# BIMERVAX (COVID-19 vaccine (recombinant, adjuvanted): Periodic safety update report assessment

30 September 2024- 29 March 2025

This document consists of:

1. The PRAC assessment report of the Bimervax periodic safety update report (PSUR) covering the period 30 September 2024 to 29 March 2025, 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.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacovigilance Risk Assessment Committee (PRAC)
Case number: EMA/PSUR/0000282290

# PRAC PSUR assessment report

## EURD list no.: PSUSA/00011045/202503

## Active substance(s): COVID-19 Vaccine (recombinant, adjuvanted) (Bimervax)

## Period covered by the PSUR: 1 year to 28 March 2025

| **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** |
| ☐ | Submission deadline | 26 June 2025 | 26 June 2025 |
| ☐ | Start date | 3 July 2025 | 3 July 2025 |
| ☐ | PRAC Rapporteur AR | 1 September 2025 | 1 September 2025 |
| ☐ | PRAC/MAH comments | 1 October 2025 | 1 October 2025 |
| ☐ | Updated PRAC Rapporteur AR | 16 October 2025 | 16 October 2025 |
| ☒ | PRAC outcome | 30 October 2025 | 30 October 2025 |

| Procedure resources | |
|---|---|
| PRAC Rapporteur | Name: Zane Neikena<br>Tel: [redacted]<br>Email: [redacted] |
| Contact person - PRAC Rapporteur | Name: [redacted]<br>Tel:<br>Email: |
| Assessor – PRAC Rapporteur | Name: [redacted]<br>Email:<br>Name:<br>Email:<br>Name:<br>Email: |
| EMA Procedure Lead | Name: [redacted]<br>Tel:<br>Email: |
| EMA Procedure Assistant | Name: [redacted]<br>Tel:<br>Email: |

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## Abbreviations

| | |
|---|---|
| ACE | Angiotensin Converting Enzyme |
| ATC | Anatomical Therapeutic Chemical classification |
| COPD | Chronic Obstructive Pulmonary Disease |
| COVID-19 | Coronavirus Disease 2019 |
| CSR | Clinical Study Report |
| DBL | Data base lock |
| DIBD | Development International Birth Date |
| DLP | Data Lock Point |
| ECDC | European Centre for Disease and Control |
| 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 |
| LPLV | Last patient last visit |
| 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 |
| TAG-CO-VAC | Technical Advisory Group on COVID-19 Vaccine Composition |
| Th | T helper cell type |
| UN | United Nations |
| 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 4th Periodic Safety Update Report (PSUR) for Hipra Human Health, S.L.U.'s BIMERVAX emulsion for injection, containing selvacovatein (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, and BIMERVAX XBB.1.16 emulsion for injection, containing damlecovatein (SARS-CoV-2 virus recombinant spike [S] protein receptor binding domain [RBD] fusion homodimer – Omicron XBB.1.16-XBB.1.16 strain) as active substance.

This PSUR summarizes the safety information for Bimervax received by Hipra Human Health, S.L.U. (hereafter referred to as Hipra) from 30 September 2024 to 29 March 2025, the data lock point (DLP).

This PSUR is the first to include both BIMERVAX (selvacovatein) and BIMERVAX XBB.1.16 (damlecovatein); previous PSURs covered only BIMERVAX. As used in this report, the term "parent vaccine" refers to BIMERVAX, the term "adapted vaccine" refers to BIMERVAX XBB.1.16, and the term "HIPRA COVID-19 vaccines" refers to both BIMERVAX and BIMERVAX XBB.1.16 (both the parent and the adapted vaccine).

BIMERVAX emulsion for injection (hereinafter referred to as Bimervax), is an emulsion for injection containing 40 µg of selvacovatein / damlecovatein as active ingredient per 0.5 mL. A single intramuscular dose (0.5 mL) of Bimervax should be administered.

Bimervax is indicated as a booster for active immunisation to prevent Coronavirus Disease 2019 (COVID-19) in individuals 16 years of age and older. In September 2025, the CHMP issued a positive opinion to extend the use of this vaccine to individuals from 12 years of age (EMA/VR/0000257408).

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

No safety-related changes were made to the RSI and no changes to the product information are proposed as part of the submission of the PSUR.

Cumulatively, 4,294 subjects have been exposed to BIMERVAX in 8 company-sponsored clinical trials cumulatively since the Development International Birth Date (DIBD). Six (6) 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, HIPRA-HH-5, HIPRA-HH-2 and HIPRA-HH-4). Two clinical trials are ongoing: 1 clinical trial which is completed but without an available Clinical Study Report (CSR) at the DLP of this report (HIPRA-HH-11) and 1 clinical trial which is not completed (HIPRA-HH-3).

Cumulative patient exposure from marketing experience is 724 vaccinated individuals and has not changed since the last PSUR.

No new important safety information is identified during the reporting interval from data in summary tabulations.

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.

At the DLP of this reporting interval two non-interventional category 3 studies VAC4EU and C-VIPER are planned with BIMERVAX to address safety concerns in the risk management plan. After the DLP of this PSUSA procedure through a variation type II procedure No. EMA/VR/0000262308 the category 3 C-VIPER study was removed from the list of additional pharmacovigilance activities of the risk management plan for Bimervax due to feasibility reasons.

During the reporting interval no new, ongoing and closed signals were identified by the MAH.

There is a risk management plan version 1.5 in place for HIPRA COVID-19 vaccines at the DLP of this report. No new information relevant to previously recognised potential and identified risks has been identified. The safety concerns remain unchanged. Routine risk minimisation measures are considered sufficient to manage the safety concerns of the medicinal product.

The medicinal product Bimervax (COVID-19 Vaccine, recombinant, adjuvanted) is under the additional monitoring list.

The safety profile of Bimervax is in accordance with expected and remains unchanged.

The current 1-year frequency of PSUR submission should remain unchanged.

No new significant information regarding efficacy has been reported.

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 **1-** year 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 the 4th Periodic Safety Update Report (PSUR) for Hipra Human Health, S.L.U.'s BIMERVAX emulsion for injection, containing selvacovatein as active substance, and BIMERVAX XBB.1.16 emulsion for injection, containing damlecovatein as active substance. This report covers a 6-month reporting period.

The first three BIMERVAX PSURs (PSUR Nº01, PSUR Nº02, and PSUR Nº03) included only BIMERVAX vaccine. Beginning with this PSUR Nº04, both the parent BIMERVAX vaccine and the adapted BIMERVAX XBB.1.16 vaccine are included.

The international birth date (IBD) for the product is the 30 March 2023.

BIMERVAX and BIMERVAX XBB.1.16 belong to the pharmacotherapeutic group: Vaccines, Covid-19 vaccines, Anatomical Therapeutic Chemical classification (ATC) code: J07BN04.

Mechanism of action: The HIPRA COVID-19 vaccines are a recombinant protein vaccine whose active substance (antigen) is SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion dimer. 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, the HIPRA COVID-19 vaccines induce antigen-specific T-cell immune response, which may contribute to protection to COVID-19.

BIMERVAX emulsion for injection (hereinafter referred to as BIMERVAX), is an emulsion for injection containing 40 µg of selvacovatein as active ingredient per 0.5 mL. Selvacovatein is a SARS-CoV-2 virus recombinant S protein RBD fusion heterodimer – B.1.351-B.1.1.7 strains. BIMERVAX XBB.1.16 emulsion for injection (hereinafter referred to as BIMERVAX XBB.1.16), is an emulsion for injection containing 40 µg of damlecovatein as active ingredient per 0.5 mL. Damlecovatein is a SARS-CoV-2 virus recombinant S protein RBD fusion homodimer – Omicron XBB.1.16-XBB.1.16 strain.

