18 September 2025
EMADOC-1700519818-2307180
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Bimervax

Common name: COVID-19 vaccine (recombinant, adjuvanted)

Procedure No. EMA/VR/0000257408

Marketing Authorisation Holder (MAH): Hipra Human Health S.L.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Table of contents

List of abbreviations

ACE2	Angiotensin-converting enzyme 2
AE	Adverse event
AESI	Adverse events of special interest
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DBL	Database lock
ECDC	European Centre for Disease Control
ELISpot	Enzyme-linked immune absorbent spot
EMA	European Medicines Agency
EU	European Union
GMFR	Geometric mean fold rise
IGP	Immunogenicity population
ITT	Intent-to-treat
MAA	Marketing authorisation application
MAAE	Medically attended adverse events
mITT	Modified intent-to-treat (ITT)
mRNA	Messenger RNA
NAb	Neutralising antibody
PBMC	Peripheral blood mononuclear cell
PBNA	Pseudovirus-based neutralisation assay
PD	Pharmacodynamic
PHH-1V	COVID-19 Vaccine HIPRA
RBD	Receptor binding domain
S	Spike
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
SP	Safety population
VOC	Variant of concern
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Hipra Human Health S.L. submitted to the European Medicines Agency on 05 March 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include the use of BIMERVAX in adolescents aged 12 years and above, based on interim results from the ongoing study HIPRA-HH-3. HIPRA-HH-3 is an open-label, multi-centre, non-inferiority study to assess the safety and immunogenicity of BIMERVAX as heterologous booster for the prevention of COVID-19 in adolescents from 12 years of age to less than 18 years of age. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0253/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet complete as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP P/0253/2024.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Beata Maria Jakline Ullrich Co-Rapporteur: Daniela Philadelphy

Timetable	Actual dates
Submission date	05 March 2025
Start of procedure:	22 March 2025
CHMP Rapporteur's preliminary assessment report circulated on:	19 May 2025
CHMP Co-Rapporteur's preliminary assessment report circulated on:	27 May 2025
Joint Rapporteur's updated assessment report circulated on:	13 June 2025
Request for supplementary information adopted by the CHMP on:	19 June 2025
MAH's responses submitted to the CHMP on:	17 July 2025
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	25 August 2025
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	12 September 2025
CHMP opinion:	18 September 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

In December 2019, the WHO informed about a cluster of cases of viral pneumonia of unknown cause in China, with the virus spreading rapidly to other countries across the world. This pathogen crossed the species barrier into humans, causing contagious, sometimes severe respiratory infection and other by now described clinical manifestations. In January 2020, the virus causing this pneumonia was identified as a novel zoonotic coronavirus (SARS-CoV-2) and the disease was named COVID-19. The disease was declared a public health of international concern (PHEIC) on 30 January 2020 and characterised as a pandemic on 11 March 2020. On 5 May 2023, more than three years into the pandemic, given that the disease was well established and ongoing, WHO considered that COVID-19 no longer met the definition of a PHEIC. COVID-19 is no longer a pandemic, but the virus is still present.

Epidemiology, and risk factors, screening tools/prevention

Globally, as of 3 August 2025, there have been over 778 million confirmed cases of COVID-19, including 7 099 716 deaths reported by the WHO. Since the COVID-19 pandemic started, over 2.2 million people in the European Region have died from the disease.

The majority of infections result in asymptomatic or mild disease with full recovery. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

COVID-19 vaccines based on the spike protein of SARS-CoV-2 have shown high efficacy against symptomatic COVID-19. At present, a large percentage of the global population (70% approximately) is estimated to have been vaccinated against COVID-19, and there is a high seroprevalence globally from natural SARS-CoV-2 infection.

Nevertheless, COVID-19 remains a global health threat, it still places a burden on healthcare systems, and due to new birth cohorts, waning immunity and antigenic evolution of the virus, there is a recognised need for periodic COVID-19 vaccination. Also, there is a recognised need for development of next-generation COVID-19 vaccines providing protection also against transmission, providing greater breadth of protection against viral variants, and longer duration of immunity.

Biologic features, aetiology and pathogenesis

COVID-19 is caused by SARS-CoV-2 (betacoronavirus genus, sarbecovirus sub-genus). SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The pathogenesis of SARS-CoV-2 involves binding of the spike protein (surface-exposed part of virions) to the human receptor (ACE2), followed by internalisation to the cytosol (facilitated by cleavage of the spike protein by the membrane-bound TMPRRS2 protease), where intracellular viral replication takes place, leading to budding/release of progeny virions from the target cell, and typically ultimately death of target cells.

Disease manifestations reflect the typical route of infection (airborne transmission) and tissue distribution of the ACE2 receptor and TMPRRS2 protease (airways, endothelium, heart muscle, gastrointestinal epithelium). The virus has continually adapted to the new human host since the start of the pandemic, which is considered to have been associated with increased transmissibility but attenuated pathogenicity. However, the actual pathogenicity of currently circulating variants compared to the original index strain is difficult to estimate, due to the high level of population immunity, and even the current variants are considered to present a significant threat for at-risk populations. The aetiology and pathogenesis of the main acute COVID-19 disease manifestations (i.e., pneumonia, myocarditis) are well understood. COVID-19 is also associated with a heterogenous group of post-acute, persistent symptoms and sequelae (currently described as long COVID), for which aetiology and pathogenesis are less well understood.

Clinical presentation, diagnosis

The ECDC provides the following description of the clinical presentation of COVID-19 at the current post-pandemic stage:

- Symptoms may vary, both in frequency and severity, depending on the SARS-CoV-2 variant causing the disease episode.
- Most cases of COVID-19 are mild or moderate and do not require hospitalisation or advanced medical care.
- Severe disease usually manifests as pneumonia with shortness of breath and pulmonary infiltrates on chest imaging. Pneumonia can be complicated by respiratory failure requiring oxygen supplementation and mechanical ventilation. Other severe complications include thromboembolism (such as pulmonary embolism and stroke), circulatory shock, myocardial

damage, arrhythmias, and encephalopathy. Severe illness usually develops approximately one week after the onset of symptoms.

- Children usually experience mild symptoms (mainly fever and cough), if any, and have a very low risk of hospitalisation or death. However, some children may develop severe disease after infection with COVID-19, defined as multi-system inflammatory syndrome in children (MIS-C).
- Some patients may experience long-term symptoms with unclear aetiology (collectively referred to as post-COVID-19 condition and long COVID). The presentation is heterogenous, often episodic, and affects multiple organ systems [respiratory, cardiovascular, neuropsychiatric/cognitive symptoms, such as chronic fatigue (most commonly), headaches and loss of smell, difficulty concentrating, sleep disturbances, and depression].

Diagnosis is by detection of viral nucleic acid and viral nucleocapsid antigen, typically in nasopharyngeal swab material (RT-PCR and rapid lateral-flow antigen tests).

Management

The most effective way to prevent COVID-19 is vaccination. There are currently 5 vaccines authorised in the EU (i.e., Comirnaty, Spikevax, Nuvaxovid, Bimervax, Kostaive). COVID-19 vaccines have been shown to be effective in reducing the risk of disease and severe disease from SARS-CoV-2 infection.

The main treatment for most patients with severe disease is supportive care, which is often highly effective, antiviral medication (monoclonal antibodies and/or available antiviral drugs) where appropriate, and immune modulators.

2.1.2. About the product

BIMERVAX (SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion dimer produced by recombinant DNA technology) is intended 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.

A single injection of 40 µg dosage of the vaccine is intended to be used.

With this application, the MAH intends to extent the use of this vaccine to individuals 12 years of age and older.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trial was performed in accordance with GCP as claimed by the MAH.

2.3.2. Pharmacokinetics

No pharmacokinetics studies have been conducted. This is because pharmacokinetics studies are generally not needed for vaccines, consistent with current Guidelines on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

2.3.3. Pharmacodynamics

In relation to vaccines, pharmacodynamic studies are essentially comprised of the immunogenicity studies that characterise the immune response to the vaccine (as per Guideline on clinical evaluation of vaccines, EMEA/CHMP/VWP/164653/05 Rev. 1). The design and outcome of the pertinent study HH-3 is described in the main study section.

Neutralising antibody responses were determined using only Pseudovirus based neutralisation assay (PBNA). No change to the assay used in the initial MAA has been indicated by the Applicant. T-cell mediated immunity has also been measured and no change to methodology compared to the initial MAA has been indicated by the Applicant.

2.3.4. Main study

Open-label, multi-centre, non-inferiority study of safety and immunogenicity of Bimervax as heterologous booster for the prevention of coronavirus disease 2019 (COVID-19) in adolescents from 12 years to less than 18 years of age (HIPRA-HH-3)

Methods

Study HIPRA-HH-3 is a Phase IIb, open label, single arm, multi-centre trial (7 sites in Spain) to assess the immunogenicity and safety of a heterologous booster dose of a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adolescents from 12 years to less than 18 years with previous primary immunisation with Comirnaty.

The study is still ongoing, the cut-off date for the present interim analysis was on 25th September 2024, the date of interim study report serving as the basis of the present submission was 27th January 2025. The interim study report presents Day 14 immunogenicity data of all enrolled participants in the Immunogenicity data set, and safety findings through Day 28 of participants in the safety population.

On-site follow-up visits were performed on Days 14, 84, 168 and 336.

The study followed a sentinel procedure, the first three participants in the study were vaccinated at least 1 hour apart and observed for 1 hour. All safety and tolerability data through 72 hours post-vaccination from these sentinel participants were reviewed before dosing the rest of adolescents. If no relevant Grade 3 or Grade 4 Adverse Events (AEs) were recorded in the sentinel participants, the remaining participants were vaccinated.

As of data cut-off date (25th September 2024), a total of 240 participants received a single BIMERVAX booster dose on Day 0. The immunogenicity was evaluated in 88 adolescents and the safety was evaluated in 240 adolescent participants.

Study participants

In this Phase IIb study, at least 300 adolescents from 12 to less than 18 years of age, primary vaccinated with 2 doses of Comirnaty were planned to receive BIMERVAX from which a group of at

least 154 adolescents, with no previous documented medical history of COVID-19, were to be evaluable for the analysis of immunogenicity and were planned to follow for 12 months.

Inclusion criteria

1. Adolescents aged from 12 to less than 18 years at Screening.
2. Participant's parent(s)/legal guardian(s) willing and able to sign the informed consent and could comply with all study visits and procedures. A written assent was required for all participants in the study.
3. Participant must had received two previous doses of Comirnaty, last dose being at least 6 months before Screening.
4. Participant had a body mass index at or above the third percentile according to local Child Growth Standards at Screening visit.
5. Healthy participants and nonimmunocompromised participants with pre-existing, chronic and stable diseases, if these were stable and well-controlled according to the investigator's judgment, were eligible for inclusion in the study.
6. Had a negative Rapid Antigen Test (RAT) at Day 0 before Bimervax vaccine administration.
7. Participants biologically able to have children could be enrolled in the study if the participant fulfilled all the following criteria:
    - Had a negative urine pregnancy test at Screening (Day 0), only for those participants who are biologically able to become pregnant.
    - Had practiced adequate contraception or had abstained from all activities that could result in pregnancy for at least 28 days prior to the booster dose, only for those participants who are biologically able to become pregnant.
    - Had agreed to continue adequate contraception or abstinence through 3 months following the booster dose.
        - Participants with female reproductive system:
            - Hormonal contraception (progestogen-only or combined): oral, injectable or transdermal (patch) started at least 28 days before Day 0 and until 8 weeks after the vaccination
            - Intrauterine device.
            - Vasectomised partner (the vasectomised partner should be the sole partner for that participant).
            - Condom
        - Participants with male reproductive system:
            - Vasectomised participants.
            - Agreed to use a male condom with partners biologically able to become pregnant from screening and for at least 8 weeks after vaccination.
8. Participant had to have a body weight >50 kg at Screening visit to be eligible for the cellular immunology assays.

Exclusion criteria

9. Acute illness with fever ≥ 38.0° C at Screening or within 24 hours prior to vaccination. Participants could be rescheduled for Screening when they had completed 24 hours without fever. Afebrile participants with minor illnesses could be enrolled at the discretion of the investigator.
10. Received medications intended to prevent or treat COVID-19 before Screening, except for Comirnaty vaccines.
11. Previous or current diagnosis of MIS-C.
12. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may have increase the risk of study participation or, in the investigator's judgment, made the participant inappropriate for the study. Note: This included both conditions that may increase the risk associated with study intervention administration or a condition that may interfere with the interpretation of study results.
13. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention(s).
14. Immunocompromised individuals defined as those with primary and secondary immune deficiencies and those receiving chemotherapy or immunosuppressant drugs other than steroids and glucocorticoids (maximum 1 mg/kg/day of prednisone or total dose of 20 mg/day by any administration route for a maximum of 30 consecutive days), within 90 days prior to vaccination or during the study.
15. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
16. Female who was pregnant or breastfeeding.
17. Receipt of blood/plasma products, immunoglobulin, monoclonal antibodies, or receipt of any passive antibody therapy, within 90 days prior to vaccination or during the study.
18. Participation in other studies involving study intervention within 28 days prior to Screening and/or during study participation.
19. Received any non-study vaccine (including seasonal Influenza vaccine) within 14 days befor after Screening. For live or attenuated vaccines, 4 weeks before or after Screening.
20. History of illegal substance use or alcohol abuse within the past 2 years.
21. History of a diagnosis or other conditions that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant’s safety.
22. Individuals with documented medical history of microbiologically confirmed.

Treatments

Test product used in Study HIPRA-HH-3 was Bimervax recombinant and adjuvanted COVID-19 HIPRA’s vaccine at 0.5 mL (40 µg of protein, B.1.351-B.1.1.7 SARS-CoV-2 variants), via single intramuscular administration. One batch was used for all participants.

Objectives

The primary objectives were to determine and compare the changes in immunogenicity measured by Pseudovirus Based Neutralisation Assay (PBNA) against Omicron BA.1 variant at Baseline and Day 14, after vaccination of adolescents with a heterologous booster dose of BIMERVAX vs post heterologous booster dose in young adults (aged 18 to 25 years) from the adults booster study (HIPRA-HH-2, EudraCT 2021-005226-26); and to assess the safety and tolerability of BIMERVAX as heterologous booster dose in adolescents primary vaccinated against COVID-19 with 2 doses of Comirnaty vaccine.

Key Secondary objectives:

- To determine the changes in immunogenicity measured by PBNA against Variants of Concern (VOCs) (at least Beta and Delta) at Baseline and at Days 14, 84, 168 and 336 after vaccination of adolescents with a heterologous booster dose of BIMERVAX.
- To determine the changes in immunogenicity analysing the Geometric Mean Fold Rise (GMFR) measured by PBNA against Omicron BA.1 and VOCs (at least Beta and Delta) from Baseline to Day 14.

