, 2023; SmPC Jcovden, 2023; SmPC Nuvaxovid, 2023; SmPC Spikevax, 2023; SmPC Vaxzevria, 2023]. 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.

16.4.3.2. Use in immunocompromised patients *(Medical history: MedDRA High Level Group Term (HLGT): Immunodeficiency syndromes; and/or Coded reaction: MedDRA SMQ: Opportunistic infection)*

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.

16.4.3.3. Use in frail patients with comorbidities (e.g., COPD), diabetes, chronic neurological disease, cardiovascular disorders) *(patients with coded severe comorbidities in medical history)*

Evidence source:

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.

16.4.3.4. Use in patients with autoimmune or inflammatory disorders *(patients with coded autoimmune or inflammatory disorders in medical history)*

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.

16.4.3.5. Interaction with other vaccines *(PT: Vaccine interaction)*

Evidence source:

BIMERVAX is indicated as a booster in individuals vaccinated against COVID-19. The safety and immunogenicity of a booster vaccination with BIMERVAX 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 studies HIPRA-HH-2 and HIPRA-HH10, and in the Phase III studies HIPRA-HH-5 and HIPRA-HH-4. A study 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 is currently being performed, phase II study HIPRA-HH-11.

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.

16.4.3.6. Long-term safety

Evidence source:

Understanding of the long-term safety profile of BIMERVAX is currently limited. 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 in the Phase IIb clinical study HIPRA-HH-2, up to 26 weeks in the Phase III study HIPRA-HH-5, up to 26 weeks in the Phase IIb HIPRA-HH-10 study, 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 of BIMERVAX is not fully known. 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 and planned post-authorisation studies.

16.5 Effectiveness of Risk Minimisation (if applicable)

Not applicable, since routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product and therefore, additional risk minimisation measures are not deemed necessary.

17. Benefit evaluation

17.1 Important Baseline Efficacy/Effectiveness Information

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.

Efficacy of BIMERVAX was inferred by immunobridging of immune responses to the previously authorised COVID-19 vaccine Comirnaty, for which vaccine efficacy had been established.

The immunogenicity of BIMERVAX was evaluated in one pivotal phase IIb double-blind clinical trial (HIPRA-HH-2) and in one phase III multi-centre clinical trial (HIPRA-HH-5). The other studies were considered supportive.

In study HIPRA-HH-2 Part A, a total of 765 subjects were vaccinated; 513 subjects received BIMERVAX, and 252 subjects received the COVID-19 mRNA vaccine (tozinameran). A total of 751 subjects were analysed (504 BIMERVAX subjects and 247 COVID-19 mRNA vaccine subjects) excluding those who tested positive for COVID-19 within 14 days of the booster. Randomisation was stratified by age group (18-64 versus ≥ 65 years). The median age was 42 years (range: 19 to 76 years), with similar age ranges in both vaccine arms, including 7.4% and 7.1% of subjects 65 years of age and older in the BIMERVAX and COVID-19 mRNA vaccine groups, respectively.

Immunogenicity of a booster dose of BIMERVAX was based on an assessment of geometric mean titres (GMT) of neutralising antibodies, measured by a PBNA against SARS-CoV-2 (D614G) strain, Beta, Delta and Omicron BA.1 variants. GMT ratio is the result of the GMT values (ID50) of COVID-19 mRNA vaccine (tozinameran)/BIMERVAX. Non-inferiority of BIMERVAX to COVID-19 mRNA vaccine (tozinameran) is concluded if the upper limit of the 2 sided 95% Confidence Interval (CI) of the GMT ratio is < 1.4. Superiority of BIMERVAX to COVID-19 mRNA vaccine (tozinameran) is concluded if the upper limit of the 2-sided 95% Confidence Interval of the GMT ratio is < 1.0.