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.

BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

Route of administration, Dose: Intramuscular injection.

BIMERVAX is a multidose vial which contains 10 doses of 0.5 mL each or a single dose vial which contains 1 dose of 0.5 mL. A single intramuscular dose (0.5 mL) of BIMERVAX should be administered at least 6 months after previous mRNA COVID-19 vaccine. BIMERVAX may also be given at least 6 months after a previous booster with BIMERVAX.

BIMERVAX XBB.1.16 is a single dose vial which contains 1 dose of 0.5 mL. A single intramuscular dose (0.5 mL) of BIMERVAX XBB.1.16 should be administered regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, BIMERVAX XBB.1.16 should be administered at least 6 months after the most recent dose of a COVID-19 vaccine.

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.

No changes to the product information are proposed as part of the submission of the PSUR.

## *1.2. Worldwide marketing authorisation status*

BIMERVAX was first approved by the European Commission via centralised procedure on 30 March 2023. BIMERVAX is authorized in all European Economic Area (EEA) countries and in the Great Britain.

Additionally, on 09 October 2023, BIMERVAX received the positive decision by the World Health Organization as a prequalified vaccine for purchase by United Nations (UN) agencies.

In 2024, to ensure continued protection against emerging Omicron SARS-CoV-2 variants, an adapted version of the parent vaccine was developed. This adapted vaccine, BIMERVAX XBB.1.16, received Marketing Authorisation from the European Commission for use in the EEA on 12 December 2024, and from MHRA for use in the United Kingdom on 27 December 2024. Additionally, on 6 February 2025, BIMERVAX XBB.1.16 also received WHO prequalification, enabling its procurement by UN agencies.

**Table 1: Worldwide Marketing Authorisation Status**

| Country /Region | Invented Name of the Medicinal Product | Marketing Authorisation Number | Date of Authorisation | Presentation | Pack size | Approved dose | Indication |
|---|---|---|---|---|---|---|---|
| EEA | BIMERVAX emulsion for injection | EU/1/22/1709/001 | 30 March 2023 | Multidose vial (5 mL): 10 doses of 0.5 mL | 10 multidose vials (100 doses) | 0.5 mL containing 40 µg of selvacovatein | 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. |
| | | EU/1/22/1709/002-004 | 07 March 2024 | Single dose vial (0.5 mL): 1 dose of 0.5 mL | 5, 10 and 20 single dose vials (5, 10 and 20 doses) | | |
| | BIMERVAX XBB.1.16 emulsion for injection | EU/1/22/1709/005-007 | 12 December 2024 | Single dose vial (0.5 mL): 1 dose of 0.5 mL | 5, 10 and 20 single dose vials (5, 10 and 20 doses) | 0.5 mL containing 40 µg of damlecovatein | BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. |
| UK | BIMERVAX emulsion for injection | PLGB 56346/0002 | 31 July 2023 | Multidose vial (5 mL): 10 doses of 0.5 mL | 10 multidose vials (100 doses) | 0.5 mL containing 40 µg of selvacovatein | 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 |
| | | PLGB 56346/0003 | 18 June 2024 | Single dose vial (0.5 mL): 1 dose of 0.5 mL | 5, 10 and 20 single dose vials (5, 10 and 20 doses) | | mRNA COVID-19 vaccine. |
| | BIMERVAX XBB.1.16 emulsion for injection | PLGB 56346/0004 | 27 December 2024 | Single dose vial (0.5 mL): 1 dose of 0.5 mL | 5, 10 and 20 single dose vials (5, 10 and 20 doses) | 0.5 mL containing 40 µg of damlecovatein | BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. |

*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:*<br><br>No actions for safety reasons were taken during the reporting period. |

### 1.3.2. Changes to reference safety information

The current Summary of Product Characteristics (SmPC) for BIMERVAX and BIMERVAX XBB.1.16 (dated 13 March 2025) is used as the Reference Safety Information (RSI).

During the period covered by this report, two new versions of the SmPC were issued:

- On 12 December 2024, following receipt of the European Commission Decision for the adapted vaccine, the SmPC was updated to include information related to the first adaptation targeting the Omicron subvariant XBB.1.16, BIMERVAX XBB.1.16.

- On 13 March 2025, sections 4.2, 4.4, and 5.1 of the SmPC were updated to include the final results of the CSR from HIPRA-HH-4 study regarding the use of BIMERVAX in immunocompromised individuals.

| |
|---|
| *Rapporteur assessment comment:*<br><br>During the reporting period, two new versions of the SmPC for BIMERVAX and BIMERVAX XBB.1.16 were issued. On 12 December 2024, the SmPC was updated to include information on the first adaptation targeting the Omicron XBB.1.16 subvariant (BIMERVAX XBB.1.16). Subsequently, on 13 March 2025, sections 4.2, 4.4, and 5.1 were revised to incorporate the final results of the HIPRA-HH-4 study regarding the use of BIMERVAX in immunocompromised individuals. Information acknowledged. |

### 1.3.3. Estimated exposure and use patterns

**Cumulative Subject Exposure in Clinical Trials**

Cumulatively, 4,294 subjects have been exposed to BIMERVAX in 8 company-sponsored clinical trials cumulatively since the Development International Birth Date (DIBD).

Six (6) 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, HIPRA-HH-5, HIPRA-HH-2 and HIPRA-HH-4). Furthermore, 2 clinical trials are ongoing: 1 clinical trial which is completed but without an available Clinical Study Report (CSR) at the DLP of this report (HIPRA-HH-11) and 1 clinical trial which is not completed (HIPRA-HH-3).

The cumulative patient exposure is based upon exposure data from completed clinical trials, and from ongoing clinical trials which are unblinded.

In the above-mentioned clinical trials, a cumulative total of **4,294** and **393** subjects were exposed to BIMERVAX and comparator treatments, respectively at the DLP of this report. Additionally, **95** patients were exposed to placebo and a co-administered treatment.

**Cumulative and Interval Patient Exposure from Marketing Experience**

As of the DLP of this PSUR, BIMERVAX has only been distributed to Spain, Belgium and Andorra. The first units of BIMERVAX were distributed in 2023, with an initial shipment to the Spanish territory on 14 June 2023. A total of 3.2 million doses were distributed to the Spanish Government; 10,000 doses to the Belgian Government; and 500 to the Andorran Government. No further doses have been supplied to any country thereafter.

BIMERVAX XBB.1.16 is not commercially available; therefore, there is no post-authorisation exposure.

During the current reporting period (30 September 2024 to 29 March 2025), no new doses of BIMERVAX or BIMERVAX XBB.1.16 have been distributed. As stated in the previous BIMERVAX PSUR (PSUR Nº03), the initial distributed batches of BIMERVAX expired in early 2024. Therefore, since no additional doses have been made available on the market, it is not expected that any doses were administered during reporting period covered by this report.

Cumulative post-authorisation exposure remains unchanged since the previous PSUR.

In the first BIMERVAX PSUR (covering the period form 30 March 2023 to 29 September 2023), an estimate of 137 doses of BIMERVAX were administered. In the second PSUR (30 September 2023 to 29 March 2024), an additional 587 doses of BIMERVAX were estimated, bringing the cumulative total to 724 doses.

As previously stated in PSUR Nº03 (30 March 2024 to 29 September 2024), no doses were expected to have been administered during that reporting period, and the same applies to the current reporting period (30 September 2024 to 29 March 2025).