Secondary objectives:

- To determine the changes in immunogenicity measured by PBNA against Omicron BA.1 variant at Days 84, 168 and 336 after vaccination of adolescents with a heterologous booster dose of BIMERVAX.
- To determine the immunogenicity measured by means of total antibody against RBD of the Spike protein of SARS-CoV-2 quantification, measured by electrochemiluminescence immunoassay (ECLIA) at Baseline, Day 14, 84, 168 and 336 after vaccination of adolescents with a heterologous booster dose of BIMERVAX.
- To determine the changes in immunogenicity measured by PBNA against Wuhan strain at Baseline and Days 14, 84, 168 and 336 after vaccination of adolescents with a heterologous booster dose of BIMERVAX.
- To assess T-cell mediated responses against the SARS-CoV-2 S glycoprotein by ELISpot at Baseline and Day 14 after vaccination of adolescents with a heterologous booster dose of BIMERVAX. T-cell mediated responses were performed in a subset of approximately 10% of adolescents and in selected study sites.
- To assess $CD4^+$ and $CD8^+$ T-cell responses against the SARS-CoV-2 S glycoprotein by intracellular cytokine staining (ICS) at Baseline and Day 14 after vaccination of adolescents with a heterologous booster dose of BIMERVAX. $CD4^+$ and $CD8^+$ T-cell mediated responses were performed in a subset of approximately 10% of adolescents and in selected study sites.

Exploratory objectives:

- To assess the number of adolescents with SARS-CoV-2 infections ≥14 days after vaccination with a heterologous booster dose of BIMERVAX.
- To assess the number of COVID-19 severe infections ≥14 days after vaccination with a heterologous booster dose of BIMERVAX.
- To describe the number of multisystem inflammatory syndrome in children (MIS-C) cases with or without previous evidence of SARS-CoV-2 infection.

Outcomes/endpoints

Primary efficacy endpoints:

- Neutralisation titre against Omicron BA.1 measured as inhibitory concentration 50 (IC_{50}) by PBNA and reported as log10 concentration for each individual sample and Geometric Mean Titre (GMT) for group comparison with HIPRA-HH-2 at Baseline and Day 14.

Key secondary efficacy endpoints:

- Neutralisation titre against VOCs (at least Beta and Delta) measured as IC_{50} by PBNA and reported as log10 concentration for each individual sample and GMT at Baseline and Days 14, 84, 168 and 336.
- GMFR in neutralising antibody titres against Omicron BA.1 and VOCs (at least Beta and Delta) from Baseline to Day 14.

Secondary efficacy endpoints:

- Neutralisation titre against Omicron BA.1 measured as IC_{50} by PBNA and reported as log10 concentration for each individual sample and GMT at Days 84, 168 and 336.
- Binding antibody titres at Baseline and Days 14, 84, 168 and 336.
- GMFR in binding antibody titres from Baseline to Day 14.
- Percentage of participants that, after a booster dose, have a ≥4-fold change in binding antibody titre from Baseline and Days 14, 84, 168 and 336.
- Neutralisation titre against Wuhan measured as IC_{50} by PBNA and reported as log10 concentration for each individual sample and GMT at Baseline, and Days 14, 84, 168 and 336.
- GMFR in neutralising antibody titres against the Wuhan strain from Baseline to Day 14.
- T-cell-mediated response in Peripheral Blood Mononuclear Cell (PBMC) stimulated with SARS-CoV-2 S peptides measured by enzyme-linked immune absorbent spot (ELISpot) at Baseline and Day 14 in a subset of approximately 10% of the adolescents included in the immunogenicity group.
- $CD4^+$ /$CD8^+$ T-cell responses in PBMC stimulated with SARS-CoV-2 S peptides measured by intracellular cytokine staining (ICS) at Baseline and at Day 14 in a subset of approximately 10% of the adolescents included in the immunogenicity group.

Exploratory endpoints included the number of microbiologically confirmed COVID-19 cases, including severe cases, from ≥14 days after vaccination and through the end of the study, and confirmed multisystem inflammatory syndrome in children (MIS-C) cases as per the World Health Organisation (WHO) criteria. Those exploratory endpoints are not in the scope of the interim analysis and will therefore be described in the final clinical study report.

Sample size

Because no specific neutralising antibody titre has yet been established to predict protection, rigorous immunobridging studies should compare the range of neutralising antibody responses in young adults vs adolescent population by evaluating the GMTs using a 1.5-fold non-inferiority margin, at a given time point.

Considering the above, an immunobridging study was planned to assess neutralising antibody responses by evaluating the GMTs using a 1.5-fold non-inferiority margin for young adults (18- 25 years old, from Study HIPRA-HH-2) vs adolescents from 12 to <18 years old (Study HIPRA-HH-3).

Young adult data from individuals previously enrolled in study HIPRA-HH-2 included approximately 83 adults aged 18-25 years who were vaccinated with BIMERVAX and had immunologic response recorded at Day 14 post-vaccination. A total of 139 paediatric participants (adolescents) were needed to have evaluable immunologic response results, targeting 88.5% power to detect non-inferiority using a one-sided 2.5% significance level, and a two-sample t-test using a SDlog=0.40 for both treatments. The immunobridging external comparator group were the youngest age group included in the HIPRA-HH-2 trial who received BIMERVAX booster vaccine with formal hypothesis testing on sufficiently stringent success criteria (i.e., younger adults 18-25 years of age) to mitigate against bias introduced by biological differences between paediatric and adult populations.

A total of 300 participants were to be enrolled and treated for safety assessments.

Randomisation and Blinding (masking)

Randomisation and blinding were not applicable for this single arm study.

Statistical methods

Definition of populations

- Enrolled (EP): All participants who had signed the assent form and whose parents or legal representatives had signed the ICF.
- Intent-to-treat (ITT): All participants who were enrolled, regardless of the participant's treatment status in the study.
- Modified ITT (mITT): All participants in the ITT who met the inclusion/exclusion criteria, received a dose of study drug and had not tested positive for COVID-19 within 14 days of receiving study drug.
- Per-protocol (PP): All participants in the mITT who received a dose of the study drug and had no major protocol deviations, as determined, and documented by the Sponsor that impact critical or key study data.
- Immunogenicity (IGP): All participants in the mITT who had no documented medical history of COVID-19 infection at Screening and a valid immunogenicity test result before receiving the study drug and at least one valid result after dosing. This population was used for all immunogenicity analyses.
- Safety (SP): All participants who received the study drug. This population was used for all analyses of safety.

The immunogenicity analyses were performed using the IGP. The safety analyses were performed using the SP.

Hypothesis testing

To show non-inferiority, GMTs of HIPRA-HH-3 participants receiving BIMERVAX were compared to GMTs for HIPRA-HH-2 participants aged 18 to 25 years who received PHH-1V (BIMERVAX).

- *Null hypothesis, H_0*: The ratio of the GMTs (Young adults external control: Adolescents) exceeds the non-inferiority margin (NI_m); equivalently the difference in log(GMT) exceeds log(NI_m).
- *Alternative hypothesis, H_1*: The ratio of GMTs (Young adults external control: Adolescents) is below NI_m; equivalently the difference in log(GMT) is less than log(NI_m).

The NI_m for this study is 1.5, whereby the upper bound of the two-sided 95% CI must be lower than to reject the null hypothesis; analysing the upper bound corresponds to a significance level of 0.025 for a one-sided test and is defined for each endpoint separately.

Formal statistical hypothesis testing was performed with all tests conducted at the two-sided, 0.05 level of significance, unless otherwise stated. Summary statistics were presented, as well as CIs on selected parameters.

Statistical analysis

Descriptive analyses were performed overall by time-point. Categorical variables were presented by means of number of cases and frequencies (%) and continuous variables were presented by number of non-missing observations, mean, standard deviation (SD), median and interquartile range, minimum and maximum. Missing data were not imputed. For the continuous variables related to the immunogenicity endpoints, values below the limit of quantification (LLOQ) and indicated as <LLOQ will be imputed as LLOQ.

The GMT, GMFR and geometric SD were calculated based on the log-transformed titres and backtransformed post-summary.

Immunogenicity analysis

- Continuous variables related to immunogenicity: mixed model for repeated measures (MMRM) was used on log-transformed data. The least square (LS) means estimates for each cohort (age group) were presented with the associated standard error and 95% CIs for each visit. The ratio of (back-transformed) GMTs (young adults external control: adolescents) was also presented with the corresponding 95% CI and p-value to assess non-inferiority. The (backtransformed) geometric mean estimates for each cohort (young adults external control, adolescents) at each visit (Baseline and Day 14) were presented with the associated standard error and 95% CIs.
- GMFR in both neutralising and binding antibody titres was analysed using a t-test on logtransformed data.
- GMFR fold change was analysed via summary statistics and CIs. Cohort estimates and differences for ≥ 4-fold change response will be analysed using a generalised estimating equations model for repeated measures, however for this IAR a logistic regression was used to analyse a single timepoint at Day 14. The LS means odds ratios for each cohort were presented with the associated 95% CIs. The cohort (age group) difference in LS means odds ratio (young adults external control: adolescents) was also presented with the corresponding 95% CI.

Results

Participant flow and numbers analysed

A summary of disposition for all participants enrolled in the study is presented for the entire study population in the below table. Overall, 242 participants were enrolled in this study, of which 240 were vaccinated and were included in the SP.

A total of 2 (0.8%) participants in the SP prematurely discontinued participation in the study. The reason for premature discontinuation for both participants was within the category "other", due to personal problems, not study related, and were no longer participating in the study.

The mean study duration for participants in the SP was 9.82 months (range: 2.66-12.98) since study is still ongoing.

Table 1. Participants Enrolment and Disposition (HIPRA-HH-3)

	Statistics	**Adolescents (12-17 years old)**
Enrolled population	n	242
Intention-to-treat (ITT)	n	240 (100.0)
Modified Intention-to-treat (mITT)	n (%)	239 (99.6)
Per-Protocol set (PP)	n (%)	232 (96.7)
Immunogenicity population (IGP)	n (%)	88 (36.7)
Safety population set (SP)	n (%)	240 (100.0)
Participants who completed the study	n (%)	146 (60.8)
Participants who prematurely discontinued study	n (%)	2 (0.8)
Reason for study withdrawal		
Other		2 (0.8)
Study duration (months)[a]	n	240
	Mean	9.82
	SD	1.90
	Minimum	2.66
	Median	10.61
	Interquartile Range	3.15
	Maximum	12.98

Recruitment

The study was conducted across 7 clinical study sites in Spain.

Date first participant enrolled: 08 June 2023

Date last participant completed: pending, study ongoing.

Data cut-off date for the present interim analysis: 25th September 2024

Date of interim study report: 27th January 2025

Conduct of the study

Protocol versions

Study Protocol v. 1.0: 14 April 2023

Study Protocol v. 2.0: 25 April 2023

Protocol deviations

A total of 44 protocol deviations were reported in HIPRA-HH-3 study at the time of the interim analysis, of which 8 were classified as major. 7 mainly from the collection of blood samples for immunogenicity analyses from participants not assigned to the immunogenicity cohort. The last one because the participant had not received both Comirnaty doses (inclusion criteria #3).

Minor protocol deviations generally resulted from procedures or activities not fully aligned with the protocol. The most commonly reported minor deviations were related to visits conducted outside the protocol-defined window and missing samples to assess safety laboratory parameters.

Baseline data

Table 2: Demographics and Baseline Characteristics (Safety Population)

	Statistics	Adolescents (12-17 years old) (N=240)	Young adults active control (18-25 years old) (N=83)	Overall (N=323)
Age (years)	n	240	83	323
	Mean	14.8	22.8	16.9
	SD	1.56	1.58	3.80
	Minimum	12	19	12
	Median	15.0	23.0	16.0
	Interquartile Range	2.0	3.0	6.0
	Maximum	17	25	25
Sex, n (%)	Male	127 (52.9)	25 (30.1)	152 (47.1)
	Female	113 (47.1)	58 (69.9)	171 (52.9)
Race, n (%)	Black or African American	2 (0.8)	0	2 (0.6)
	American Indian or Alaska Native	4 (1.7)	0	4 (1.2)
	Asian	1 (0.4)	1 (1.2)	2 (0.6)
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	231 (96.3)	82 (98.8)	313 (96.9)
	Other	2 (0.8)	0	2 (0.6)
Ethnicity, n (%)	Hispanic or Latino	21 (8.8)	23 (27.7)	44 (13.6)
	Not Hispanic or Latino	217 (90.4)	60 (72.3)	277 (85.8)
	Not Reported	0	0	0
	Unknown	2 (0.8)	0	2 (0.6)
Height (cm) at Screening	n	240	83	323
	Mean	165.81	169.79	166.83
	SD	14.517	8.552	13.344
	Minimum	1.6	147.0	1.6
	Median	166.00	170.00	167.00
	Interquartile Range	14.00	13.00	14.00
	Maximum	192.0	190.0	192.0
Weight (kg) at Screening	n	240	83	323
	Mean	57.76	65.92	59.86
	SD	11.036	11.711	11.750
	Minimum	29.7	48.5	29.7
	Median	56.00	65.00	59.50
	Interquartile Range	13.85	13.00	15.00
	Maximum	90.0	104.8	104.8
Body mass index (kg/m^2) at Screening	n	239	83	322
	Mean	20.700	22.761	21.232
	SD	2.7422	2.8995	2.9220
	Minimum	14.67	18.17	14.67
	Median	20.520	22.590	20.985
	Interquartile Range	3.590	3.610	3.970
	Maximum	29.39	35.42	35.42
Systolic blood pressure (mmHg) at Screening	n	240	83	323
	Mean	113.3	121.5	115.4
	SD	11.74	13.42	12.70
	Minimum	85	97	85
	Median	113.0	120.0	116.0
	Interquartile Range	16.0	13.0	16.0
	Maximum	142	163	163
Diastolic blood pressure (mmHg) at Screening	n	240	83	323
	Mean	68.6	72.4	69.6
	SD	8.88	9.75	9.24
	Minimum	44	46	44
	Median	68.0	72.0	69.0
	Interquartile Range	12.0	10.0	12.0
	Maximum	98	104	104
Pulse rate (beats per minute) at Screening	n	240	83	323
	Mean	76.3	75.3	76.1
	SD	13.47	14.19	13.65
	Minimum	51	47	47
	Median	76.0	74.0	76.0
	Interquartile Range	18.0	19.0	18.0
	Maximum	125	113	125
Pulse oximetry (%) at Screening	n	238	82	320
	Mean	98.4	93.4	97.1
	SD	0.97	21.30	10.99
	Minimum	95	0	0
	Median	99.0	98.0	99.0
	Interquartile Range	1.0	2.0	1.0
	Maximum	100	100	100
Body temperature (°C) at Screening	n	240	83	323
	Mean	36.18	35.58	36.03
	SD	0.454	3.983	2.065
	Minimum	34.0	0.0	0.0
	Median	36.20	36.00	36.10
	Interquartile Range	0.50	0.60	0.60
	Maximum	36.9	37.0	37.0

Outcomes and estimation

Primary immunogenicity endpoint: Neutralising antibodies against Omicron BA.1

A summary of log10-transformed neutralising antibody titres against Omicron BA.1 variant at baseline and at Day 14 is presented below for the primary analysis.