In Part B, extension of HIPRA-HH-2 study to assess a fourth dose of BIMERVAX, 301 subjects were screened, of which 288 subjects were vaccinated with BIMERVAX as dose 4. A total of 106 subjects received BIMERVAX in Cohort 1 (primary vaccination with 2 doses of Comirnaty and a booster dose of BIMERVAX), and 182 subjects received BIMERVAX in Cohort 2 (primary vaccination with 2 doses of Comirnaty and a booster dose of Comirnaty). The median age was 49 years (range: 20 to 82 years) with similar age ranges in the 2 cohorts. Most subjects were 18 to 64 years old (88.5%), female (59.4%), and White (98.6%).

Immunogenicity of BIMERVAX as dose 4 was based on an assessment of geometric mean titres (GMT) of neutralising antibodies, measured by a pseudovirion-based neutralisation assay (PBNA) against Beta, Delta, Omicron BA.1 and Omicron BA.4/5 variants. GMT ratio is the result of the GMT values (ID50) of 3 doses of COVID-19 mRNA vaccine (tozinameran)/4th dose of BIMERVAX administered after 3 doses of COVID-19 mRNA vaccine (tozinameran) or administered after 2 doses of COVID-19 mRNA and one dose of BIMERVAX. Superiority of the fourth dose with BIMERVAX was met if the upper limit of the 2 sided 95% Confidence Interval (CI) of the GMT ratio was < 1. Superiority was met for all variants.

Study HIPRA-HH-5 includes data from a total of 2661 subjects who were vaccinated with BIMERVAX as a booster dose in healthy individuals (at least 16 years old) previously vaccinated with different COVID-19 vaccines. Immunogenicity was assessed at Baseline, Day 14, Day 91, Day 182, and Day 365/ETV in a subset of 235 subjects vaccinated with two doses of Comirnaty/Comirnaty (individuals 16-17 years old), Spikevax/Spikevax, Vaxzevria/Vaxzevria, or a combination of Vaxzevria and another brand of vaccine. Overall, the median age was 33 years (range: 16-85 years). Subjects were generally balanced between the sexes, 52.16% male and 47.80% female. Most subjects were White (98.95%), not Hispanic or Latino (84.25%), and ≥ 18 years old (98.65%).

Immunogenicity was measured by PBNA against SARS-CoV-2 (D614G) strain and against Beta, Delta and Omicron BA.1.

The results of the studies performed were considered indicative of a superior neutralizing immune response of BIMERVAX over the active comparator Comirnaty against Omicron BA.1 and Beta, as well as non-inferior neutralizing immune response against Delta, 14 days

after booster administration. Additionally, long-term data indicated that antibodies may wane to a lesser degree after BIMERVAX administration than after Comirnaty administration for subjects above or below 65 years of age and irrespective of the virus strain [Bimervax. Public Assessment Report, 2023].

Clinical data demonstrate immunogenic activity of BIMERVAX, which is effective against the SARS-CoV-2 Wuhan strain and the different variants, including the Beta, Delta and Omicron variants. Clinical data demonstrates a more duration of the immune response against Wuhan, Beta, Delta and Omicron BA.1 for the booster with BIMERVAX compared to the Comirnaty vaccine, which is an important characteristic for a vaccine. A more sustained immune response against Wuhan, Beta, Delta and Omicron BA.1 is shown in individuals below 65 years old and in individuals 65 years old and older.

No severe COVID-19 infections were reported in the clinical studies, which supports that BIMERVAX provides protection to moderate, severe, life-threatening, and fatal forms of SARS-CoV-2 infections.

17.2 Newly Identified Information on Efficacy/Effectiveness

No additional information on efficacy or effectiveness of BIMERVAX in authorised indications has become available during the reporting interval.

17.3 Characterisation of Benefits

No new information relating to the efficacy and effectiveness of BIMERVAX has become available during the reporting interval. The benefits of BIMERVAX as summarised in Section 17.1 remain unchanged.