**Table 7: Cumulative exposure data from IBD* to 29 March 2025**

| Region | Brand name | Patients vaccinated |
|---|---|---|
| EU/EEA countries | BIMERVAX | 724 |
| | BIMERVAX XBB.1.16 | 0 |
| | **Total** | **724** |

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

*Rapporteur assessment comment:*

Cumulatively patient exposure in clinical trials has not changed from previous PSUR, there have been 4,294 subjects exposed to Bimervax.

Cumulative patient exposure from marketing experience has not changed since last PSUR, it is 724 vaccinated individuals.

## 1.3.4. Data in summary tabulations

Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 27.1) is used for coding adverse reactions described in case reports.

**Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials**

For BIMERVAX, a total of 143 SAEs have been reported in the studies HIPRA-HH-1, HIPRA-HH-2, HIPRA-HH-3, HIPRA-HH-4, HIPRA-HH-5, HIPRA-HH-10, and HAN-01. One hundred and forty-two (142) SAEs were considered non-related, and 1 SAE was considered as possibly related.

For BIMERVAX XBB.1.16, a total of 16 SAEs have been reported in clinical study HIPRA-HH-14. All 16 SAEs were assessed as non-related to the investigational medicinal products.

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

During the reporting period, a total of 2 non-serious cases were received from post-marketing sources. Of these, one was considered valid and included 2 PTs, while the other was classified as an invalid case and included a single PT.

Cumulatively, a total of 5 ICSRs (4 non-serious and 1 serious) have been received from post-marketing sources, comprising a total of 22 PTs.

*Rapporteur assessment comment:*

During the reporting period, two cases comprising three PTs were received from post-marketing data sources. One case was deemed invalid as it originated from an internet source and did not meet the minimum criteria for case reporting. The other case concerned a participant from the HIPRA-HH-11 study who was administered an expired dose from an unopened BIMERVAX vial that had been properly stored in a refrigerator. As the administration occurred outside the scope of the study protocol, it was classified as a post-marketing medication error without impact to the safety profile of Bimervax. Further details of this case are provided in section 1.3.5. of this assessment report.

This is in line with the known safety profile of the medicinal product Bimervax. No new important safety information is identified during the reporting interval.

## 1.3.5. Findings from clinical trials and other sources

For BIMERVAX, a total of 8 clinical trials were either ongoing or completed during the current reporting period. Specifically, 6 of them were completed and the remaining 2 are ongoing.

For BIMERVAX XBB.1.16, a single clinical trial was ongoing during the reporting interval.

**Completed Clinical Trials**

6 clinical trials were completed during the period covered by this report.

*Rapporteur assessment comment:*

The six clinical trials were analysed in the previous reporting period, and no major findings were identified.

**Ongoing Clinical Trials**

The clinical trials described below are either ongoing (HIPRA-HH-3) or completed but without an available CSR at the DLP of the present report and thus considered ongoing (HIPRA-HH-11 and HIPRA-HH-14).

**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 7 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 242 participants have been enrolled and 240 of them have been vaccinated (127 males and 113 females). Two (2) patients did not meet the inclusion criteria and were considered screening failures.

Cumulatively, 2 non-related SAEs have been reported.

An interim report was issued on 27 January 2025 and there are no major findings in regard to safety at the DLP of this PSUR.

**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 65 years of age fully vaccinated against COVID-19. The study was conducted at 8 sites in Spain, and the main objective was 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 sample size of 300 adults aged 65 or older was proposed. Finally, 283 participants were enrolled, 279 patients were randomized in the study, and 278 (154 males and 124 females) were vaccinated and followed for 1 month after study treatment. The participants were randomised 1:1:1 to one of the following three Cohorts:

- Cohort 1: 95 participants (41 males and 54 females) received one dose of SIIV in one arm + one dose of placebo in the other arm, at Day 0.
- Cohort 2: 91 participants (55 males and 36 females) received one dose of BIMERVAX in one arm + 1 dose of placebo in the other arm, at Day 0.
- Cohort 3: 92 participants (58 males and 34 females) received one dose SIIV in one arm + one dose of BIMERVAX in the other arm, at Day 0.

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

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

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-14**

The study HIPRA-HH-14 is a phase IIb/III, double-blind, randomised, active-controlled, multi-centre, non-inferiority clinical trial, to assess the safety and immunogenicity of a booster vaccination with an adapted recombinant protein RBD fusion homodimer candidate (PHH-1V81) against SARS-CoV-2, in adults vaccinated against COVID-19.

In this study, 905 adults aged 18 or older were randomly assigned to the following two treatment arms in a BIMERVAX XBB.1.16: Comirnaty Omicron XBB.1.5, 2:1 ratio. Finally, 903 participants received the treatments:

- A total of 602 adults (370 females and 232 males) received a booster dose of BIMERVAX XBB.1.16.
- A total of 301 adults (175 females and 126 males) received a booster dose of Comirnaty Omicron XBB.1.5.

Cumulatively, a total of 16 non-product related SAEs were reported throughout the duration of the study.

An interim report was issued on 3 January 2024. Last patient last visit (LPLV) in this study was on 17 June 2024 and the DBL of the clinical trial was performed on 25 February 2025. As of the DLP of this report, no major findings were reported with regard to safety.

**Medication Errors**

During the reporting period, 1 case of medication error was received from post-marketing sources.

The case originated from the HIPRA-HH-11 study, where a participant received an expired dose from an unopened BIMERVAX vial after unblinding. This dose was administered in error, fell outside the study protocol, and was classified as a post-marketing medication error.

HIPRA-HH-11 was a double-blind clinical trial evaluating the safety and immunogenicity of BIMERVAX when co-administered with an influenza vaccine. Participants were distributed into the following cohorts:

- Cohort 1: Influenza vaccine + placebo
- Cohort 2: BIMERVAX + placebo
- Cohort 3: Influenza vaccine + BIMERVAX

After unblinding, participants were contacted to inform them about the vaccines they had received. Those who had received placebo were offered vaccination with BIMERVAX or the influenza vaccine, as applicable.

In this case, a participant received a dose of BIMERVAX from an unopened study vial that had expired, although it had been stored appropriately under refrigeration conditions. No adverse reactions related to the administration of the expired product were reported at the time of vaccination. Approximately four months later, during routine follow-up visits for chronic conditions, the patient reported episodes of bronchitis, which tested COVID-19 negative. No emergency visits, hospitalisations, or other significant events were reported.

The case was classified as post-marketing medication error, with the PTs "Expired product administered" and "Bronchitis". This case is included in Appendix 2.2.

Given that only a single non-serious medication error with no associated safety concerns has been received during the reporting period, no additional mitigation activities are deemed necessary at this time. While some medication errors are expected to occur despite clear written instructions for handling

the vaccine, the potential for such errors is already mitigated through the comprehensive information included in the vaccine labelling.

This medication error does not impact the known safety profile of HIPRA COVID-19 vaccines or alter their overall benefit-risk balance.

**Literature**

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.

**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 and endorsed by EMA PRAC on 25 April 2024. 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 and endorsed by EMA PRAC on 30 May 2024. A final report is planned for submission within 12 months after study completion (estimated date: 31 July 2029)

*Rapporteur assessment comment:*

As per MAHs information, 3 clinical trials were ongoing. Two of them (HIPRA-HH-3 and HIPRA-HH-11) were reported in the previous PSUSA reporting period and there were no major findings which remains unchanged.