Table 3: Summary of IC_{50} in Neutralising Antibody Titres Against Omicron BA.1 (HIPRA-HH-3)

		Adolescents (12-17 yoa) (N=88)	Young adults external control (18-25 yoa) (N=81)	Overall (N=169)
Visit	**Statistics**	**Observed value**	**Observed value**	**Observed value**
Baseline	n	88	81	169
	Geometric mean	1 303.54	48.48	269.12
	Geometric SD	3.34	3.19	7.60
	Minimum	1.34	1.30	1.30
	Q1	2.76	1.30	1.48
	Median	3.14	1.45	2.55
	Q3	3.48	1.86	3.18
	Maximum	4.69	3.47	4.69
Day 14	n	88	80	168
	Geometric mean	24 081.34	2 346.67	7 945.90
	Geometric SD	2.45	2.70	4.48
	Minimum	2.91	2.37	2.37
	Q1	4.13	3.09	3.38
	Median	4.63	3.38	3.94
	Q3	4.69	3.67	4.67
	Maximum	4.69	4.31	4.69

Abbreviations: IC50 = inhibitory concentration 50; N = number of participants in the population; n = number of participants with data; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation
Baseline is defined as the most recent measurement prior or equal to the first administration of study drug.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 7

A statistical analysis of neutralising antibody titres against Omicron BA.1 variant by Mixed effects model for repeated measures at Baseline and Day 14 is presented in the table below.

Table 4: Analysis of IC50 in Neutralising Antibody Titres Against Omicron BA.1 (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Baseline Visit		
Number of participants with data, n (%)	88 (100.0)	81 (100.0)
Adjusted group mean (LS Mean)[a]	3.12	1.69
Standard error	0.055	0.057
95% CI	3.007, 3.223	1.573, 1.798
GMT for adjusted group mean[b]	1 303.54	48.48
95% CI	1 016.05, 1672.39	37.39, 62.86
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.04
95% CI for adjusted ratio	-	0.026, 0.053
p-value for adjusted ratio = 1	-	<0.0001
Day 14 Visit		
Number of participants with data, n (%)	88 (100.0)	80 (98.8)
Adjusted group mean (LS Mean)[a]	4.38	3.37
Standard error	0.044	0.046
95% CI	4.295, 4.468	3.279, 3.460

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
GMT for adjusted group mean[b]	24 081.34	2 340.57
95% CI	19 741.36, 29 375.43	1 900.42, 2 882.66
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.10
95% CI for adjusted ratio	-	0.07, 0.13
p-value for adjusted ratio = 1	-	<0.0001

Abbreviations: CI = confidence interval; GMT = geometric mean titre; IC50 = inhibitory concentration 50; N = number of participants in the population; n = number of participants with data
aA Mixed-Effects Model for Repeated Measures was fitted to assess the endpoint on the log10 scale. In the model, the age group (12-17 years old, 18-25 years old), the visit (Baseline and Day 14) and age group-by-visit interaction were included as fixed effects. An unstructured covariance matrix was used to model the within-participant error and Kenward-Roger approximation was employed to estimate the degrees of freedom.
bThe GMT for age group means and the GMT ratio were estimated using Least-Squares Means from the fitted model on the log10 scale and back-transformed.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 8

Secondary immunogenicity endpoints

The comparison between groups is not in the scope for the secondary endpoints of the study; however, it has been included as additional information.

Neutralising antibodies against Beta

Table 5: Summary of IC_{50} in Neutralising Antibody Titres Against Beta (HIPRA-HH-3)

		Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Visit	**Statistics**	**Observed value**	**Observed value**	**Observed value**
Baseline	n	88	81	169
	Geometric mean	1 874.67	98.26	456.23
	Geometric SD	3.12	3.48	6.66
	Minimum	1.86	1.30	1.30
	Q1	2.93	1.61	1.95
	Median	3.31	1.92	2.71
	Q3	3.68	2.22	3.33
	Maximum	4.22	3.70	4.22
Day 14	n	88	80	168
	Geometric mean	16 037.66	5 575.20	9 696.75
	Geometric SD	1.95	3.27	2.96
	Minimum	3.37	2.70	2.70
	Q1	4.05	3.44	3.69
	Median	4.20	3.75	4.05
	Q3	4.42	4.01	4.28
	Maximum	4.59	5.32	5.32

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 9

Table 6: Analysis of IC_{50} in Neutralising Antibody Titres Against Beta (HIPRA-HH-3)

Visit	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Baseline Visit		
Number of participants with data, n (%)	88 (100.0)	81 (100.0)
Adjusted group mean (LS Mean)[a]	3.27	1.99
Standard error	0.055	0.058
95% CI	3.164, 3.382	1.879, 2.106
GMT for adjusted group mean[b]	1874.67	98.26
95% CI	1 458.82, 2409.07	75.66, 127.62
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.05
95% CI for adjusted ratio	-	0.036, 0.075
p-value for adjusted ratio = 1	-	<0.0001
Day 14 Visit		
Number of participants with data, n (%)	88 (100.0)	80 (98.8)
Adjusted group mean (LS Mean)[a]	4.21	3.75
Standard error	0.044	0.046
95% CI	4.118, 4.292	3.654, 3.836
GMT for adjusted group mean[b]	16 037.66	5 562.91
95% CI	13 136.20, 19579.97	4 512.64, 6857.61
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.35
95% CI for adjusted ratio	-	0.26, 0.46
p-value for adjusted ratio = 1	-	<0.0001

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 10

Neutralising antibodies against Delta

Table 7: Summary of IC_{50} in Neutralising Antibody Titres Against Delta (HIPRA-HH-3)

		Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Visit	**Statistics**	**Observed value**	**Observed value**	**Observed value**
Baseline	n	88	81	169
	Geometric mean	694.11	64.55	222.34
	Geometric SD	2.98	3.06	5.06
	Minimum	1.86	1.30	1.30
	Q1	2.52	1.37	1.77
	Median	2.89	1.75	2.37
	Q3	3.13	2.05	2.97
	Maximum	4.29	3.37	4.29
Day 14	n	88	80	168
	Geometric mean	9 781.04	1 650.20	4 191.42
	Geometric SD	2.22	2.36	3.37

		Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Visit	**Statistics**	**Observed value**	**Observed value**	**Observed value**
	Minimum	3.09	2.46	2.46
	Q1	3.78	2.98	3.12
	Median	4.00	3.10	3.65
	Q3	4.18	3.42	4.07
	Maximum	4.71	4.31	4.71

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 11

Table 8: Analysis of IC_{50} in Neutralising Antibody Titres Against Delta (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Baseline Visit		
Number of participants with data, n (%)	88 (100.0)	81 (100.0)
Adjusted group mean (LS Mean)[a]	2.84	1.81
Standard error	0.051	0.053
95% CI	2.741, 2.942	1.705, 1.915
GMT for adjusted group mean[b]	694.11	64.55
95% CI	550.21, 875.66	50.66, 82.23
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.09
95% CI for adjusted ratio	-	0.066, 0.130
p-value for adjusted ratio = 1	-	<0.0001
Day 14 Visit		
Number of participants with data, n (%)	88 (100.0)	80 (98.8)
Adjusted group mean (LS Mean)[a]	3.99	3.22
Standard error	0.038	0.040
95% CI	3.915, 4.066	3.138, 3.297
GMT for adjusted group mean[b]	9 781.04	1 649.95
95% CI	8 217.07, 11642.67	1 374.40, 1980.75
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.17
95% CI for adjusted ratio	-	0.13, 0.22
p-value for adjusted ratio = 1	-	<0.0001

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 12

Neutralising antibodies against Wuhan

Table 9: Summary of IC_{50} in Neutralising Antibody Titres Against Wuhan (HIPRA-HH-3)

		Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Visit	**Statistics**	**Observed value**	**Observed value**	**Observed value**
Baseline	n	88	81	169
	Geometric mean	780.09	113.03	309.06
	Geometric SD	2.64	2.41	3.81
	Minimum	1.89	1.30	1.30
	Q1	2.60	1.83	2.02
	Median	2.85	2.01	2.46
	Q3	3.21	2.31	2.90
	Maximum	3.87	2.99	3.87
Day 14	n	88	80	168
	Geometric mean	9 674.93	2 290.11	4 871.37
	Geometric SD	2.11	2.55	3.02
	Minimum	2.70	2.46	2.46
	Q1	3.83	3.09	3.31
	Median	4.07	3.32	3.79
	Q3	4.25	3.58	4.11
	Maximum	4.31	4.50	4.50

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th August 2025 – Table 13

Table 10: Analysis of IC_{50} in Neutralising Antibody Titres Against Wuhan (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Baseline Visit		
Number of participants with data, n (%)	88 (100.0)	81 (100.0)
Adjusted group mean (LS Mean)[a]	2.89	2.05
Standard error	0.043	0.045
95% CI	2.807, 2.977	1.965, 2.142
GMT for adjusted group mean[b]	780.09	113.03
95% CI	641.73, 948.28	92.22, 138.54
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.14
95% CI for adjusted ratio	-	0.109, 0.192
p-value for adjusted ratio = 1	-	<0.0001
Day 14 Visit		
Number of participants with data, n (%)	88 (100.0)	80 (98.8)
Adjusted group mean (LS Mean)[a]	3.99	3.36
Standard error	0.039	0.041
95% CI	3.909, 4.063	3.278, 3.439
GMT for adjusted group mean[b]	9 674.93	2 283.44
95% CI	8 104.12, 11 550.20	1 896.33, 2 749.58

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.24
95% CI for adjusted ratio	-	0.18, 0.31
p-value for adjusted ratio = 1	-	<0.0001

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 14

Geometric Mean Fold Rise in neutralising antibodies against Omicron BA.1

Table 11: Summary of Fold Rise in Neutralising Antibody Titres Against Omicron BA.1 (HIPRA-HH-3)

Visit	Statistics	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Day 14	n	88	80	168
	Geometric mean	18.47	47.87	29.07
	Geometric SD	3.23	4.00	3.90
	Minimum	−0.02	−0.26	−0.26
	Q1	0.94	1.37	1.08
	Median	1.25	1.71	1.48
	Q3	1.59	2.08	1.88
	Maximum	2.37	2.83	2.83

Abbreviations: N = number of participants in the population; n = number of participants with data; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation
Fold rise is calculated as post-baseline titre/baseline titre.
Baseline is defined as the most recent measurement prior or equal to the administration of study drug date.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 - Table 15

Table 12: Analysis of GMFR in Neutralising Antibody Titres Against Omicron BA.1 (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Day 14		
Number of participants included in the analysis, n (%)	88 (100.0)	80 (98.8)
Fold rise group mean[a]	1.27	1.68
Standard error	0.05	0.07
95% CI	1.16, 1.37	1.55, 1.81
GMFR group mean[b]	18.47	47.87
95% CI	14.41, 23.69	35.16, 65.18
GMFR group ratio (Young adults vs Adolescents)[b,c]		
Ratio	-	2.59
95% CI for ratio	-	1.75, 3.83
p-value for ratio = 1	-	<0.0001

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; N = number of participants in the population; n = number of participants included in the analysis
aA t-test was performed to assess the endpoint on the log10 scale.
bThe GMFR group means and the GMFR for the age group ratio are estimated on the log10 back-transformed.

c95% CI and p-value from the pooled test (equality of variances).
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 16

Geometric Mean Fold Rise in neutralising antibodies against Beta

Table 13: Summary of Fold Rise in Neutralising Antibody Titres Against Beta (HIPRA-HH-3)

Visit	Statistics	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Day 14	n	88	80	168
	Geometric mean	8.55	56.12	20.95
	Geometric SD	3.04	4.58	5.06
	Minimum	−0.12	0.01	−0.12
	Q1	0.60	1.38	0.79
	Median	0.84	1.72	1.24
	Q3	1.19	2.23	1.80
	Maximum	2.12	3.27	3.27

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 17

Table 14: Analysis of GMFR in Neutralising Antibody Titres Against Beta (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Day 14		
Number of participants included in the analysis, n (%)	88 (100.0)	80 (98.8)
Fold rise group mean[a]	0.93	1.75
Standard error	0.05	0.07
95% CI	0.83, 1.04	1.60, 1.90
GMFR group mean[b]	8.55	56.12
95% CI	6.76, 10.83	40.00, 78.72
GMFR group ratio (Young adults vs Adolescents)[b,c]		
Ratio	-	6.56
95% CI for ratio	-	4.35, 9.88
p-value for ratio = 1	-	<0.0001

Source: Interim Study Report – HIPRA-HH.3, Version 1.0, 27th January 2025 – Table 18

Geometric Mean Fold Rise in neutralising antibodies against Delta

Table 15: Summary of Fold Rise in Neutralising Antibody Titres Against Delta (HIPRA-HH-3)

Visit	Statistics	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Day 14	n	88	80	168
	Geometric mean	14.09	25.53	18.70
	Geometric SD	3.33	4.00	3.75
	Minimum	−0.06	−0.33	−0.33
	Q1	0.79	1.00	0.90
	Median	1.12	1.48	1.25
	Q3	1.53	1.73	1.66
	Maximum	2.76	2.92	2.92

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 19

Table 16: Analysis of GMFR in Neutralising Antibody Titres Against Delta (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Day 14		
Number of participants included in the analysis, n (%)	88 (100.0)	80 (98.8)
Fold rise group mean[a]	1.15	1.41
Standard error	0.06	0.07
95% CI	1.04, 1.26	1.27, 1.54
GMFR group mean[b]	14.09	25.53
95% CI	10.92, 18.18	18.75, 34.75
GMFR group ratio (Young adults vs Adolescents)[b,c]		
Ratio	-	1.81
95% CI for ratio	-	1.22, 2.69
p-value for ratio = 1	-	0.0034

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 20

Geometric Mean Fold Rise in neutralising antibodies against Wuhan

Table 17: Summary of Fold Rise in Neutralising Antibody Titres Against Wuhan (HIPRA-HH-3)

Visit	Statistics	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Day 14	n	88	80	168
	Geometric mean	12.40	19.98	15.56
	Geometric SD	2.90	3.11	3.07
	Minimum	−0.20	0.11	−0.20
	Q1	0.83	1.00	0.90
	Median	1.13	1.27	1.20
	Q3	1.37	1.58	1.48
	Maximum	2.42	2.37	2.42

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 21

Table 18: Analysis of GMFR in Neutralising Antibody Titres Against Wuhan (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Day 14		
Number of participants included in the analysis, n (%)	88 (100.0)	80 (98.8)
Fold rise group mean[a]	1.09	1.30
Standard error	0.05	0.06
95% CI	1.00, 1.19	1.19, 1.41
GMFR group mean[b]	12.40	19.98
95% CI	9.90, 15.55	15.52, 25.72
GMFR group ratio (Young adults vs Adolescents)[b,c]		
Ratio	-	1.61
95% CI for ratio	-	1.15, 2.25
p-value for ratio = 1	-	0.0056

Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 22

Binding antibody titres

Table 19: Summary of Binding Antibody Titres

		Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Visit	**Statistics**	**Observed value**	**Observed value**	**Observed value**
Baseline	n	87	81	168
	Geometric mean	8 005.56	854.88	2 722.67
	Geometric SD	2.82	2.79	4.58
	Minimum	2.20	2.03	2.03
	Q1	3.68	2.60	2.85
	Median	4.00	2.89	3.46
	Q3	4.19	3.22	4.02
	Maximum	4.71	4.41	4.71
Day 14	n	88	79	167
	Geometric mean	98 038.63	43 538.34	66 778.05
	Geometric SD	1.88	2.08	2.21
	Minimum	4.27	3.88	3.88
	Q1	4.83	4.45	4.58
	Median	5.05	4.64	4.84
	Q3	5.20	4.83	5.11
	Maximum	5.35	5.35	5.35

Abbreviations: N = number of participants in the population; n = number of participants with data; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation
Baseline is defined as the most recent measurement prior or equal to the administration of study drug.
Raw data provided as <0.4 have been imputed as 0.4 for the purposes of analysis for binding antibodies.
Transformations have been made on the imputed data.
Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 23

Table 20: Analysis of Binding Antibody Titres (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Baseline		
Number of participants with data, n (%)	87 (98.9)	81 (100.0)
Adjusted group mean (LS Mean)[a]	3.90	2.93
Standard error	0.048	0.050
95% CI	3.81, 4.00	2.83, 3.03
GMT for adjusted group mean[b]	7 960.79	854.88
95% CI	6 398.63, 9 904.35	681.60, 1072.20
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.11
95% CI for adjusted ratio	-	0.08, 0.15
p-value for adjusted ratio = 1	-	<0.0001
Day 14		
Number of participants with data, n (%)	88 (100.0)	79 (97.5)
Adjusted group mean (LS Mean)[a]	4.99	4.64
Standard error	0.032	0.033
95% CI	4.93, 5.05	4.57, 4.71
GMT for adjusted group mean[b]	98 038.63	43 565.17
95% CI	84 938.91, 113158.65	37 451.68, 50 676.61
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.44
95% CI for adjusted ratio	-	0.36, 0.55
p-value for adjusted ratio = 1	-	<0.0001

Abbreviations: CI = confidence interval; GMT = geometric mean titre; N = the number of participants in the population; n = number of participants with data.
aA Mixed-Effects Model for Repeated Measures was fitted to assess the endpoint on the log10 scale. In the model, the age group (12-17 years old, 18-25 years old), the visit (Baseline and Day 14) and age group-by-visit interaction were included as fixed effects. An unstructured covariance matrix was used to model the within-participant error and Kenward-Roger approximation was employed to estimate the degrees of freedom.
bThe GMT for age group means and the GMT for the ratio are estimated using Least Square Means from the fitted model on the log10 scale and back-transformed.
Raw data provided as <0.4 have been imputed as 0.4 for the purposes of analysis.
Transformations have been made on the imputed data.
Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 24

Geometric Mean Fold Rise in binding antibody titres

Table 21: Summary of Fold Rise in Binding Antibody Titres

Visit	Statistics	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
Day 14	n	87	79	166
	Geometric mean	12.39	51.08	24.31
	Geometric SD	3.01	2.64	3.51
	Minimum	0.05	0.48	0.05
	Q1	0.75	1.53	0.99

Visit	Statistics	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)	Overall (N=169)
	Median	1.08	1.76	1.38
	Q3	1.33	1.98	1.78
	Maximum	2.63	2.55	2.63

Abbreviations: N = number of participants in the population; n = number of participants with data; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation
Fold rise is calculated as post-baseline titre/baseline titre.
Baseline is defined as the most recent measurement prior or equal to the administration of study drug.
Raw data provided as <0.4 have been imputed as 0.4 for the purposes of analysis.
Transformations have been made on the imputed data.
Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 25

Table 22: Analysis of GMFR in Binding Antibody Titres (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Day 14		
Number of participants included in the analysis, n (%)	87 (98.9)	79 (97.5)
Fold rise group mean[a]	1.09	1.71
Standard error	0.051	0.047
95% CI	0.99, 1.20	1.61, 1.80
GMFR group mean[b]	12.39	51.08
95% CI	9.80, 15.67	41.11, 63.47
GMFR group ratio (Young adults vs Adolescents)[b,c]		
Ratio	-	4.12
95% CI for ratio	-	3.00, 5.67
p-value for ratio = 1	-	<0.0001

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; N = number of participants in the population; n = number of participants with data.
aA t-test was performed to assess the endpoint on the log10 scale.
bThe GMFR for group means and the GMFR for the age group ratio are estimated on the log10 back-transformed.
c95% CI and p-value from the pooled test (equality of variances).
Raw data provided as <0.4 have been imputed as 0.4 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 26

Fold change analysis in binding antibodies

Table 23: Analysis of Fold Change in Binding Antibody Titres (HIPRA-HH-3)

	Adolescents (12-17 years old) (N=88)	Young adults external control (18-25 years old) (N=81)
Day 14		
Number of participants included in the analysis, n (%)	87 (98.9)	79 (97.5)
Number of participants with ≥ 4-fold change from baseline, n (%)[a]	73 (83.9)	78 (98.7)
95% CI[b]	(74.5, 90.9)	(93.1, 100.0)
Adjusted odds (Back-transformed LS Mean)[c]	5.21	78.00
Standard error (log scale)	0.29	1.01
95% CI	2.94, 9.24	10.85, 560.71
Adjusted Odds Ratio (Young adults vs Adolescents)[d]		
Adjusted ratio	-	14.96
95% CI for adjusted ratio	-	1.92, 116.63
p-value for adjusted ratio = 1	-	0.0098

Abbreviations: CI=confidence interval; LS mean=least square mean; N= number of participants in the population; n= number of participants meeting the criterion
a% = n / number of participants in the analysis. Fold rise is calculated as post-baseline titre/baseline titre.
bExact CI for the proportion of participants with ≥ 4 fold change from baseline has been calculated using the Clopper-Pearson method.
cTo assess the endpoint, a logistic regression model was fitted with a binomial family and logit link. The analysis was conducted using data from Day 14. The odds ratios were estimated using the Least Squares (LS) Means from the fitted model and back-transformed to provide adjusted estimates. Confidence intervals were also calculated for the odds ratios.
dThe adjusted odds and the adjusted odds ratio were estimated using LS Means from the fitted model and back-transformed.
Source: Interim Study Report – HIPRA-HH-3, Version 1.0, 27th January 2025 – Table 27

Post-hoc analysis of ≥4-fold change

Table 24: Analysis of ≥4-fold change in neutralising antibody titres against Omicron BA.1

Visit	Statistics	Adolescents (12-17 years old) (N = 88)	Adolescents (12-15 years old) (N = 61)
		Observed value	**Observed value**
Day 14	Number of participants included in the analysis, n (%)	88 (100)	61 (100)
	Number of participants with ≥ 4-fold change from baseline, n (%)	81 (92)	54 (88.5)
	95% Confidence Interval	84.3; 96.7	77.8; 95.3

Source: Listing 16.2.6.1 – Interim Study Report HIPRA-HH-3 (version 1.0, 27 January 2025)

The ≥4-fold change in neutralising antibody titres against Omicron BA.1 was n=54 (88.5%, 95%CI: (77.8; 95.3) in adolescents 12 to 15 years old. The one observed in adolescents aged 16 to 17 years was n=27 (100% (87.2; 100)).

Table 25: Analysis of ≥4-fold change in neutralising antibody titres against Beta

Visit	Statistics	Adolescents (12-17 years old) (N = 88)	Adolescents (12-15 years old) (N = 61)
		Observed value	**Observed value**
	Number of participants included in the analysis, n (%)		

Day 14		88 (100)	61 (100)
	Number of participants with ≥ 4-fold change from baseline, n (%)	66 (75)	47 (77)
	95% Confidence Interval	64.6; 83.6	64.5; 86.8

Source: Listing 16.2.6.1 – Interim Study Report HIPRA-HH-3 (version 1.0, 27 January 2025)

Table 26: Analysis of ≥4-fold change in neutralising antibody titres against Delta

Visit	**Statistics**	**Adolescents (12-17 years old) (N = 88)**	**Adolescents (12-15 years old) (N = 61)**
		Observed value	**Observed value**
Day 14	Number of participants included in the analysis, n (%)	88 (100)	61 (100)
	Number of participants with ≥ 4-fold change from baseline, n (%)	75 (85.2)	55 (90.2)
	95% Confidence Interval	76.1; 91.9	79.8; 96.3

Source: Listing 16.2.6.1 – Interim Study Report HIPRA-HH-3 (version 1.0, 27 January 2025)

Table 27: Analysis of ≥4-fold change in neutralising antibody titres against Wuhan

Visit	**Statistics**	**Adolescents (12-17 years old) (N = 88)**	**Adolescents (12-15 years old) (N = 61)**
		Observed value	**Observed value**
Day 14	Number of participants included in the analysis, n (%)	88 (100)	61 (100)
	Number of participants with ≥ 4-fold change from baseline, n (%)	77 (87.5)	54 (88.5)
	95% Confidence Interval	78.7; 93.6	77.8; 95.3

Source: Listing 16.2.6.1 – Interim Study Report HIPRA-HH-3 (version 1.0, 27 January 2025)

Post-hoc subgroup analysis in individuals 12 to 15 years of age

A *post-hoc* additional subgroup descriptive assessment of the neutralising immune response against Omicron BA.1 variant for 12 to 15 age group (new population to be covered in the indication) is provided below. Data of the neutralising antibody response of adolescents 16 to 17 years of age is also provided.

A summary of log10-transformed neutralising antibody titres against Omicron BA.1 variant at Baseline and at Day 14 is presented in Table 28 for adolescents aged 12 to 15 years and for adolescents aged 16 to 17 years. A summary of fold rise in neutralising antibodies against Omicron BA.1 from Baseline to Day 14 of those cohorts is presented in Table 29.

Table 28: Summary of IC50 in neutralising antibody titres against Omicron BA.1 by age range (HIPRA-HH-3)

Visit	**Statistics**	**Adolescents (12-15 years old) (N = 61)**	**Adolescents (16-17 years old) (N = 27)**

		Observed value	Observed value
Baseline	n	61	27
	Geometric mean	1240.77	1457.30
	Geometric SD	3.62	2.75
	Minimum	1.34	2.30
	Q1	2.76	2.85
	Median	3.13	3.17
	Q3	3.45	3.53
	Maximum	4.69	3.86
Day 14	n	61	27
	Geometric mean	22970.81	26792.00
	Geometric SD	2.61	2.10
	Minimum	2.91	3.76
	Q1	4.13	4.18
	Median	4.61	4.65
	Q3	4.69	4.69
	Maximum	4.69	4.69

Source: Listing 16.2.6.1 – Interim Study Report (version 1.0, 27 January 2025).

Table 29: Summary of Fold Rise in Neutralising Antibody Titres Against Omicron BA.1

Visit	Statistics	Adolescents (12-15 years old) (N = 61)	Adolescents (16-17 years old) (N = 27)
		Observed value	Observed value
Day 14	n	61	27
	Geometric mean	18.51	18.38
	Geometric SD	3.66	2.33
	Minimum	-0.02	0.67
	Q1	0.87	1.00
	Median	1.26	1.21
	Q3	1.64	1.52
	Maximum	2.37	2.13

Source: Listing 16.2.6.1 – Interim Study Report (version 1.0, 27 January 2025).

The geometric mean (95% CI) fold rise in neutralising antibody titres against Omicron BA.1 was 18.51 (13.28; 25.81) in adolescents 12 to 15 years old. This geometric mean (95% CI) fold rise is comparable to that observed in adolescents aged 16 to 17 years (18.38 (13.15; 25.71)), age range already included in the approved BIMERVAX indication.

2.3.5. Discussion on clinical efficacy

Design and conduct of clinical studies

According to the MAH, Study HIPRA-HH-3 is a Phase IIb, open label, single arm, multi-centre trial (7 sites in Spain) to assess the immunogenicity and safety of a heterologous booster dose of a recombinant protein RBD fusion heterodimer (B.1.351-B.1.1.7 SARS-CoV-2 variants) vaccine candidate (PHH-1V) against SARS-CoV-2, in adolescents from 12 years to less than 18 years with previous

primary immunisation with Comirnaty. The study is still ongoing, the first participant was enrolled on June 8th 2023, the cut-off date for the present interim analysis was on 25th September 2024, the date of interim study report serving as the basis of the present submission was 27th January 2025. The interim study report presents Day 14 immunogenicity data of all enrolled participants in the Immunogenicity data set, and safety findings through Day 28 of participants in the safety population (refer to safety section). Data from the remaining immunogenicity sampling time points on Day 84, Day 168, and Day 336 (as per schedule) have not yet been submitted.

Inclusion and exclusion criteria of Study HH-3 are acceptable. Note that non-immunocompromised participants with pre-existing chronic but stable and well controlled diseases, were also eligible for inclusion in the study, according to the investigator's judgement.

A total of 300 adolescents were to be enrolled and followed for 12 months, and a total of 240 participants were vaccinated (i.e., ITT). According to the protocol (Version 2.0, 25th April 2023), immunogenicity was planned to be evaluated in at least 154 adolescents (targeting 88.5% power to detect non-inferiority using a one-sided 2.5% significance level) with no documented medical history of SARS-CoV-2 infection and who had previously received two doses of Comirnaty vaccine. In contrast, immunogenicity was only measured in 88 (36.7% of ITT [n=240]) adolescents, i.e. the Immunogenicity Population (IGP). Criterion for inclusion in the IGP was being a subject compliant with the inclusion/exclusion criteria who had no documented medical history of COVID-19 infection at screening and a valid immunogenicity test result before receiving the study drug and at least one valid result after dosing. This population was used for all immunogenicity analyses.

The MAH justified the reduced sample size of n=88 individuals by arguing that the study's expected statistical power (81.5%) remains adequate for assessing the immunogenicity of BIMERVAX in adolescents, as it exceeds 80%. Furthermore, upon request, the MAH stated that the reasons for the discontinuation of recruitment before reaching the planned immunogenicity sample size of 154 participants were mainly the encountered recruitment challenges during the study (e.g., vaccine hesitancy among adolescents and/or their parent(s)/legal guardians, the requirement that adolescents had no prior documented medical history of microbiologically confirmed SARS-CoV-2 infection, and the option or availability of other COVID-19 vaccines authorised for the relevant age group) and the lack of unexpired study's test vaccine batch as no new batches were available.

Participants received their dose at least 6 months after primary vaccination with Comirnaty. This interval is considered acceptable as it is the per approved BIMERVAX posology.