18. Integrated benefit-risk analysis for authorised indications

18.1 Benefit-risk Context – Medical Need and Important Alternatives

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.

Prevention of COVID-19

COVID-19 is an infectious disease caused by a betacoronavirus scientifically named SARS-CoV-2. 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, 2020].

While most adults experience no symptoms or mild to moderate respiratory illness with symptoms such as fever, cough, fatigue, shortness of breath, myalgias, nasal congestion, headache, diarrhoea, nausea, vomiting, anosmia or ageusia; patients with severe to critical disease can require oxygen support and develop complications such as respiratory failure, ARDS, sepsis and septic shock, thromboembolism, multi-organ failure and death [WHO, 2023a].

The incidence and prevalence of COVID-19 is difficult to estimate. In Europe, as of October 2023, there have been more than 276 million confirmed cases of COVID-19 and more than 2 million deaths reported to the World Health Organization [WHO, 2023b].

The COVID-19 situation towards the end of 2023, almost four years after the start of the pandemic, has changed significantly. Globally, population-level immunity has increased significantly, due to substantial and increasing vaccine use along with infection-induced

immunity, or the combination of both (hybrid immunity). Nonetheless, certain subgroups continue to be at greater risk of severe disease and mortality and account for most of the ongoing COVID-19-related mortality (WHO roadmap).

The main existing options

Approaches to dealing with the impact of the COVID-19 pandemic can be divided into two main approaches:

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

  Vaccination

  During the 2021 European summer season, the incidence of SARS-CoV-2 declined in almost all European Union/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 COVID-19 vaccines.

  At the DLP of this PSUR, 8 vaccines have received approval by European Medicines Agency (EMA): Bimervax (recombinant protein, adjuvated), Comirnaty (mRNA), Spikevax (mRNA), Jcovden (adenovirus), Vaxzevria (adenovirus), Nuvaxovid (recombinant protein, adjuvanted), COVID-19 Vaccine (inactivated, adjuvated) Valneva and VidPrevtyn Beta (recombinant protein, adjuvanted) [EMA, 2023].

  Importantly, evidence suggests that vaccine efficacy may wane over time [Gupta, 2021; Keehner., 2021; Naaber, 2021; Thomas, 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 variety of concerns [Dolgin, 2021; Juno, 2021].

  On March 2023, WHO's Strategic Advisory Group on Immunization (SAGE) updated the recommendations on COVID-19 vaccination in the context of the circulating Omicron variant and high population immunity. The updated recommendations outline three priority groups for COVID-19 vaccination: high, medium, and low. The high priority group includes: older adults, younger adults with significant comorbidities or severe obesity, people with serious immunocompromising conditions, pregnant women and frontline healthcare professionals.

  Non-pharmaceutical interventions

  Non-pharmaceutical interventions are actions that people and communities take to help slowing down the spread of SARS-COV-2 [Flaxman, 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. Most non-pharmaceutical interventions can have a negative impact on the general well-being of people, the functioning of society, and the economy [Müller, 2021].

  Nowadays, countries have lifted most or all public health and social measures, and while the SARS-CoV-2 virus continues to circulate, the COVID-19 pandemic has seen significant reduction in rates of hospitalization, admission to intensive care units and deaths across all age groups.

- **Direct treatment measures to address the symptomology**

  A SARS-CoV-2 infection and mild to moderate COVID-19 disease in adults does usually not require specific treatment [European Centre for Disease prevention and Control, 2023].

For patients with mild or moderate COVID-19 disease and increased risk for progression (e.g. due to advanced age and/or comorbidities), early medical treatment may be indicated [European Centre for Disease prevention and Control, 2023].

Antivirals and antiviral monoclonal antibodies can be considered in consultation with respective clinical specialists and available guidelines for adults and adolescents at risk of developing severe disease such as moderately to severely immunocompromised patients that may have an inadequate immune response to COVID-19 vaccination [European Centre for Disease prevention and Control, 2023].