The study HIPRA-HH-14 is a phase IIb/III, double-blind, randomised, active-controlled, multi-centre, non-inferiority clinical trial, to assess the safety and immunogenicity of a booster vaccination with an adapted recombinant protein RBD fusion homodimer candidate (PHH-1V81) against SARS-CoV-2, in adults vaccinated against COVID-19.In this study, 905 adults aged 18 or older were randomly assigned to the following two treatment arms in a BIMERVAX XBB.1.16:Comirnaty Omicron XBB.1.5, 2:1 ratio. Finally, 903 participants received the treatments.

Cumulatively, a total of 16 non-product related SAEs were reported throughout the duration of the study. As of the DLP of this report, no major findings were reported with regard to safety.

The MAH has indicated that during the reporting interval one non-serious case of medication error was received from post-marketing sources. The MAH`s conclusion that this case does not impact the known safety profile of HIPRA COVID-19 vaccines or alter their overall benefit-risk balance is supported.

At the DLP of this reporting interval two non-interventional category 3 studies VAC4EU and C-VIPER are planned with BIMERVAX to address safety concerns of the RMP. After the DLP of this PSUSA procedure through a variation type II procedure No. EMA/VR/0000262308 the category 3 C-VIPER study was removed from the list of additional pharmacovigilance activities in the risk management plan for Bimervax due to feasibility reasons.

### 1.3.6. Lack of efficacy in controlled clinical trials

N/A

### 1.3.7. Late-breaking information

N/A

# 2. Signal and risk evaluation

## *2.1. Summary of safety concerns*

There is a Risk Management Plan (RMP) in place for HIPRA COVID-19 vaccines at the DLP of this report, RMP version 1.5, which listed the following safety concerns:

| | |
|---|---|
| Important identified risks | Pericarditis |
| Important potential risks | Myocarditis<br>Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) |
| Missing information | Use in pregnancy and while breastfeeding<br>Use in frail patients with comorbidities (e.g., Chronic Obstructive Pulmonary Disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)<br>Interaction with other vaccines<br>Long-term safety |

## *2.2. Signal evaluation*

No safety signals were closed during the reporting interval.

*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 has been identified.

*Rapporteur assessment comment:*

*Information acknowledged. No further action is considered warranted at this stage.*

## *2.4. 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.

**Important identified risks**

**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-authorisation 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-authorisation surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than HIPRA COVID-19 vaccines [Twentyman, 2022].

Post-marketing experience:

No post-marketing events of pericarditis have been reported with HIPRA COVID-19 vaccines.

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.

**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-authorisation 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 HIPRA COVID-19 vaccines.

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-authorisation surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than HIPRA COVID-19 vaccines [Twentyman, 2022].

Post-marketing experience:

No post-marketing events of myocarditis have been reported with HIPRA COVID-19 vaccines.

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.

**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 HIPRA COVID-19 vaccines clinical development programme.

Post-marketing experience:

No post-marketing events of VAED/VAERD have been reported with HIPRA COVID-19 vaccines.

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 HIPRA COVID-19 vaccines 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 HIPRA COVID-19 vaccines 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, 2025; SmPC Nuvaxovid, 2025; SmPC Spikevax, 2025]. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development. Administration of HIPRA COVID-19 vaccines in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. It is unknown whether HIPRA COVID-19 vaccines are 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 HIPRA COVID-19 vaccines in pregnant and/or breastfeeding women will occur.

**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:

HIPRA COVID-19 vaccines have 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 HIPRA COVID-19 vaccines 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.

**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, was evaluated in the Phase IIb clinical studies HIPRA-HH-2 and HIPRA-HH-10, 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 HIPRA COVID-19 vaccines.

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 HIPRA COVID-19 vaccines 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 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 HIPRA COVID-19 vaccines 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.

**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 that alters previous assessments, and 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 724 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.

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 balance for Bimervax remains unchanged.

The current 1-year frequency for the submission of PSURs should remain unchanged. Bimervax is under the additional monitoring list, and no changes are warranted on that respect.

# 5. Rapporteur Request for supplementary information

N/A

HIPRA

# PERIODIC SAFETY UPDATE REPORT

for

**COVID-19 Vaccine (recombinant, adjuvanted)**

**ACTIVE SUBSTANCES:** Selvacovatein / Damlecovatein

**ATC CODE:** J07BN04

**MEDICINAL PRODUCTS COVERED:**

| Invented Name of the Medicinal Products | Marketing Authorisation Numbers | Dates of Authorisation | Marketing Authorisation Holder |
|---|---|---|---|
| BIMERVAX® | EU/1/22/1709/001<br>EU/1/22/1709/002-004 | 30 March 2023<br>07 March 2024 | Hipra Human Health, S.L.U. |
| BIMERVAX® XBB.1.16 | EU/1/22/1709/005-007 | 12 December 2024 | Hipra Human Health, S.L.U. |
| BIMERVAX® | PLGB 56346/0002<br>PLGB 56346/0003 | 31 July 2023<br>18 June 2024 | Hipra Human Health, S.L.U. |
| BIMERVAX® XBB.1.16 | PLGB 56346/0004 | 27 December 2024 | 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 September 2024 to 29 March 2025

**DATE OF THIS REPORT**

**APPLICANT'S NAME AND ADDRESS:**

**Hipra Human Health, S.L.U.**

Avda. la Selva, 135, 17170 Amer (Girona), Spain

**NAME AND CONTACT DETAILS OF THE EEA QPPV:**

Irina Güell
Official address: Hipra Human Health, S.L.U.
Avda. la Selva, 135, 17170 Amer (Girona), Spain
Email: [redacted]
24-hour contact number: [redacted]
For communication and assessment of this report: pvhumanhealth@hipra.com

**SIGNATURE EEA QPPV:** _____

# Executive Summary

## Introduction

This is the 4th Periodic Safety Update Report (PSUR) for Hipra Human Health, S.L.U.'s BIMERVAX emulsion for injection, containing selvacovatein (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, and BIMERVAX XBB.1.16 emulsion for injection, containing damlecovatein (SARS-CoV-2 virus recombinant spike [S] protein receptor binding domain [RBD] fusion homodimer – Omicron XBB.1.16-XBB.1.16 strain) as active substance.

It is 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 September 2024 to 29 March 2025.

This PSUR is the first to include both BIMERVAX (selvacovatein) and BIMERVAX XBB.1.16 (damlecovatein); previous PSURs covered only BIMERVAX. As used in this report, the term "parent vaccine" refers to BIMERVAX, the term "adapted vaccine" refers to BIMERVAX XBB.1.16, and the term "HIPRA COVID-19 vaccines" refers to both BIMERVAX and BIMERVAX XBB.1.16 (both the parent and the adapted vaccine).

## Reporting interval

This executive summary provides a concise summary of the content and the most important information in the PSUR collected during a 6-month interval, from 30 September 2024 to 29 March 2025.

In line with the PRAC recommendation following assessment of the third BIMERVAX PSUR (procedure number: EMEA/H/C/PSUSA/00011045/202409), this is the last report with a 6-month periodicity; future submissions will follow an annual cycle. The first yearly PSUR to be submitted will be PSUR Nº05.

## Medicinal products

| | **BIMERVAX** | **BIMERVAX XBB.1.16** |
|---|---|---|
| Name of the product | BIMERVAX emulsion for injection | BIMERVAX XBB.1.16 emulsion for injection |
| Active substance | Selvacovatein | Damlecovatein |
| Pharmaceutical form | Emulsion for injection | 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 | BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV- |

| | | |
|---|---|---|
| | previously received a messenger Ribonucleic Acid (mRNA) COVID-19 vaccine | 2 in individuals 16 years of age and older |
| Regime of Dosage | A single intramuscular dose (0.5 mL) of BIMERVAX should be administered at least 6 months after previous mRNA COVID-19 vaccine. BIMERVAX may also be given at least 6 months after a previous booster with BIMERVAX | A single intramuscular dose (0.5 mL) of BIMERVAX XBB.1.16 should be administered regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, BIMERVAX XBB.1.16 should be administered at least 6 months after the most recent dose of a COVID-19 vaccine |

**Number of countries in which the medicinal products are authorised**

The parent BIMERVAX vaccine was first authorised 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 authorised in the above-mentioned countries and in United Kingdom. Additionally, on 09 October 2023, BIMERVAX was prequalified by the World Health Organization (WHO) for purchase by United Nations (UN) agencies.