Objectives and endpoints

Neutralising antibody responses against strains or variants Omicron BA.1, Beta, Delta, and Wuhan were measured with PBNA. Those strains are not of clinical relevance anymore. However, this is of no critical concern as the purpose of the HH-3 study and the purpose of this procedure, is to conclude whether the indication could be extended to individuals 12 yoa to 15 yoa, which can be assessed irrespective of the examined strain or variant.

The primary objectives were to determine and compare 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 vs post heterologous booster dose in young adults (aged 18 to 25 years) from the adults booster study (HIPRA-HH-2, EudraCT 2021-005226-26); and to assess the safety and tolerability of BIMERVAX as heterologous booster dose in adolescents primary vaccinated against COVID-19 with 2 doses of Comirnaty vaccine. However, the primary immunogenicity objective of the study is not sufficiently addressed by the primary (immunogenicity) endpoint *Neutralisation titre against Omicron BA.1 measured as inhibitory concentration 50 (IC_{50}) by PBNA and reported as log10 concentration for each individual sample and Geometric Mean Titre (GMT)*

for group comparison with HIPRA-HH-2 at Baseline and Day 14. Comparisons of post-booster GMTs to other groups would only be informative on potential changes if pre-booster GMTs could be assumed zero or comparable between groups. In this context, also the study title is misleading as the trial does not permit a self-standing non-inferiority conclusion with respect to post-booster GMTs in young adults. GMTs (as well as other endpoints) for the latter were obtained from previous study HH-2, which was the pivotal study of the initial MAA. On top, no meaningful conclusions in terms of immunobridging can be drawn by comparison of GMTs across different studies with individuals having differences in baseline GMTs as it was the case in the current study. Key secondary objectives were to determine the changes in immunogenicity measured by PBNA against Variants of Concern (VOCs) (at least Beta and Delta) at Baseline and at Days 14, 84, 168 and 336 after vaccination of adolescents with a heterologous booster dose of BIMERVAX, however the same concern of different pre-booster GMTs mentioned for the primary immunogenicity endpoints applies for the secondary immunogenicity endpoints as well.

Efficacy data and additional analyses

Protocol deviations

The MAH provided the list of protocol deviations (minor and major issues) already known to date. Majority (7 of 8) of major protocol deviations (MPDs) resulted from the collection of blood samples for immunogenicity analyses from participants not assigned to the immunogenicity cohort. One more MPD resulted from an incorrect information on a subject's primary immunisation status which resulted in the subject's non-compliance to Inclusion criterion #3. Since the subjects in question were excluded from the PP analysis set, these protocol deviations have no effect on the B/R conclusion of Study HIPRA HH-3. Minor PDs included missing biochemistry and/or haematology parameter assessments, as well as follow-up visits performed slightly out of window.

Immunogenicity results

The presented results of neutralising antibody titres are indicative of an anamnestic immune activation in response to the administered 40 µg BIMERVAX dose after a primary vaccination with two Comirnaty doses, e.g., GMFR in neutralising antibodies against Omicron BA.1 on Day 14 (SD) was 18.47 (3.23). Results of binding antibodies corroborate this finding. T-cell mediated immunity is planned to be investigated in a considerably limited subset of approximately 10% of the IGP (and thus likely uninformative) and no data have been presented as those will be provided in the final CSR. Numbers of confirmed (severe) COVID-19 cases from ≥14 days after vaccination and through the end of the study and confirmed MIS-C cases as per the WHO criteria are listed as exploratory but no data has been provided, which is expected with the final CSR (**REC**).

The most critical issue is that the primary (immunogenicity) endpoint (*Neutralisation titre against Omicron BA.1 measured as inhibitory concentration 50 (IC50) by PBNA and reported as log10 concentration for each individual sample and Geometric Mean Titre (GMT) for group comparison with HIPRA-HH-2 at Baseline and Day 14*) can only be interpreted with respect to comparable immune response if baseline titres between groups are comparable. This was not the case (with IC 50 higher baseline titres in adolescents vs HIPRA-HH-2 Young adults external control: 1303.54 [SD: 3.34] vs 48.48 [SD: 3.19]). Consequently, the informative value of the primary analysis results with respect to B/R is strongly impaired. It is, however, reassuring that results indicate that Day 14 (i.e., post-booster) GMTs in adolescents reach levels comparable or higher (absolute) than post-booster GMTs in young adults (24081.34 [SD: 2.45] vs 2346.67 [SD: 2.70], respectively) – which were considered acceptable to infer sufficient protection. Moreover, and according to the ICH E10 Guideline – *Choice of Control Group in Clinical Trials*, the comparison of results from single-arm trials to external control

groups carries substantial risks for various biases (including different baseline characteristics which is the case for Study HH-3 and its external control population from Study HH-2).

In contrast to the Day 14 GMT results, GMFR may be a suitable measure to evaluate and compare changes in immunogenicity. In line with the *Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design* (Doc. Ref. CHMP/EWP/2459/02), success criteria for GMFR in adolescence could suffice to conclude adequate immune response. Titre changes do not occur spontaneously absent vaccination or infection and therefore could permit isolation of a treatment effect, albeit it is unclear whether GMFRs starting from different baseline levels are comparable. Contextualisation of GMFR in adolescence against young adults from Study HH-2 could provide supportive evidence, though is hampered by potential biases related to external control comparisons. Upon request, the MAH elaborated on their measures to mitigate potential sources of bias (i.e., HH-2 data was well-characterised; same success criterion for primary efficacy endpoint of study HH-3 as for respective efficacy endpoint in HH-3; application of the same and validated assays [PBNA]; similarity as regards demographics [except age, of course], prior COVID-19 vaccination status and history of symptomatic COVID-19 infection), which are overall acknowledged. Of note, the factor most likely contributing to the observed difference in baseline between studies HH-2 and HH-3 was identified to be that enrolment for study HH-3 was approximately 2 years after that for study HH-2 and thus at a time when an increased number of people had baseline immunity, in general, against SARS-CoV-2 due to natural exposure.

Moreover, upon request, the MAH clarified that the values for the external comparator group were taken from HH-2 study data and samples were not re-measured. Assay drift was not addressed. However, considering that the comparison between HH-2 and HH-3 data is impaired anyway, this is of minor relevance.

No corresponding success criteria were defined for the present study. In the absence of an established correlate of protection, post-hoc evaluation whether observed changes could be sufficient to indicate adequate protection is difficult.

In addition, saturation effects in the PBNA were observed, i.e., titres of most studied VOCs appear to be censored above and below. Those may also have implications on the validity on assumptions required for both the primary and secondary statistical analysis model. Therefore, the Applicant was requested to discuss: Saturation effects observed in PBNA for several VOCs; its potential impact on the validity of assay readings; its potential impact on the reliability of statistical analysis (importantly estimates and comparisons of pre/post GMTs and GMFRs) and propose (and justify) potential sensitivity analyses that could address them. With their response, the Applicant provided additional sensitivity analyses using a generalized linear model for censored data to take into account the censored assay readouts. Corresponding results indicate larger Day 14 GMTs in the adolescent group (compared to the original analysis) while corresponding GMTs in the young adults group remain unchanged, whereas results for Baseline GMTs see a decrease in the young adults group and little change in the adolescents group. In terms of GMFRs, sensitivity analyses indicate slight increases in either group. This would be consistent with the observation that low levels in the young adults were left censored and higher levels in the adolescents right censored. Overall, these results do not challenge the result that adolescents experienced substantial increases in titre levels compared to baseline measurements.

Furthermore, upon request, the MAH provided percentages of subjects with ≥4-fold change from baseline in neutralising antibodies for all tested strains, for the 12-17 yoa and 12-15 yoa cohorts separately. For the currently most relevant Omicron BA.1 variant, the percentage in the 12-17 yoa cohort was higher than that in the 12-15 yoa cohort (92% vs 88.5%), whereas for the other strains percentages were closer (Beta: 75% vs 77%, Delta: 85.2% vs 90.2%, Wuhan: 87.5% vs 88.5%).

Considering the extremely high baseline GMTs in adolescents and the consequently somewhat reduced potential for an anamnestic immune response (compared to truly naïve or less primed subjects), the reported percentages are not unexpected.

The MAH applied for an extension of the indication to individuals aged 12 and above, which is effectively an extension to the age cohort 12 to 15 yoa since BIMERVAX is already indicated for individuals 16 years of age and above. Taking this in consideration, the age cohort 12 yoa to 15 yoa is of particular interest and, therefore, to allow a more detailed assessment of immunogenicity regarding that age cohort but also the distribution of titres regarding age, the MAH was requested to provide the data of the neutralising antibody responses concerning that age range. With their response, the MAH provided data (Omicorn BA.1) depicting baseline and Day 14 GMTs and Day 14 GMFRs for the 12-15 yoa cohort and the 16-17 yoa cohort. The baseline and Day 14 GMTs of the 12-15 yoa cohort (1240.77 and 22970.81, respectively) were marginally lower than those of the 16-17 yoa cohort (1457.30 and 26792.00, respectively). In contrast, the GMFRs at Day 14 of both cohorts were similar (12-15 yoa: 18.51, 16-17 yoa: 18.38). Whilst the marginally lower baseline and Day 14 GMTs of the 12-15 yoa cohort compared to the 16-17 yoa cohort are unexpected and may be explained by the in total limited sample size of both groups (n=88) but especially the low sample size of the 16-17 yoa cohort (n=27), the overall immunogenicity data are indicative of efficacy in the relevant age group of those being 12 to 15 yoa.

2.3.6. Conclusions on the clinical efficacy

The reported immunogenicity data are indicative of an anamnestic immune response to the administered 40 µg BIMERVAX in populations 12 to 17 years of age. This holds also true for study participants between 12 to 15 years of age, which constitute the most relevant age group for the current procedure as BIMERVAX is already indicated for individuals 16 years of age and older.

2.4. Clinical safety

Introduction

The most common adverse reactions reported after a booster dose with BIMERVAX in individuals aged 16 years and older who received a primary series with mRNA COVID-19 vaccine, were injection site pain (82.8%), headache (30.8%), fatigue (31.1%), and myalgia (20.6%). 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.

AEs and SAEs were categorised according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE terms were grouped by Medical Dictionary of Regulatory Authorities (MedDRA) Primary System Organ Classes (SOCs). Within each SOC, AEs were listed and accompanied by descriptions of intensity (Grade).

Summaries of local and systemic solicited AEs were presented by SOC and Preferred Term (PT) for events occurring through Day 7. In addition, AEs were summarised by maximum intensity and causal relationship to study drug. A separate summary of AESIs, including potentially immune-mediated medical conditions (PIMMCs) and MAAEs was reported.

Laboratory parameters changing to Grades 2, 3 or 4, were summarised as actual values and change from Baseline over time. Shift tables from Baseline to worst on-study value and Baseline to Day 14 are not included in the scope of this IAR. This data will be available in the final CSR. All laboratory data from Baseline and Day 14 including pregnancy test results were recorded and will be available in data listings in the final CSR.

Participants were provided with a Participant Diary on Day 0 to record solicited local and systemic reactions after vaccination through Day 7. Unsolicited local and systemic AEs were recorded through Day 28. Related adverse Events (AEs), SAEs, AESIs and related MAAEs are being recorded through study duration. Sentinels were contacted through telephone 72 hours after vaccination for a safety assessment. On Days 7 and 28 all participants were contacted through telephone for a safety assessment. Participants were requested to return to the site on Days 14, 84, 168 and 336 (final visit).

Participants exposure

The safety analyses were performed using the Safety Population (SP), made of 240 participants between the age of 12 and 17 years The mean duration of follow-up was 9.82 months (range: 2.66-12.98; median age 15 years, maximum age 17 years) after vaccination with Bimervax.

For demographics and baseline characteristics refer to Table 2.

Adverse events

A Treatment-Emergent Adverse Events (TEAE) is defined as an AE that started on or after the date of administration of study treatment until 28 days thereafter.

A summary of TEAEs incidence for participants aged 12 to 15 years (population of interest) is presented in Table 30.

Table 30: Summary of Treatment-Emergent Adverse Events (Adolescents 12 to 15 years old – Safety Population; HIPRA-HH-3)

	Adolescents (12-15 years old) (N=148)	
	Events	**Participants (%)**
Total number of TEAEs	504	125 (84.5)
Total number of serious TEAEs	0	0
Total number of participants with TEAEs leading to death	0	0
TEAE intensity[a]		
Grade 1	426	124 (83.8)
Grade 2	62	31 (20.9)
Grade 3	12	5 (3.4)
Grade 4*	4	2 (1.4)
Relationship to study treatment[a]		
Unrelated[b]	68	34 (23.0)
Related[c]	436	120 (81.1)
Maximum intensity of solicited local reactions and solicited systemic events[a]		
Grade 1	372	116 (78.4)
Grade 2	59	30 (20.3)
Grade 3	12	5 (3.4)
Grade 4*	4	2 (1.4)
Relationship of solicited local reactions and solicited systemic events to study treatment[a]		

Unrelated[b]	22	9 (6.1)
Related[c]	425	118 (79.7)
Maximum intensity of solicited systemic events[a]		
Grade 1	187	69 (46.6)
Grade 2	33	17 (11.5)
Grade 3	6	4 (2.7)
Grade 4*	4	2 (1.4)
Relationship of solicited systemic events to study treatment[a]		
Unrelated[b]	21	8 (5.4)
Related[c]	209	72 (48.6)
Maximum intensity of solicited local reactions[a]		
Grade 1	185	107 (72.3)
Grade 2	26	21 (14.2)
Grade 3	6	3 (2.0)
Relationship of solicited local reactions to study treatment[a]		
Unrelated[b]	1	1 (0.7)
Related[c]	216	115 (77.7)
Maximum intensity of unsolicited adverse events[a]		
Grade 1	53	35 (23.6)
Grade 2	3	3 (2)
Relationship of unsolicited adverse events to study treatment[a]		
Unrelated[b]	46	30 (20.3)
Related[c]	10	8 (5.4)
Maximum intensity of treatment-emergent MAAEs[a]		
Grade 1	8	8 (5.4)
Grade 2	1	1 (0.7)
Relationship of treatment-emergent MAAEs to study treatment[a]		
Unrelated[b]	9	7 (4.7)

Abbreviations: MAAE = medically attended adverse event; N = number of participants in the population; TEAE = treatment-emergent adverse event
A TEAE is defined as an adverse event that started on or after the date of administration of study treatment until 28 days thereafter.
[a] If a participant experienced more than one TEAE, the participants is counted once at the most severe or most related event.
[b] Unrelated adverse events are those classified as not related and unlikely related.
[c] Related adverse events are those classified as possibly, probably and related. If a TEAE has a missing relationship it is assumed to be related to the study treatment for analysis purposes.
* At the cut-off date for the Interim Analysis, 4 solicited systemic adverse events were reported as Grade 4 in 2 participants. However, these were later confirmed by the PI to be data entry errors and these typos were corrected to Grade 3 events in the eCRF after the cut-off date.
Source: Listing 16.2.7.1 - HIPRA-HH-3: Interim Study Report, version 1.0, 27th January 2025

TEAEs reported by MedDRA SOC and PT for the adolescent age range of interest are presented in Table 31.