Medical treatment of COVID-19 is mostly supportive, including oxygen for severely ill patients and patients at risk of developing severe disease, and ventilation for critically ill patients. WHO strongly recommends the use of systemic corticosteroids, interleukin-6 receptor blockers such as tocilizumab, or baricitinib as an alternative to interleukin-6 receptor blockers for severe or critical COVID-19 disease, in combination with corticosteroids [European Centre for Disease prevention and Control, 2023].

18.2 Benefit-risk Analysis Evaluation

COVID-19 is an infectious disease caused by the novel betacoronavirus SARS-CoV-2 [WHO, 2023a]. The WHO characterised the outbreak as a pandemic from 11 March 2020 to 05 May 2023 [WHO, 2023b]. As stated above, while most adults experience no symptoms or mild to moderate symptoms, other patients can develop severe to critical disease that can require oxygen support and even result in death [WHO, 2023a].

The COVID-19 situation towards the end of 2023, almost four years after the start of the pandemic, has changed significantly. Globally, population-level immunity has increased significantly, due to substantial and increasing vaccine use along with infection-induced immunity, or the combination of both (hybrid immunity). Countries have lifted most or all public health and social measures, and while the SARS-CoV-2 virus continues to circulate, the COVID-19 pandemic has seen significant reduction in rates of hospitalization, admission to intensive care units and deaths across all age groups. Nonetheless, certain subgroups continue to be at greater risk of severe disease and mortality and account for most of the ongoing COVID-19-related mortality (WHO roadmap).

On March 2023, WHO's SAGE updated the recommendations on COVID-19 vaccination in the context of the circulating Omicron variant and high population immunity. The updated recommendations outline three priority groups for COVID-19 vaccination: high, medium, and low. The high priority group includes: older adults, younger adults with significant comorbidities or severe obesity, people with serious immunocompromising conditions, pregnant women and frontline healthcare professionals.

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 clinical trials, BIMERVAX showed a good safety profile, with most common adverse reactions reported being injection site pain, headache, fatigue and myalgia. The median duration of local and systemic adverse reactions was 1 to 3 days. Most adverse reactions occurred within 3 days following vaccination and were mild to moderate in severity.

After its distribution to the market on 14 June 2023, a total of 137 patients have been administered with BIMERVAX, and no ICSRs have been received during the reporting period of the PSUR.

Pericarditis and myocarditis have been classified as important identified and potential risk for BIMERVAX, respectively. Most vaccine-associated pericarditis and myocarditis events have been mild and self-limiting. However, both events 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, their impact on the risk-balance of the vaccine is considered minimal. Only one case of a pericarditis event was detected in a clinical study using BIMERVAX, while no myocarditis events have been reported cumulatively. This single case of pericarditis was idiopathic, completely resolved with appropriate treatment, and was considered probably related to the vaccine due to temporal association.

VAED/VAERD has also been identified as an important potential risk for BIMERVAX. 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, 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. Up to the DLP of this report, no events of VAED or VAERD have been reported in clinical trials.

During the period covered by this PSUR, no signals were identified or evaluated.

All in all, during the period covered by this report, there has been no new or important data identified for the approved indication that could impact on the safety and efficacy specifications described in the current RSI.

Based on the data held on file by the MAH and the available scientific and medical literature, BIMERVAX remains an effective product for the approved indication when used as stated in the product reference information, and the benefits outweigh the risks to the patient by its administration.

19. Conclusions and actions

In this PSUR (from 30 March 2023 to 29 September 2023), all available safety-relevant data obtained during the reporting period and all available cumulative data obtained since launch have been reviewed.

During the period under review:

- No new data on efficacy/effectiveness was identified,
- No case reports have been received,
- No other new information affecting the known safety profile of BIMERVAX has been found,
- No safety related actions or safety related investigations have been performed.

The evaluation of the collected information confirmed that the benefit-risk balance remains positive. Therefore, no changes to the RSI are required.