The adapted BIMERVAX XBB.1.16 vaccine received Marketing Authorisation from the European Commission for use in the EEA on 12 December 2024, and from MHRA for use in the United Kingdom on 27 December 2024. Additionally, on 6 February 2025, BIMERVAX XBB.1.16 also received WHO prequalification, enabling its procurement by UN agencies.

**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**

A total of 4,294 subjects were exposed to BIMERVAX in 8 company-sponsored clinical trials cumulatively since the Development International Birth Date (DIBD). The cumulative patient exposure is based upon exposure data from completed clinical trials and from ongoing clinical trials which are unblinded.

Regarding BIMERVAX XBB.1.16, a total of 602 subjects were exposed to the medicinal product in a single company-sponsored clinical trial, which is completed but without an available CSR at the DLP of this report and thus, considered ongoing.

**Estimated interval and cumulative exposure from marketing experience**

No doses of BIMERVAX or BIMERVAX XBB.1.16 have been administered during the period covered by this safety report until 29 March 2025. Cumulatively, the estimated exposure from marketing experience is seven hundred and twenty-four (724) doses, equivalent to 724 patients vaccinated.

**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 HIPRA COVID-19 vaccines has been identified. Therefore, the benefit-risk balance of the products remains positive.

**Conclusions**

In this PSUR (from 30 September 2024 to 29 March 2025), 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,
- Two cases have been received from post-marketing sources (including one non-serious medication error and one invalid case),
- No other new information affecting the known safety profile of HIPRA COVID-19 vaccines 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.

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# 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 |
| **DBL** | Data base lock |
| **DIBD** | Development International Birth Date |
| **DLP** | Data Lock Point |
| **ECDC** | European Centre for Disease and Control |
| **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 |
| **IRIS** | Intelligent Regulatory Information System |
| **LPLV** | Last patient last visit |
| **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 |
| **TAG-CO-VAC** | Technical Advisory Group on COVID-19 Vaccine Composition |
| **Th** | T helper cell type |
| **UN** | United Nations |
| **VAED** | Vaccine-Associated Enhanced Disease |
| **VAERD** | Vaccine-Associated Enhanced Respiratory Disease |
| **WHO** | World Health Organisation |

# 1. Introduction

This is the 4th Periodic Safety Update Report (PSUR) for Hipra Human Health, S.L.U.'s BIMERVAX emulsion for injection, containing selvacovatein as active substance, and BIMERVAX XBB.1.16 emulsion for injection, containing damlecovatein as active substance.

This report covers a 6-month reporting period and has been 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.

It summarises the safety data received from world-wide sources by Hipra Human Health, S.L.U. Pharmacovigilance's Unit from 30 September 2024 to 29 March 2025, and presents a comprehensive and critical assessment of the benefit-risk profile of the authorised BIMERVAX and BIMERVA XBB.1.16 vaccines, based on the review of both cumulative and interval safety information collected during this period.

Currently, the PSUR for HIPRA COVID-19 vaccines is submitted on a 6-monthly schedule, in accordance with the European Union Reference Dates (EURD). In line with the PRAC recommendation following assessment of the third BIMERVAX PSUR (procedure number: EMEA/H/C/PSUSA/00011045/202409), this fourth PSUR (covering the period from 30 September 2024 to 29 March 2025) will be the last to follow the 6-monthly periodicity. From the next submission onwards, the PSUR frequency will transition to an annual cycle. The first yearly PSUR to be submitted will be PSUR Nº05, covering the period from 30 March 2025 to 29 March 2026.

The first three BIMERVAX PSURs (PSUR Nº01, PSUR Nº02, and PSUR Nº03) included only BIMERVAX vaccine. Beginning with this PSUR Nº04, both the parent BIMERVAX vaccine and the adapted BIMERVAX XBB.1.16 vaccine are included.

## 1.1 International Birth Date (IBD)

The IBD for BIMERVAX is 30 March 2023.

## 1.2 Medicinal Products

The HIPRA COVID-19 vaccines are a recombinant protein vaccine whose active substance (antigen) is SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion dimer. 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, the HIPRA COVID-19 vaccines induce antigen-specific T-cell immune response, which may contribute to protection to COVID-19.

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

BIMERVAX XBB.1.16 emulsion for injection (hereinafter referred to as BIMERVAX XBB.1.16), is an emulsion for injection containing 40 µg of damlecovatein as active ingredient per 0.5 mL. Damlecovatein is a SARS-CoV-2 virus recombinant S protein RBD fusion homodimer – Omicron XBB.1.16-XBB.1.16 strain.

BIMERVAX and BIMERVAX XBB.1.16 belong to the pharmacotherapeutic group: Vaccines, Covid-19 vaccines, Anatomical Therapeutic Chemical classification (ATC) code: J07BN04.

**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.

BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

**Pharmaceutical form**

Emulsion for injection.

White homogeneous emulsion.

**Route of administration, Dose**

Intramuscular injection.

BIMERVAX is a multidose vial which contains 10 doses of 0.5 mL each or a single dose vial which contains 1 dose of 0.5 mL. A single intramuscular dose (0.5 mL) of BIMERVAX should be administered at least 6 months after previous mRNA COVID-19 vaccine. BIMERVAX may also be given at least 6 months after a previous booster with BIMERVAX.

BIMERVAX XBB.1.16 is a single dose vial which contains 1 dose of 0.5 mL. A single intramuscular dose (0.5 mL) of BIMERVAX XBB.1.16 should be administered regardless of prior COVID-19 vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, BIMERVAX XBB.1.16 should be administered at least 6 months after the most recent dose of a COVID-19 vaccine.

## 1.3 Populations being treated and studied

As mentioned above, BIMERVAX and BIMERVAX XBB.1.16 are indicated in individuals 16 years of age and older.

The safety and efficacy of HIPRA COVID-19 vaccines 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 7.2.1 of this report).

The efficacy and safety of the vaccine has been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. Clinical trial HIPRA-HH-4 assessed the immunogenicity and safety of BIMERVAX in adults with pre-existing immunosuppressive conditions vaccinated against COVID-19 (please refer to section 7.1.6 of this report).

There is no experience with the use of HIPRA COVID-19 vaccines in pregnant women and it is unknown whether they are excreted in human milk.

HIPRA COVID-19 vaccines are contraindicated in patients with hypersensitivity to the active substances or to any of the excipients contained in the product.

# 2. World-wide marketing authorisation status

The parent BIMERVAX vaccine was first authorised by the European Commission via centralised procedure on 30 March 2023, and is therefore authorised for use in all European Economic Area (EEA) countries. In addition to its approval across the EEA, BIMERVAX was also authorised for use in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA) on 31 July 2023.

Additionally, on 09 October 2023, BIMERVAX received the positive decision by the World Health Organization (WHO) as a prequalified vaccine for purchase by United Nations (UN) agencies.