Table 31: Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Adolescents 12 to 15 years old – Safety Population; HIPRA- HH-3)

	Adolescents (12-15 years old)

	(N=148)	
System Organ Class Preferred Term	**Events**	**Participants (%)**
Total number of TEAEs	504	125 (84.5)
General disorders and administration site conditions	**335**	**119 (80.4)**
Injection site pain	195	115 (77.7)
Fatigue	45	39 (26.4)
Malaise	42	36 (24.3)
Axillary pain	18	18 (12.2)
Injection site induration	14	14 (9.5)
Injection site erythema	10	10 (6.8)
Pyrexia	6	6 (4.1)
Discomfort	3	3 (2.0)
Vessel puncture site pain	1	1 (0.7)
Secretion discharge	1	1 (0.7)
Nervous system disorders	**52**	**39 (26.4)**
Headache	49	39 (26.4)
Dizziness	1	1 (0.7)
Presyncope	1	1 (0.7)
Migraine	1	1 (0.7)
Musculoskeletal and connective tissue disorders	**49**	**30 (20.3)**
Arthralgia	24	23 (15.5)
Myalgia	24	20 (13.5)
Pain in extremity	1	1 (0.7)
Gastrointestinal disorders	**25**	**19 (12.8)**
Diarrhoea	11	8 (5.4)
Vomiting	7	7 (4.7)
Nausea	4	4 (2.7)
Odynophagia	2	2 (1.4)
Abdominal pain	1	1 (0.7)
Infections and infestations	**15**	**14 (9.5)**
Pharyngitis	4	4 (2.7)
Nasopharyngitis	3	3 (2.0)

Viral infection	2	2 (1.4)
Pustule	1	1 (0.7)
Postoperative wound infection	1	1 (0.7)
Rhinitis	1	1 (0.7)
Gastroenteritis	1	1 (0.7)
Conjunctivitis	1	1 (0.7)
Pharyngotonsillitis	1	1 (0.7)
Blood and lymphatic system disorders	**13**	**11 (7.4)**
Lymphadenopathy	9	9 (6.1)
Splenomegaly	1	1 (0.7)
Neutropenia	1	1 (0.7)
Anaemia	1	1 (0.7)
Mesenteric lymphadenitis	1	1 (0.7)
Respiratory, thoracic and mediastinal disorders	**6**	**6 (4.1)**
Cough	3	3 (2.0)
Oropharyngeal pain	2	2 (1.4)
Rhinitis allergic	1	1 (0.7)
Reproductive system and breast disorders	**4**	**3 (2.0)**
Premenstrual pain	2	2 (1.4)
Intermenstrual bleeding	1	1 (0.7)
Menstruation irregular	1	1 (0.7)
Skin and subcutaneous tissue disorders	**4**	**2 (1.4)**
Rash	1	1 (0.7)
Erythema	1	1 (0.7)
Social circumstances	**1**	**1 (0.7)**
Menarche	1	1 (0.7)
Injury, poisoning and procedural complications	**1**	**1 (0.7)**
Ligament sprain	1	1 (0.7)
Psychiatric disorders	**1**	**1 (0.7)**
Insomnia	1	1 (0.7)

Abbreviations: MedDRA = medical dictionary for regulatory activities; N = the number of participants in the population; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event
A TEAE is defined as an adverse event that started on or after the date of administration of study treatment until 28 days thereafter. If a participant experienced more than one TEAE, the participant is counted once for each SOC and once for each PT.

SOCs are ordered in decreasing frequency of the total number of participants with TEAEs reported in each SOC and PTs are ordered within a SOC in decreasing frequency of the total number of participants with each TEAE.
Adverse events were coded using the MedDRA Dictionary, version 27.0.
Source: Listing 16.2.7.1 - HIPRA-HH-3: Interim Study Report, version 1.0, 27th January 2025.

Table 32: Summary of Treatment-related Emergent Adverse Events by MeDRA System Organ Class and Preferred Term (safety population 12 to <18 years ; HIPRA-HH-3)

	Adolescents (12-17 years old) (N=240)		
System Organ Class (SOC) Preferred Term	**Events**	**Subjects**	**(%)**
Total number of related TEAEs	750	198	82.50
General disorders and administration site conditions	**536**	**194**	**80.83**
Injection site pain	313	187	77.92
Fatigue	76	70	29.17
Malaise	68	62	25.83
Axillary pain	28	27	11.25
Injection site induration	26	26	10.83
Injection site erythema	15	15	6.25
Pyrexia	6	6	2.50
Discomfort	3	3	1.25
Injection site swelling	1	1	0.42
Nervous system disorders	**81**	**71**	**29.58**
Headache	81	71	29.58
Musculoskeletal and connective tissue disorders	**78**	**50**	**20.83**
Myalgia	41	39	16.25
Arthralgia	37	34	14.17
Gastrointestinal disorders	**34**	**26**	**10.83**
Diarrhoea	17	14	5.83
Vomiting	10	10	4.17
Nausea	6	6	2.50
Odynophagia	1	1	0.42
Blood and lymphatic system disorders	**15**	**15**	**6.25**
Lymphadenopathy	15	15	6.25
Skin and subcutaneous tissue disorders	**4**	**4**	**1.67**
Erythema	4	4	1.67
Respiratory, thoracic and mediastinal disorders	**2**	**2**	**0.83**
Oropharyngeal pain	2	2	0.83

Table 33: Percentage of individuals with the most frequent Treatment-Emergent Adverse Events in the general population (pooled safety data), in young adults (pooled safety data) and in adolescents (safety population; HIPRA-HH-3)

TEAEs	Pooled safety data N=3192	Young adults 18-25 yoa (pooled safety data) N=987	HIPRA-HH-3 (adolescents) N=240
Preferred Term	**%**	**%**	**%**
Injection site pain	82.83	87.74	77.92
Injection site swelling	7.71	9.73	0.42
Injection site erythema	7.08	6.69	6.67
Injection site induration	2.35	1.62	10.83
Headache	31.42	37.69	32.08
Fatigue	31.20	41.54	30.42
Malaise/Myalgia	21.55	28.88	34.58
Diarrhoea	7.64	10.13	7.50
Nausea/Vomiting	6.73	8.51	8.33
Pyrexia	1.94	2.53	3.75
Lymphadenopathy	1.35	1.52	7.92
Axillary pain	1.25	2.13	11.67
Arthralgia	0.63	0.51	14.58

Solicited adverse events

Solicited Local reactions by time

Table 34: Summary of Solicited Local Reactions from Day 0 through Day 7 (Safety Population of Adolescents 12 to 15 years old; HIPRA-HH-3)

		Adolescents (12-15 years old) (N=148)	
Timepoint	**Events**	**Events**	**Participants (%)**
Cumulative events from Day 0 to Day 7	Total number of events	457	115 (77.7)
	Pain	215	106 (71.6)
	Tenderness	193	86 (58.1)
	Induration/swelling	31	13 (8.8)
	Erythema/redness	18	11 (7.4)
Day 0	Total number of events	170	95 (64.2)
	Pain	81	81 (54.7)
	Tenderness	75	75 (50.7)
	Induration/swelling	10	10 (6.8)
	Erythema/redness	4	4 (2.7)
Day 1	Total number of events	173	96 (64.9)
	Pain	87	87 (58.8)
	Tenderness	68	68 (45.9)
	Induration/swelling	10	10 (6.8)
	Erythema/redness	8	8 (5.4)
Day 2	Total number of events	70	42 (28.4)
	Pain	30	30 (20.3)
	Tenderness	33	33 (22.3)
	Induration/swelling	5	5 (3.4)
	Erythema/redness	2	2 (1.4)
Day 3	Total number of events	22	13 (8.8)
	Pain	9	9 (6.1)
	Tenderness	9	9 (6.1)
	Induration/swelling	3	3 (2.0)

	Erythema/redness	1	1 (0.7)
Day 4	Total number of events	8	4 (2.7)
	Pain	3	3 (2.0)
	Tenderness	3	3 (2.0)
	Induration/swelling	1	1 (0.7)
	Erythema/redness	1	1 (0.7)
Day 5	Total number of events	6	2 (1.4)
	Pain	2	2 (1.4)
	Tenderness	2	2 (1.4)
	Induration/swelling	1	1 (0.7)
	Erythema/redness	1	1 (0.7)
Day 6	Total number of events	6	2 (1.4)
	Pain	2	2 (1.4)
	Tenderness	2	2 (1.4)
	Induration/swelling	1	1 (0.7)
	Erythema/redness	1	1 (0.7)
Day 7	Total number of events	2	1 (0.7)
	Pain	1	1 (0.7)
	Tenderness	1	1 (0.7)
	Induration/swelling	0	0
	Erythema/redness	0	0

N = the number of participants in the population. (%) = Participants/N*100.
If a participant experienced more than one event, the participant is counted once for each type of event.
Source: Listing 16.2.7.2 - HIPRA-HH-3: Interim Study Report, version 1.0, 27th January 2025.

Solicited Systemic Adverse Events

Table 35: Summary of Solicited Systemic Events from Day 0 through Day 7 (Safety Population of Adolescents 12 to 15 years old; HIPRA-HH-3)

		Adolescents (12-15 years old) (N=148)	
Timepoint	**Events**	**Events**	**Participants (%)**
	Total number of events	398	76 (51.4)

Cumulative events from Day 0 to Day 7	Malaise	72	39 (26.4)
	Fatigue	69	39 (26.4)
	Headache	79	39 (26.4)
	Muscle pain	49	23 (15.5)
	Joint pain	38	20 (13.5)
	Axillary pain	37	17 (11.5)
	Enlarged lymph nodes (lymphad enopathy)	23	9 (6.1)
	Nausea/vomiting	14	9 (6.1)
	Fever	5	4 (2.7)
	Diarrhoea	12	7 (4.7)
Day 0	Total number of events	87	39 (26.4)
	Malaise	18	18 (12.2)
	Fatigue	15	15 (10.1)
	Headache	14	14 (9.5)
	Muscle pain	14	14 (9.5)
	Joint pain	10	10 (6.8)
	Axillary pain	8	8 (5.4)
	Enlarged lymph nodes (lymphad enopathy)	3	3 (2.0)
	Nausea/vomiting	3	3 (2.0)
	Fever	2	2 (1.4)
	Diarrhoea	0	0
Day 1	Total number of events	138	60 (40.5)
	Malaise	26	26 (17.6)
	Fatigue	27	27 (18.2)
	Headache	23	23 (15.5)
	Muscle pain	22	22 (14.9)
	Joint pain	17	17 (11.5)
	Axillary pain	12	12 (8.1)
	Enlarged lymph nodes (lymphad enopathy)	5	5 (3.4)

	Nausea/vomiting	4	4 (2.7)
	Fever	2	2 (1.4)
	Diarrhoea	0	0
Day2	Total number of events	72	34 (23.0)
	Malaise	8	8 (5.4)
	Fatigue	13	13 (8.8)
	Headache	16	16 (10.8)
	Muscle pain	10	10 (6.8)
	Joint pain	6	6 (4.1)
	Axillary pain	6	6 (4.1)
	Enlarged lymph nodes (lymphad enopathy)	4	4 (2.7)
	Nausea/vomiting	2	2 (1.4)
	Fever	0	0
	Diarrhoea	3	3 (2.0)
Day 3	Total number of events	35	19 (12.8)
	Malaise	5	5 (3.4)
	Fatigue	7	7 (4.7)
	Headache	9	9 (6.1)
	Muscle pain	2	2 (1.4)
	Joint pain	3	3 (2.0)
	Axillary pain	6	6 (4.1)
	Enlarged lymph nodes (lymphad enopathy)	3	3 (2.0)
	Nausea/vomiting	0	0
	Fever	0	0
	Diarrhoea	0	0
Day 4	Total number of events	15	9 (6.1)
	Malaise	3	3 (2.0)
	Fatigue	1	1 (0.7)
	Headache	3	3 (2.0)
	Muscle pain	1	1 (0.7)

	Joint pain	1	1 (0.7)
	Axillary pain	1	1 (0.7)
	Enlarged lymph nodes (lymphad enopathy)	3	3 (2.0)
	Nausea/vomiting	0	0
	Fever	0	0
	Diarrhoea	2	2 (1.4)
Day 5	Total number of events	22	12 (8.1)
	Malaise	6	6 (4.1)
	Fatigue	2	2 (1.4)
	Headache	7	7 (4.7)
	Muscle pain	0	0
	Joint pain	0	0
	Axillary pain	0	0
	Enlarged lymph nodes (lymphad enopathy)	3	3 (2.0)
	Nausea/vomiting	2	2 (1.4)
	Fever	0	0
	Diarrhoea	2	2 (1.4)
Day 6	Total number of events	17	10 (6.8)
	Malaise	4	4 (2.7)
	Fatigue	2	2 (1.4)
	Headache	4	4 (2.7)
	Muscle pain	0	0
	Joint pain	1	1 (0.7)
	Axillary pain	0	0
	Enlarged lymph nodes (lymphad enopathy)	1	1 (0.7)
	Nausea/vomiting	1	1 (0.7)
	Fever	1	1 (0.7)
	Diarrhoea	3	3 (2.0)
	Total number of events	12	7 (4.7)

Day 7	Malaise	2	2 (1.4)
	Fatigue	2	2 (1.4)
	Headache	3	3 (2)
	Muscle pain	0	0
	Joint pain	0	0
	Axillary pain	0	0
	Enlarged lymph nodes (lymphad enopathy)	1	1 (0.7)
	Nausea/vomiting	2	2 (1.4)
	Fever	0	0
	Diarrhoea	2	2 (1.4)

Abbreviations: N = the number of participants in the population.
If a participant experienced more than one event, the participant is counted once for each type of event. Source: Listing 16.2.7.2 - HIPRA-HH-3: Interim Study Report, version 1.0, 27th January 2025.