In 2024, to ensure continued protection against emerging Omicron SARS-CoV-2 variants, an adapted version of the parent vaccine was developed. This adapted vaccine, BIMERVAX XBB.1.16, received Marketing Authorisation from the European Commission for use in the EEA on 12 December 2024, and from MHRA for use in the United Kingdom on 27 December 2024. Additionally, on 6 February 2025, BIMERVAX XBB.1.16 also received WHO prequalification, enabling its procurement by UN agencies.

In accordance with the European Medicines Agency's (EMA) *Post-authorisation Procedural Advice for Users of the Centralised Procedure*, the marketing status report of the HIPRA COVID-19 vaccines has been downloaded from the IRIS system and is appended to this PSUR (please refer to Appendix 8 of this report).

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

**Table 1: Worldwide Marketing Authorisation Status**

| Country /Region | Invented Name of the Medicinal Product | Marketing Authorisation Number | Date of Authorisation | Presentation | Pack size | Approved dose | Indication |
|---|---|---|---|---|---|---|---|
| EEA | BIMERVAX emulsion for injection | EU/1/22/1709/001 | 30 March 2023 | Multidose vial (5 mL): 10 doses of 0.5 mL | 10 multidose vials (100 doses) | 0.5 mL containing 40 µg of selvacovatein | 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. |
| | | EU/1/22/1709/002-004 | 07 March 2024 | Single dose vial (0.5 mL): 1 dose of 0.5 mL | 5, 10 and 20 single dose vials (5, 10 and 20 doses) | | |
| | BIMERVAX XBB.1.16 emulsion for injection | EU/1/22/1709/005-007 | 12 December 2024 | Single dose vial (0.5 mL): 1 dose of 0.5 mL | 5, 10 and 20 single dose vials (5, 10 and 20 doses) | 0.5 mL containing 40 µg of damlecovatein | BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. |
| UK | BIMERVAX emulsion for injection | PLGB 56346/0002 | 31 July 2023 | Multidose vial (5 mL): 10 doses of 0.5 mL | 10 multidose vials (100 doses) | 0.5 mL containing 40 µg of selvacovatein | 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 |

| Country /Region | Invented Name of the Medicinal Product | Marketing Authorisation Number | Date of Authorisation | Presentation | Pack size | Approved dose | Indication |
|---|---|---|---|---|---|---|---|
| | | PLGB 56346/0003 | 18 June 2024 | Single dose vial (0.5 mL): 1 dose of 0.5 mL | 5, 10 and 20 single dose vials (5, 10 and 20 doses) | | mRNA COVID-19 vaccine. |
| | BIMERVAX XBB.1.16 emulsion for injection | PLGB 56346/0004 | 27 December 2024 | Single dose vial (0.5 mL): 1 dose of 0.5 mL | 5, 10 and 20 single dose vials (5, 10 and 20 doses) | 0.5 mL containing 40 µg of damlecovatein | BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. |

# 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 and BIMERVAX XBB.1.16 (dated 13 March 2025) is used as the Reference Safety Information (RSI) and is presented in Appendix 1.

During the period covered by this report, two new versions of the SmPC were issued:

- On 12 December 2024, following receipt of the European Commission Decision for the adapted vaccine, the SmPC was updated to include information related to the first adaptation targeting the Omicron subvariant XBB.1.16, BIMERVAX XBB.1.16.
- On 13 March 2025, sections 4.2, 4.4, and 5.1 of the SmPC were updated to include the final results of the CSR from HIPRA-HH-4 study regarding the use of BIMERVAX in immunocompromised individuals.

# 5. Estimated exposure and use patterns

## 5.1 Cumulative Subject Exposure in Clinical Trials

Cumulatively, 4,294 subjects have been exposed to BIMERVAX in 8 company-sponsored clinical trials cumulatively since the Development International Birth Date (DIBD).

Six (6) 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, HIPRA-HH-5, HIPRA-HH-2 and HIPRA-HH-4). Furthermore, 2 clinical trials are ongoing: 1 clinical trial which is completed but without an available Clinical Study Report (CSR) at the DLP of this report (HIPRA-HH-11) and 1 clinical trial which is not completed (HIPRA-HH-3).

The cumulative patient exposure is based upon exposure data from completed clinical trials, and from ongoing clinical trials which are unblinded.

In the above-mentioned clinical trials, a cumulative total of 4,294 and 393 subjects were exposed to BIMERVAX and comparator treatments, respectively at the DLP of this report. Additionally, 95 patients were exposed to placebo and a co-administered treatment.

Regarding BIMERVAX XBB.1.16, there is a single company-sponsored clinical trial which is clinically completed but without an available CSR at the DLP of this report (HIPRA-HH-14). A cumulative total of 602 subjects have been exposed to BIMERVAX XBB.1.16 and 301 subjects to comparator treatment in this study at the DLP of this report.

Cumulative patient exposure for both BIMERVAX and BIMERVAX XBB.1.16 are provided in the tables below.

**Table 2: Cumulative subject exposure from clinical trials**

| Treatment | BIMERVAX | BIMERVAX XBB.1.16 |
|---|---|---|
| Medicinal Product | 4,294* | 602 |
| Comparator | 393 | 301 |
| Placebo and co-administered treatment | 95** | NA |

**Among the total number of subjects that received the medicinal product, 92 of them also received seasonal inactivated adjuvanted influenza vaccine (SIIV) as co-administration in HIPRA-HH-11 study.*
***The co-administered treatment is seasonal inactivated adjuvanted influenza vaccine (SIIV) in HIPRA-HH-11 study.*

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 | BIMERVAX | BIMERVAX XBB.1.16 |
|---|---|---|
| <18 | 276 | 0 |
| 18-64 | 3,679 | 547 |
| >=65 | 339 | 55 |
| **Total** | **4,294** | **602** |

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

| Sex | BIMERVAX | BIMERVAX XBB.1.16 |
|---|---|---|
| Male | 2160 | 231 |
| Female | 2133 | 371 |
| Undifferentiated | 1 | 0 |
| **Total** | **4,294** | **602** |

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 | BIMERVAX | BIMERVAX XBB.1.16 |
|---|---|---|
| White | 4,083 | 566 |
| Hispanic/Caucasian | 24 | 0 |
| American Indian or Alaska Native | 15 | 0 |
| Black or African American | 12 | 0 |
| Asian | 138 | 0 |
| Other | 22 | 36 |
| **Total** | **4,294** | **602** |

## 5.2 Cumulative and Interval Patient Exposure from Marketing Experience

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

BIMERVAX and BIMERVAX XBB.1.16 are to be procured and distributed through the Governments; therefore, information on post-authorisation (non-clinical trial) exposure is

requested to the Government of each country in which the vaccines have been distributed. Should the Governments not provide these data, data from the European Centre for Disease and Control (ECDC) website is used.

As of the DLP of this PSUR, BIMERVAX has only been distributed to Spain, Belgium and Andorra. The first units of BIMERVAX were distributed in 2023, with an initial shipment to the Spanish territory on 14 June 2023. A total of 3.2 million doses were distributed to the Spanish Government; 10,000 doses to the Belgian Government; and 500 to the Andorran Government. No further doses have been supplied to any country thereafter.

BIMERVAX XBB.1.16 is not commercially available; therefore, there is no post-authorisation exposure.

During the current reporting period (30 September 2024 to 29 March 2025), no new doses of BIMERVAX or BIMERVAX XBB.1.16 have been distributed. As stated in the previous BIMERVAX PSUR (PSUR Nº03), the initial distributed batches of BIMERVAX expired in early 2024. Therefore, since no additional doses have been made available on the market, it is not expected that any doses were administered during reporting period covered by this report.

Patient exposure is shown in the following table:

**Table 6: Interval exposure data from 30 September 2024 to 29 March 2025**

| Region | Brand name | Patients vaccinated |
|---|---|---|
| EU/EEA countries | BIMERVAX | 0 |
| | BIMERVAX XBB.1.16 | 0 |
| | **Total** | **0** |

Cumulative post-authorisation exposure remains unchanged since the previous PSUR.

In the first BIMERVAX PSUR (covering the period form 30 March 2023 to 29 September 2023), an estimate of 137 doses of BIMERVAX were administered. In the second PSUR (30 September 2023 to 29 March 2024), an additional 587 doses of BIMERVAX were estimated, bringing the cumulative total to 724 doses.

As previously stated in PSUR Nº03 (30 March 2024 to 29 September 2024), no doses were expected to have been administered during that reporting period, and the same applies to the current reporting period (30 September 2024 to 29 March 2025).

Therefore, the cumulative post-authorisation exposure remains at 724 doses, as summarised in the table below.

**Table 7: Cumulative exposure data from IBD* to 29 March 2025**

| Region | Brand name | Patients vaccinated |
|---|---|---|
| EU/EEA countries | BIMERVAX | 724 |
| | BIMERVAX XBB.1.16 | 0 |
| | **Total** | **724** |

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

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 27.1) 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, comparator treatments and placebo with co-administered treatment), as applicable.

For BIMERVAX, a total of 143 SAEs have been reported in the studies HIPRA-HH-1, HIPRA-HH-2, HIPRA-HH-3, HIPRA-HH-4, HIPRA-HH-5, HIPRA-HH-10, and HAN-01. One hundred and forty-two (142) SAEs were considered non-related, and 1 SAE was considered as possibly related.

For BIMERVAX XBB.1.16, a total of 16 SAEs have been reported in clinical study HIPRA-HH-14. All 16 SAEs were assessed as non-related to the investigational medicinal products.

## 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.

During the reporting period, a total of 2 non-serious cases were received from post-marketing sources. Of these, one was considered valid and included 2 PTs, while the other was classified as an invalid case and included a single PT.

Cumulatively, a total of 5 ICSRs (4 non-serious and 1 serious) have been received from post-marketing sources, comprising a total of 22 PTs.

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

For BIMERVAX, a total of 8 clinical trials were either ongoing or completed during the current reporting period. Specifically, 6 of them were completed and the remaining 2 are ongoing.

For BIMERVAX XBB.1.16, a single clinical trial was ongoing during the reporting interval.

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 products that were completed or ongoing during the reporting interval is available in Appendix 4.

## 7.1 Completed Clinical Trials

The following 6 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 patient last visit (LPLV) in this study was on 03 March 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.

### 7.1.5 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.

<u>Part A</u>

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).

Overall, 4 subjects prematurely discontinued study participation and 2 subjects were lost to follow-up. None of them were discontinued due to safety reasons.

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 and 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 males and 109 females.

Overall, 4 subjects prematurely discontinued study participation. None of such discontinuations were due to safety reasons.

Cumulatively, 15 non-related SAEs have occurred throughout this study. Specifically, 14 SAEs in Part A and 1 SAE in Part B.

The Data Base Lock (DBL) of the clinical trial was performed on 11 August 2023. According to the CSR, no major findings were reported with regard to safety. The CSR was signed on 31 October 2023.

### 7.1.6 HIPRA-HH-4

HIPRA-HH-4 was a phase IIb/III, open label, single arm, multi-centre, trial to assess the immunogenicity and safety of an additional dose vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults with pre-existing 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 had one 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 Day 0;
- Kidney transplant at least >1 year and with last anti-CD20/anti-CD3 biological treatment given at least >1 year prior to Day 0 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 was proposed. Finally, a total of 240 participants were enrolled. Among them, a total of 238 participants were vaccinated: 231 participants (85 females and 146 males) received the study treatment in Spain and 7 participants (6 males and 1 female) received the study treatment in Turkey.

Cumulatively, 93 non-related SAEs were reported throughout this study. The Data Base Lock (DBL) of the clinical trial was performed on 21 February 2024 and the final CSR was issued on 23 July 2024. Note that PTs were considered for SAEs calculation, and there were some cases codified with more than one PT, resulting in a different number of SAEs as stated in final CSR. No major findings were reported with regard to safety. Overall, the results of the study indicated that vaccination with PHH-1V was safe and well tolerated in participants with underlying immunosuppressive conditions.

## 7.2 Ongoing Clinical Trials

The clinical trials described below are either ongoing (HIPRA-HH-3) or completed but without an available CSR at the DLP of the present report, and thus considered ongoing (HIPRA-HH-11 and HIPRA-HH-14).

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

### 7.2.1 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 7 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 242 participants have been enrolled and 240 of them have been vaccinated (127 males and 113 females). Two (2) patients did not meet the inclusion criteria and were considered screening failures.

Cumulatively, 2 non-related SAEs have been reported.

An interim report was issued on 27 January 2025 and there are no major findings in regard to safety at the DLP of this PSUR.

### 7.2.2 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 65 years of age fully vaccinated against COVID-19. The study was conducted at 8 sites in Spain and the main objective was 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 sample size of 300 adults aged 65 or older was proposed. Finally, 283 participants were enrolled, 279 patients were randomized in the study, and 278 (154 males and 124 females) were vaccinated and followed for 1 month after study treatment. The participants were randomised 1:1:1 to one of the following three Cohorts:

- Cohort 1: 95 participants (41 males and 54 females) received one dose of SIIV in one arm + one dose of placebo in the other arm, at Day 0.
- Cohort 2: 91 participants (55 males and 36 females) received one dose of BIMERVAX in one arm + 1 dose of placebo in the other arm, at Day 0.
- Cohort 3: 92 participants (58 males and 34 females) received one dose SIIV in one arm + one dose of BIMERVAX in the other arm, at Day 0.

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

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

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.

### 7.2.3 HIPRA-HH-14

The study HIPRA-HH-14 is a phase IIb/III, double-blind, randomised, active-controlled, multi-centre, non-inferiority clinical trial, to assess the safety and immunogenicity of a booster vaccination with an adapted recombinant protein RBD fusion homodimer candidate (PHH-1V81) against SARS-CoV-2, in adults vaccinated against COVID-19.

In this study, 905 adults aged 18 or older were randomly assigned to the following two treatment arms in a BIMERVAX XBB.1.16:Comirnaty Omicron XBB.1.5, 2:1 ratio. Finally, 903 participants received the treatments:

- A total of 602 adults (370 females and 232 males) received a booster dose of BIMERVAX XBB.1.16.
- A total of 301 adults (175 females and 126 males) received a booster dose of Comirnaty Omicron XBB.1.5.

Cumulatively, a total of 16 non-product related SAEs were reported throughout the duration of the study.

An interim report was issued on 3 January 2024. Last patient last visit (LPLV) in this study was on 17 June 2024 and the DBL of the clinical trial was performed on 25 February 2025. As of the DLP of this report, no major findings were reported with regard to safety.

### 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 and endorsed by EMA PRAC on 25 April 2024. 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 and endorsed by EMA PRAC on 30 May 2024. 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

During the reporting period, 1 case of medication error was received from post-marketing sources.

The case originated from the HIPRA-HH-11 study, where a participant received an expired dose from an unopened BIMERVAX vial after unblinding. This dose was administered in error, fell outside the study protocol, and was classified as a post-marketing medication error.