Unsolicited Adverse Events

Table 36: Summary of Local and Systemic Unsolicited Adverse Events from Day 0 through Day 28 (Safety Population of Adolescents 12 to <16 years old; HIPRA-HH-3)

	Adolescents (12-15 years old) (N=148)	
System Organ Class Preferred Term	**Events**	**Participants (%)**
Total number of unsolicited AEs	**56**	**36 (24.3)**
Related	10	8 (5.4)
Unrelated	46	30 (20.3)
Infections and infestations	**15**	**14 (9.5)**
Pharyngitis	4	4 (2.7)
Nasopharyngitis	3	3 (2.0)
Viral infection	2	2 (1.4)
Pustule	1	1 (0.7)
Postoperative wound infection	1	1 (0.7)
Rhinitis	1	1 (0.7)

Gastroenteritis	1	1 (0.7)
Conjunctivitis	1	1 (0.7)
Pharyngotonsillitis	1	1 (0.7)
General disorders and administration site conditions	**9**	**7 (4.7)**
Pyrexia	2	2 (1.4)
Injection site pain	2	2 (1.4)
Secretion discharge	1	1 (0.7)
Injection site induration	1	1 (0.7)
Vessel puncture site pain	1	1 (0.7)
Axillary pain	1	1 (0.7)
Fatigue	1	1 (0.7)
Respiratory, thoracic and mediastinal disorders	**6**	**6 (4.1)**
Cough	2	3 (2.0)
Oropharyngeal pain	2	2 (1.4)
Rhinitis allergic	1	1 (0.7)
Gastrointestinal disorders	**6**	**4 (2.7)**
Vomiting	6	2 (1.4)
Odynophagia	3	2 (1.4)
Abdominal pain	2	1 (0.7)
Diarrhoea	1	1 (0.7)
Nervous system disorders	**4**	**4 (2.7)**
Presyncope	1	1 (0.7)
Migraine	1	1 (0.7)
Dizziness	1	1 (0.7)
Headache	1	1 (0.7)
Reproductive system and breast disorders	**4**	**3 (2.0)**
Premenstrual pain	2	2 (1.4)
Intermenstrual bleeding	1	1 (0.7)
Menstruation irregular	1	1 (0.7)
Blood and lymphatic system disorders	**4**	**3 (2.0)**
Splenomegaly	1	1 (0.7)

Neutropenia	1	1 (0.7)
Anaemia	1	1 (0.7)
Mesenteric lymphadenitis	1	1 (0.7)
Musculoskeletal and connective tissue disorders	**4**	**3 (2.0)**
Arthralgia	2	2 (1.4)
Pain in extremity	1	1 (0.7)
Myalgia	1	1 (0.7)
Social circumstances	**1**	**1 (0.7)**
Menarche	1	1 (0.7)
Skin and subcutaneous tissue disorders	**1**	**1 (0.7)**
Rash	1	1 (0.7)
Injury, poisoning and procedural complications	**1**	**1 (0.7)**
Ligament sprain	1	1 (0.7)
Psychiatric disorders	**1**	**1 (0.7)**
Insomnia	1	1 (0.7)

N = the number of participants in the population. (%) = Participants/N*100.
Unsolicited adverse event means any adverse event happening between Day 0 and Day 28 that is not solicited. If a participant experienced more than one event, the participant is counted once for each type of event.
SOCs are ordered in decreasing frequency of the total number of participants with AEs reported in each SOC and PTs are ordered within a SOC in decreasing frequency of the total number of participants with each AE.
Some events reported as unsolicited occurred within 7 days and could be considered as solicited.
Source: Listing 16.2.7.3 - HIPRA-HH-3: Interim Study Report, version 1.0, 27th January 2025.

Serious adverse event/deaths/other significant events/AESIs

Deaths

Until the DBL, no death occurred in Study HIPRA-HH-3.

Serious Adverse Events

Overall, 2 SAEs were reported in 2 (0.83%) participants. Both were deemed unrelated to the study drug. One participant (0.42%) had a Grade 2 event (knee operation) and 1 participant (0.42%) had a Grade 3 event (appendicitis). The latter was in a subject 12 to <16 years of age.

AESI

There were no AESIs reported during the interim evaluation period.

Medically Attended Adverse Events (MAAEs)

No related MAAEs were reported during the interim evaluation period.

For the total safety population of study HH-3 (i.e. 12 to <18 years of age), there were 120 MAAEs in 66 (27.5%) participants which were deemed unrelated to the study drug. Of these, 109 events occurred in 55 (22.9%) participants which were Grade 1 in intensity and 11 events occurred in 11

(4.6%) participants which were Grade 2 in intensity. A summary of MAAEs for HIPRA-HH-3 participants aged 12 to 15 years is presented below.

Table 37: Summary of Medically Attended Adverse Events (Adolescents 12 to 15 years old – Safety Population; HIPRA-HH-3)

	Adolescents (12-15 years old) (N=148)	
System Organ Class Preferred Term	**Events**	**Participants (%)**
Total number of MAAEs	**55**	**32 (21.6)**
Related	0	0
Unrelated	55	32 (21.6)
Infections and infestations	**22**	**19 (12.8)**
Nasopharyngitis	4	3 (2.0)
Pharyngitis	3	3 (2.0)
Viral infection	2	2 (1.4)
Gastroenteritis	2	2 (1.4)
Influenza	2	2 (1.4)
Pharyngitis streptococcal	1	1 (0.7)
Cellulitis	1	1 (0.7)
Tinea infection	1	1 (0.7)
Tinea versicolour	1	1 (0.7)
Tonsillitis streptococcal	1	1 (0.7)
Tooth abscess	1	1 (0.7)
Otitis media	1	1 (0.7)
Abscess limb	1	1 (0.7)
Pertussis	1	1 (0.7)
Injury, poisoning and procedural complications	**9**	**8 (5.4)**
Ligament sprain	4	4 (2.7)
Eye injury	2	1 (0.7)
Muscle strain	1	1 (0.7)
Arthropod bite	1	1 (0.7)
Hand fracture	1	1 (0.7)

Gastrointestinal disorders	**5**	**5 (3.4)**
Abdominal pain	3	3 (2.0)
Odynophagia	1	1 (0.7)
Abdominal pain upper	1	1 (0.7)
Respiratory, thoracic and mediastinal disorders	**4**	**4 (2.7)**
Cough	2	2 (1.4)
Rhinitis allergic	1	1 (0.7)
Catarrh	1	1 (0.7)
Musculoskeletal and connective tissue disorders	**3**	**3 (2.0)**
Arthralgia	1	1 (0.7)
Myalgia	1	1 (0.7)
Mandibular mass	1	1 (0.7)
Skin and subcutaneous tissue disorders	**3**	**3 (2.0)**
Dermatitis contact	1	1 (0.7)
Pityriasis alba	1	1 (0.7)
Hidradenitis	1	1 (0.7)
Blood and lymphatic system disorders	**3**	**2 (1.4)**
Anaemia	1	1 (0.7)
Splenomegaly	1	1 (0.7)
Mesenteric lymphadenitis	1	1 (0.7)
Metabolism and nutrition disorders	**2**	**2 (1.4)**
Iron deficiency	1	1 (0.7)
Diabetes mellitus	1	1 (0.7)
Psychiatric disorders	**1**	**1 (0.7)**
Anxiety	1	1 (0.7)
General disorders and administration site conditions	**1**	**1 (0.7)**
Vessel puncture site pain	1	1 (0.7)
Renal and urinary disorders	**1**	**1 (0.7)**
Renal colic	1	1 (0.7)
Reproductive system and breast disorders	**1**	**1 (0.7)**
Menstruation irregular	1	1 (0.7)

N = the number of participants in the population. (%) = Participants/N*100.

If a participant experienced more than one event, the participant is counted once for each type of event.
SOCs are ordered in decreasing frequency of the total number of participants with AEs reported in each SOC and PTs are ordered within a SOC in decreasing frequency of the total number of participants with each AE.
Source: Listing 16.2.7.6 - HIPRA-HH-3: Interim Study Report, version 1.0, 27th January 2025.

Laboratory findings

All laboratory data from Baseline and Day 14, including pregnancy test results, were recorded in the eCRF and will be available in the final Clinical Study Report data listings. Laboratory assessments are out of the scope of the Interim Analysis (Interim Study Report - HIPRA-HH-3, Version 1.0, 27th January 2025).

Vital Signs, Physical Findings, and Other Observations Related to Safety

A summary for vital signs measurements (body temperature, systolic and diastolic blood pressure, pulse rate and pulse oximetry) at Screening visit for the safety population was presented. Vital sign measurements and physical examination findings were recorded for each participant, for Baseline and Day 14 visits. These data will be presented in the final Clinical Study Report.

Discontinuation due to adverse events

As of cut-off date 25th September 2024, there was no discontinuation due to AEs from HIPRA-HH-3.

2.4.1. Discussion on clinical safety

HIPRA-HH-3 is an ongoing Phase IIb, open label, uncontrolled, single-agent, multi-centre, non-inferiority clinical trial to assess the safety and immunogenicity of Bimervax (PHH-1V, selvacovatein) as a heterologous booster for the prevention of COVID-19 in adolescents from 12 to less than 18 years of age primed with Comirnaty. The study started in June 2023, is being conducted in 7 centres in Spain and still ongoing until all included participants have completed the observation period of 12 months after vaccination. This submission is based on an interim analysis with DBL on 25th September 2024. The respective interim clinical study report presents solicited AE data for the first 7 days of study HH-3, unsolicited AEs observed during the first 28 days of the study, as well as Serious Adverse Events (SAEs), observed through the study. Adverse Events of Special Interest (AESIs) and Medically Attended Adverse Events (MAAEs) were also planned to be recorded through the study duration.

In total 240 participants were followed for a mean duration of 9.82 months (range: 2.66-12.98; median age 15 years, maximum age 17 years) after vaccination with Bimervax, but n=300 subjects were planned to be enrolled. The MAH justifies the reduced study sample size with recruitment challenges, which can be principally followed. However, only n=148 of the subjects included in the study were <16 years of age. Notably, the study population 16 years of age and older is already covered in the existing indication of Bimervax. This reduced sample size in the actual target population for the extension of indication (i.e. 12 to <16 years of age) also reduces the probability to detect AEs, especially those of lower frequency. However, considering that a larger amount of subjects that were followed in various clinical studies after vaccination with Bimervax before and without major clinical safety concerns identified, and considering that no immediate safety risk appears apparent for the intended population, the safety database could be sufficient to support an extension of indication to individuals 12 to <16 years of age.

It is also critically noted that interpretation of data is compromised as no internal control was included in the study. For contextualisation, the reported safety profile was compared to the available data as reported in the EPAR of Bimervax (in subjects ≥16 years). Still, this approach leaves considerable

uncertainty, e.g. that identified differences in safety profiles might not be caused by the distinct age of subjects, but could also be attributed to other (possibly unknown) factors of the studies (e.g. study centres, investigators, baseline characteristics, geographical location).

Since immunogenicity endpoints of Study HH-3 were compared to a young adult (18-25 yoa) subpopulation from Study HH-2 as external control, the demography and baseline characteristics data of these populations (Immunogenicity Population) have also been compared during the assessment. The Applicant provided the baseline characteristics for the Immunogenicity Population of Study HH-3 separately; both Immunogenicity and Safety populations from Study HH-3 were compared with baseline characteristics of young adult population from Study HH-2. Differences in baseline characteristics were not remarkable: apart from differences of natural causes (i.e. bodyweight, height) two differences seem to occur: in the young adult population the proportion of female participants and subjects with Hispanic ethnicity are higher. Further, as it was already mentioned in the discussion of immunogenicity results, Study HH-2 was initiated almost 19 months earlier (Date first subject enrolled: 15 November 2021) than Study HH-3 (Date first subject enrolled: 08 June 2023), therefore participants of the later might have not been immunologically naive to SARS-CoV-2 even at the time of their primary immunisation with Comirnaty.

Upon request the MAH provided safety data from study HH-3 restricted to those subjects of immediate relevance for the extension of the present indication, i.e. those 12 to <16 years of age at the time of study vaccination.

As for overall safety of Bimervax in adolescent population of Study HH-3, the majority (85.5% for the total population, 84.5% of 12 to <16 year old subjects) of subjects experienced at least one TEAE. The majority of them was Grade 1 or Grade 2 in severity. Related SAEs and death cases were not observed during the first 28 days of Study HH-3. The majority of TEAEs were considered to be related to study treatment. AESIs have not been observed during the first 28 days of study HH-3. Discontinuation due to AEs have not occurred either.

Common TEAEs were led by AEs in General disorders and administration site conditions, Nervous system disorders, Musculoskeletal and connective tissue disorders and GI disorders SOCs. AEs observed with the highest frequency were Injection site pain (77.9% for the total population, 77.7% of 12 to <16 year old subjects), Headache (32.1% for the total population, 26.4% of 12 to <16 year old subjects), Fatigue (30.4% for the total population, 26.4% of 12 to <16 year old subjects), Malaise (27.9% for the total population, 24.3% of 12 to <16 year old subjects), Myalgia (16.4% for the total population, 13.5% of 12 to <16 year old subjects) and Arthralgia (14.6% for the total population, 15.5% of 12 to <16 year old subjects), all of them occurred among the treatment related AEs as well.

In the total study population one event of intermittent tachycardia was reported as grade 1 event that has resolved during the study duration. Grade 4 events were reported in 2 subjects, but the MAH noted that all 4 events were erroneously entered as grade 4, but were in fact grade 3 events. All of these were solicited systemic reactions. Considering the nature of the events (joint pain and muscle pain in one subject, expanded lymph nodes and malaise in another subject), it can be followed that neither of those events was indeed life-threatening. Thus, the re-classification as grade 3 events can be followed. Additional 15 grade 3 events (besides the erroneously grade 4 events that were actually grade 3) were reported in 2.5% of subjects, all were solicited reactions (n=7 local and n=8 systemic). Of the 865 TEAEs listed by the MAH (504 in 12 to <16 year old subjects), 768 events were solicited local or solicited systemic events (447 in 12 to <16 year old subjects) and 95 (56 in 12 to <16 year old subjects) were unsolicited AEs. A total of 152 AEs in 76 (31.67%) participants were reported in study HH-3 beyond Day 28 up to interim cut-off of the provided study report. None of those were assessed as related to the study vaccine and two of those were serious AEs (appendicitis and knee operation).

The proportion of subjects with **solicited systemic** events seems mildly higher in the adolescent population of study HH-3 compared to the pooled adult data set as reported in the EPAR of the initial authorisation (studies HH-2, HH-5 and HH-10), at least for the first 4 days (Day 0: 33.3% vs. 27.88%, Day 1: 43.8% vs. 31.64%, Day 2: 27.1% vs. 18.11%, Day 3: 14.2% vs. 11.78% , Day 4: 9.2% vs. 8.96%). This difference seems even less marked for the lower age group (12 to <16 years) of trial HH-3 (Day 0: 26.4% vs. 27.33%, Day 1: 40.5% vs. 31.64%, Day 2: 23% vs. 18.11%, Day 3: 12.8% vs. 11.78% and Day 4: 6.1% vs. 8.96% with event in study HH-3 <16 years of age vs. pooled data reported in the EPAR, respectively).

However, especially malaise (highest rate at day 1 in 20% of the total population, 17.6% of 12 to <16 year old subjects) and joint pain (highest rate at day 1 in 10.4% of the total population, 11.5% of 12 to <16 year old subjects) appear substantially more common compared to adults (both events in <0.2% of subjects throughout the 7-day observation period), especially in the early days after vaccination. Axillary pain (highest rate at day 1 in 7.1% of the total population, 8.1% of 12 to <16 year old subjects) and enlarged lymph nodes (highest rate at day 1 in 4.6% of the total population, 3.4% of 12 to <16 year old subjects) were not listed to be reported as solicited events for adult subjects in studies HH-2, HH-5 and HH-10, but are now reported for the adolescent population as solicited events (Day 0 to Day 7). However, both events were reported as unsolicited events (Day 0 to Day 28) in adults in a clearly lower proportion of subjects (axillary pain with 45 events in 41 [1.28%] subjects and lymphadenopathy with 42 events in 42 [1.32%] subjects).