HIPRA-HH-11 was a double-blind clinical trial evaluating the safety and immunogenicity of BIMERVAX when co-administered with an influenza vaccine. Participants were distributed into the following cohorts:

- Cohort 1: Influenza vaccine + placebo
- Cohort 2: BIMERVAX + placebo
- Cohort 3: Influenza vaccine + BIMERVAX

After unblinding, participants were contacted to inform them about the vaccines they had received. Those who had received placebo were offered vaccination with BIMERVAX or the influenza vaccine, as applicable.

In this case, a participant received a dose of BIMERVAX from an unopened study vial that had expired, although it had been stored appropriately under refrigeration conditions. No adverse reactions related to the administration of the expired product were reported at the time of vaccination. Approximately four months later, during routine follow-up visits for chronic conditions, the patient reported episodes of bronchitis, which tested COVID-19 negative. No emergency visits, hospitalisations, or other significant events were reported.

The case was classified as post-marketing medication error, with the PTs “Expired product administered” and “Bronchitis”. This case is included in Appendix 2.2.

Given that only a single non-serious medication error with no associated safety concerns has been received during the reporting period, no additional mitigation activities are deemed necessary at this time. While some medication errors are expected to occur despite clear written instructions for handling the vaccine, the potential for such errors is already mitigated through the comprehensive information included in the vaccine labelling.

This medication error does not impact the known safety profile of HIPRA COVID-19 vaccines or alter their overall benefit-risk balance.

# 10. Non-clinical data

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

# 11. Literature

From 30 September 2024 to 29 March 2025, 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) and BIMERVAX XBB.1.16 (SARS-CoV-2 virus recombinant S protein RBD fusion homodimer – Omicron XBB.1.16-XBB.1.16 strain). 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 HIPRA COVID-19 vaccines 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 HIPRA COVID-19 vaccines 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 HIPRA COVID-19 vaccines at the DLP of this report, RMP version 1.5, which listed the following safety concerns:

| Summary of safety concerns | |
|---|---|
| Important identified risks | Pericarditis |
| Important potential risks | Myocarditis<br>Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) |
| Missing information | Use in pregnancy and while breastfeeding<br>Use in frail patients with comorbidities (e.g., Chronic Obstructive Pulmonary Disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)<br>Interaction with other vaccines<br>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 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-authorisation 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-authorisation surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than HIPRA COVID-19 vaccines [Twentyman, 2022].

Post-marketing experience:

No post-marketing events of pericarditis have been reported with HIPRA COVID-19 vaccines.

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-authorisation 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 HIPRA COVID-19 vaccines.

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-authorisation surveillance of Novavax COVID-19 vaccine, which is manufactured using a different protein platform and a different adjuvant system than HIPRA COVID-19 vaccines [Twentyman, 2022].

Post-marketing experience:

No post-marketing events of myocarditis have been reported with HIPRA COVID-19 vaccines.

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 HIPRA COVID-19 vaccines clinical development programme.

Post-marketing experience:

No post-marketing events of VAED/VAERD have been reported with HIPRA COVID-19 vaccines.

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 HIPRA COVID-19 vaccines 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 HIPRA COVID-19 vaccines 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, 2025; SmPC Nuvaxovid, 2025; SmPC Spikevax, 2025]. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development. Administration of HIPRA COVID-19 vaccines in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. It is unknown whether HIPRA COVID-19 vaccines are 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 HIPRA COVID-19 vaccines in pregnant and/or breastfeeding women will occur.

**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:

HIPRA COVID-19 vaccines have 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 HIPRA COVID-19 vaccines 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.

**16.4.3.5. 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, was evaluated in the Phase IIb clinical studies HIPRA-HH-2 and HIPRA-HH-10, 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 HIPRA COVID-19 vaccines.

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 HIPRA COVID-19 vaccines 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 HIPRA COVID-19 vaccines 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. BIMERVAX may also be given at least 6 months after a previous booster with BIMERVAX.

BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. For individuals who have previously been vaccinated with a COVID-19 vaccine, BIMERVAX XBB.1.16 should be administered at least 6 months after the most recent dose of a 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.

On the other hand, efficacy of BIMERVAX XBB.1.16 was inferred by immunobridging of immune responses to an authorised XBB adapted COVID-19 vaccine, for which vaccine efficacy had been established.

The immunogenicity of BIMERVAX XBB.1.16 was evaluated in one phase IIb/III double-blind clinical trial (HIPRA-HH-14). A total of 903 subjects were vaccinated; 602 received BIMERVAX XBB.1.16 and 301 received the Comirnaty Omicron XBB.1.5 vaccine.

Immunogenicity of a booster dose of BIMERVAX XBB.1.16 was based on an assessment of GMT of neutralising antibodies, measured by a PBNA against multiple SARS-CoV-2 variants. BIMERVAX XBB.1.16 vaccine demonstrated a non-inferior or even superior immune response against SARS-CoV-2 Omicron XBB.1.16 and Omicron XBB.1.5 variants compared to Comirnaty Omicron XBB.1.5 vaccine at Day 14 post-vaccination.

No severe COVID-19 infections were reported in the clinical studies, which supports that BIMERVAX and BIMERVAX XBB.1.16 provide 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 HIPRA COVID-19 vaccines 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 HIPRA COVID-19 vaccines has become available during the reporting interval.

The benefits of HIPRA COVID-19 vaccines 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. BIMERVAX may also be given at least 6 months after a previous booster with BIMERVAX.

BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. For individuals who have previously been vaccinated with a COVID-19 vaccine, BIMERVAX XBB.1.16 should be administered at least 6 months after the most recent dose of a 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]. It was declared a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO) on the 30 January 2020 and an end to this PHEIC was declared on 05 May 2023 [WHO, 2023].

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, 2023].

The incidence and prevalence of COVID-19 is difficult to estimate. In Europe, as of April 2025, there have been more than 777 million confirmed cases of COVID-19 and more than 7 million deaths reported to the World Health Organization [WHO, 2025].

The COVID-19 situation at the beginning of 2025, five 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, 5 vaccines are authorised by the European Medicines Agency (EMA): Bimervax (recombinant protein, adjuvated), Comirnaty (mRNA), Spikevax (mRNA), Nuvaxovid (recombinant protein, adjuvanted) and Kostaive (mRNA) [EMA, 2025].

  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].

  Since the emergence of the pandemic situation, there are serious concerns about the emergence of new variants of the SARS-CoV-2 virus. On April 2024, the World Health Organization's Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) recommended that COVID-19 vaccines incorporate a monovalent antigen from the JN.1 lineage [WHO, 2024b]. WHO's Strategic Advisory Group on Immunization

(SAGE) reaffirmed the importance of revaccination for groups at higher risk of severe disease and death, including older adults, individuals with comorbidities, immunocompromised persons, and pregnant individuals. Revaccination of health workers was also recommended.

*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].

- **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 30 January 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 by the beginning of 2025, five 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). 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 April 2024, the TAG-CO-VAC updated the recommendations on COVID-19 vaccination in the context of the circulating JN.1 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. BIMERVAX may also be given at least 6 months after a previous booster with BIMERVAX.

BIMERVAX XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

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 intensity.

After its distribution to the market on 14 June 2023, a total of 724 patients have been administered with BIMERVAX. A total of 2 ICSRs have been received from post-marketing sources during the reporting period of the PSUR, being one of them a non-serious medication errors and the other one, an invalid case.

Pericarditis and myocarditis have been classified as important identified and potential risk for HIPRA COVID-19 vaccines, 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 HIPRA COVID-19 vaccines. 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 and BIMERVAX XBB.1.16 remains as effective products for the approved indications 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 September 2024 to 29 March 2025), 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,
- Two cases have been received from post-marketing sources (including one non-serious medication error and one invalid case),
- No other new information affecting the known safety profile of HIPRA COVID-19 vaccines 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.