According to the MAH explanation, the higher incidences of some AEs in adolescents may reflect age-related differences in immune system maturity and reactogenicity. The higher incidence of certain local and systemic AEs observed in adolescents may therefore reflect this heightened immune reactivity, consistent with their ongoing immune system maturation. Therefore, differences observed in adolescents in HIPRA-HH-3 study are not unexpected in the context of vaccine safety evaluation and are consistent with patterns previously observed with other COVID-19 vaccines. The above findings are appropriately presented in the Section 4.8 of the SmPC of Bimervax.

In contrast to the solicited systemic reactions, no obvious divergence is evident between age groups for **solicited local reactions**. Events with ≥1% higher rate in subjects 12-16 years old compared to those reported in the current EPAR of Bimervax were: Pain at day 1 (60% vs. 57.93%) and erythema/redness at day 1 (6.3% vs. 4.86%). Solicited local reactions seem otherwise comparable, or, in some cases, lower proportions of subjects with event are reported for the adolescent population of study HH-3. Similarly, also for subjects of study HH-3 that were 12 to <16 years old the rates in reported solicited local reactions were rather comparable or have affected a lower proportion of subjects compared to the pooled set in the EPAR.

As for time course of **solicited systemic reactions**, highest overall AE frequency was observed on Day 1 (43.8% of the total population, 40.5% of 12 to <16 year old subjects), however, AE frequency on Day 0 (33.3% of the total population, 26.4% of 12 to <16 year old subjects) was not far from that on Day 1. Remarkable decrease in AE frequencies was observed from Day 3 (14.3% of the total population, 12.8% of 12 to <16 year old subjects). However, from Day 4 vaning of solicited systemic AEs seems to become slower and 16 of 240 subjects experienced solicited systemic AEs even on Day 7 (of the total population, 7 of 148 subjects 12 to <16 year old). Similar time course was observed in Study HH-2 part A, however, in Study HH-5 (which has the biggest safety analysis set) no such characteristics of solicited systemic AEs was observed, and on Day 7 the overall AE frequency was 1.92%.

As for time course of **solicited local reactions**, AE frequencies were the highest on Day 0 and Day 1 , from Day 2 a remarkable decrease in AE frequencies was observed. By Day 5, almost all AE vaned. Both overall and by day AE frequencies were lead by Pain and Tenderness AEs.

Most PTs within the **unsolicited AEs** by PT were experienced by one or two participants. Unsolicited AEs were lead by Cough, Pharyngitis, Premenstrual pain (2.1% each) Injection site pain, nasopharyngitis and viral infection (1.7% each) AEs. Some AEs presented within the unsolicited AEs seem to be administration site AE not vaned by Study Day 7 very likely (Injection site pain, Injection site induration, Injection site anaemia) or might be continuation of previous solicited systemic AEs after Day 7 (Myalgia, Headache, Migraine, Fatigue, Dizziness, Axillary pain, Vomiting, Pyrexia, Presyncope-Syncope, Lymphadenopathia and Arthralgia). Narratives of participants experiencing these AEs and also the outcome of them were provided.

Unsolicited local and systemic adverse events that were reported in ≥1% of subjects from pooled studies HH-2, HH-5 and HH-10 were COVID-19 in 1.50% of subjects, lymphadenopathy in 1.32% of subjects, headache in 1.28% of subjects and axillary pain in 1.28% of subjects.

Two **serious AEs** occurred (appendicitis and knee operation), but a relation to the study vaccine does not seem apparent and both events have resolved during the study. None of the protocol-defined **AESIs** was reported, no adverse event has led to **study discontinuation** and no participant **died** during the study. MAAEs have occurred in 27.5% of paediatric subjects (120 MAAEs in 66 subjects of the total population, 21.6% of 12 to <16 year old subjects), in 4.6% of subjects these were of grade 2 (11 events in 11 subjects), otherwise all were grade 1. The most frequently reported MAAEs belonged to the Infections and Infestations SOC (16.3% of the total population, 12.8% of 12 to <16 year old subjects), the most common event within this SOC was pharyngitis (2.1% of the total population, 2% of 12 to <16 year old subjects). Other frequently reported MAAEs belonged to Injury, Poisoning and Procedural Complications SOC (7.1% of the total population, 5.4% of 12 to <16 year old subjects) with ligament sprain (2.9% of the total population, 2.7% of 12 to <16 year old subjects) as the most frequent event within this SOC. All MAAEs have recovered/resolved during the study or were recovering/resolving at the time of the study report completion and were considered not related or unlikely related (only one event of renal colic) by the investigator. Notably, the reported proportion is substantially higher than for the population reported in the existing EPAR (Studies HH-2, HH-5, and HH-10) with only 7.08% (295 MAAEs in 226 subjects) of subjects with an AE that required hospitalization. However, reporting intervals were longer in study HH-3 (12 months) compared to most of the studies contributing to the pooled set (6 months). The only study of the pooled safety dataset with observation period of 12 months was study HH-2 with a comparable rate in MAAEs as reported for study HH-3 (24.2% and 27.5%, respectively).

The MAH did not provide Laboratory (haematology and clinical chemistry) data, as these were planned to be reported once the final CSR is available. The MAH submitted on request the listing of haematology and biochemistry parameters, assessed at Baseline and Day 14 per protocol. No noteworthy changes or trends occurred in haematology and biochemistry laboratory evaluations among adolescent participants up to interim cut-off date was noted, although some values had to be clarified by the MAH during the procedure.

Albeit participants were required to have practiced adequate contraception, one pregnancy occurred in a participant during the study.

In conclusion, the comparison of the most frequent TEAEs, MAAE frequencies and time course of solicited AEs between Safety population of Study HH-3 and the young adult population of the pooled safety data of Bimervax, and also taking into consideration clinical chemistry/haematology findings, no new safety concern seems apparent for the vaccination of adolescent subjects with Bimervax.

2.4.2. Conclusions on clinical safety

Whereas the currently reported safety profile on TEAEs as well as on solicited local and unsolicited (local and systemic) level seems roughly comparable to the proportions reported in the EPAR (of subjects ≥16 years), and also despite the fact that most part of AEs occurred in Study HH-3 were Grade 1 or Grade 2 in severity and also that no related SAEs, Deaths and AESIs were observed, the proportion of subjects with solicited systemic events (especially driven by malaise, joint pain, axillary pain and enlarged lymph nodes) seems higher in the adolescent population of study HH-3. Data interpretation is compromised by the very low number of subjects in the relevant age range (12 to <16 years) that were included in the study (n=148). Still, considering that a larger amount of subjects were followed in various clinical studies after vaccination with Bimervax before and without major clinical safety concerns identified, and considering that no safety risk appears apparent for the intended population based on the submitted interim CSR, the safety database is sufficient to support an extension of indication to individuals from 12 to <16 years of age.

2.4.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, editorial changes have been included in the SmPC and Annex II.

2.5.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is a disease caused by the coronavirus SARS-CoV-2. The clinical manifestation of COVID-19 is non-specific and variable. It can range from no symptoms (asymptomatic) to severe pneumonia and death. The disease burden is highest amongst individuals with increased age; however, all age groups are susceptible. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer, and obesity are considered risk factors for developing severe COVID-19.

3.1.2. Available therapies and unmet medical need

Several products are currently authorised for the treatment of COVID-19. These encompass antiviral therapy (nirmatrelvir / ritonavir, remdesivir), anti-inflammatory therapy (dexamethasone), IL-6 inhibitor (tocilizumab), IL-1 inhibitor (anakinra) as well as monoclonal antibodies directed against the SARS-CoV-2 spike protein (casirivimab/imdevimab, sotrovimab and tixagevimab / cilgavimab). These

therapies have shown variable efficacy depending on the severity and duration of illness as well as against different variants of concern.

Besides Bimervax, there are 4 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease: Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Nuvaxovid (EMEA/H/C/005808) and Kostaive (EMEA/H/C/006207).

3.1.3. Main clinical studies

The main evidence supporting the extension of indication to the population between 12 and 15 years of age, is the interim results of study HIPRA-HH-3, a Phase IIb, open label, single arm, multi-centre trial aiming to assess the immunogenicity and safety of a heterologous booster dose of a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adolescents from 12 years to less than 18 years with previous primary immunisation with Comirnaty.

3.2. Favourable effects

In Study HIPRA-HH-3, immunogenicity endpoints were used as surrogate endpoints to clinical efficacy. This approach is widely used in clinical studies with adapted COVID-19 vaccines, among others.

As regards the primary immunogenicity endpoint Neutralisation titre against Omicron BA.1 measured as inhibitory concentration 50 (IC50) by PBNA and reported as log10 concentration for each individual sample and Geometric Mean Titre (GMT) for group comparison with HIPRA-HH-2 at Baseline and Day 14, the Day 14 GMT for Omicron BA.1 of the adolescent group (12-17 yoa) was higher compared to that of the external young adults group (18-25 yoa), with 24081.34 (SD: 2.45) vs 2346.67 (SD: 2.70), respectively. Results of secondary endpoints that compare Day 14 GMTs and of which data is available so far (baseline and Day 14), i.e., Neutralisation titre against VOCs (at least Beta and Delta) measured as IC50 by PBNA and reported as log10 concentration for each individual sample and GMT at Baseline and Days 14, Binding antibody titres at Baseline and Days 14, and Neutralisation titre against Wuhan measured as IC50 by PBNA and reported as log10 concentration for each individual sample and GMT at Baseline, and Days 14, show also higher GMTs in the adolescent group (12-17 yoa) compared to those of the external young adults group (18-25 yoa). GMFR results (i.e., GMFR in neutralising antibody titres against Omicron BA.1 and VOCs (at least Beta and Delta) from Baseline to Day 14, GMFR in binding antibody titres from Baseline to Day 14, Percentage of participants that, after a booster dose, have a ≥4-fold change in binding antibody titre from Baseline and Days 14, and GMFR in neutralising antibody titres against the Wuhan strain from Baseline to Day 14 demonstrated a rise in titres from baseline until Day 14 in both study groups.

Additionally, study subjects 12 to 15 yoa, which constitute the most relevant age group as BIMERVAX is already indicated for individuals 16 yoa and older, had a Day 14 nAb GMT of 22970.81 (SD: 2.61). Moreover, those subjects had a nAb GMFR at Day 14 of 18.51 and 88.5% of subjects had ≥4-fold change from baseline in neutralising antibodies, as regards Omicron BA.1.

In summary, the presented results are indicative of an anamnestic immune response to the administered 40 µg BIMERVAX dose after primary vaccination with two Comirnaty doses.

3.3. Uncertainties and limitations about favourable effects

Although the Day 14 neutralising and binding antibodies GMTs were higher in the adolescents compared to those of the external young adults group, the sole comparison of GMTs across studies and across populations with different baseline values is not considered informative and required further

contextualisation with comparison of GMFRs, albeit it is unclear whether GMFRs starting from different baseline levels are comparable.

The comparison of results from single-arm trials to external control groups carries substantial risks for various biases, even though measures to mitigate potential sources of bias had been implemented (i.e., same assays, same success criteria, etc.). Of note, the factor most likely contributing to the observed difference in baseline between studies HH-2 and HH-3 was identified to be that enrolment for study HH-3 was approximately 2 years after that for study HH-2 and thus at a time when an increased number of people had baseline immunity, in general, against SARS-CoV-2 due to natural exposure.

The sample size was rather limited. Instead of planned 154 subjects, only 88 subjects were included in the Immunogenicity Population. Moreover, the sample size of the relevant age group outside the currently approved indication (i.e., 12 to 15 years of age) was even lower (n=61).

Immunogenicity results were only limited to Day 14.

3.4. Unfavourable effects

84.5% of participants have reported Treatment-Emergent Adverse Events (TEAEs) during the study period of 12 months, most of these were of grade 1 or 2. The most common events were injection site pain (in 77.7% of subjects), headache (in 26.4%), fatigue in (26.4%), malaise (in 24.3%) and myalgia (in 13.5%).

Solicited systemic events were most common in the first day after vaccination (in 51.4%) and faded over the time of 7 days observation period (4.7% at day 7). Highest rates were reported for fatigue and malaise at day 1 (in 18.2% and 17.6% of subjects, respectively).

Solicited local reactions were most common in the first day after injection (in 64.9%) with pain (in 58.8%) and tenderness (in 45.9%) being most common, before induration/swelling (in 6.8%) and erythema/redness (5.4%).

Unsolicited events that have occurred in ≥1% of subjects were (naso)pharyngitis (4.7%), cough (2%), as well as viral infection, pyrexia, injection site pain, oropharyngeal pain, vomiting, odynophagia, postmenstrual pain and arthralgia (each 1.4%).

MAAEs have occurred in 21.6% of subjects. Most of the events on SOC level (in >5%) were reported in Infections and infestations (in 12.8% of subjects), before Injury, poisoning and procedural complications (in 5.4% of subjects). All recovered/resolved and were considered not related or unlikely related (only one event of renal colic) by the investigator.

Two serious AEs occurred, none considered related to Bimervax. No protocol-defined AESIs was reported, no adverse event has led to study discontinuation and no participant died during the study.

3.5. Uncertainties and limitations about unfavourable effects

Safety population is limited, especially for the population of most interest (i.e. the 12-15 years of age) with only 148 subjects included for safety assessment. Longer term (beyond 28 days for safety data) are scarce.

No suitable in- or external study control was provided.

Sampling for the assessment of clinical chemistry/haematology parameters was carried out per protocol at Day 0 and Day 14 only. This sparse sampling is considered an additional uncertainty in the assessment of clinical chemistry/haematology parameters.

3.6. Effects Table

Table 38: Effects Table for Bimervax extension of indication to the 12-15 age cohort (data cut-off: 25th September 2024)

Effect	Short description	Unit	12-15 yoa (Study HH-3, n=61)	16-17 yoa (Study HH-3, n=27)	Uncertainties / Strength of evidence	References
Favourable Effects						
Immunogenicity (IGP)	Neutralising antibody (nAb) Geometric Mean Titre (GMT) at Baseline and Day 14, against variant Omicron BA.1	GMT (95% CI)	Baseline: 1240.77 (894.78; 1720.55) Day 14: 22970.81 (18033.27; 29260.25)	Baseline: 1457.30 (984.9; 2156.3) Day 14: 26792.00 (20150.31; 35622.86)	Unc: Limited sample size.	Study HH-3
Immunogenicity (IGP)	Neutralising antibody (nAb) Geometric Mean Fold Rise (GMFR) from Baseline to Day 14, against variant Omicron BA.1	GMFR (95% CI)	18.51 (13.28; 25.81)	18.38 (13.15; 25.71)	same as for GMT	Study HH-3
Immunogenicity (IGP)	Number (n) and percentage (%) of subjects with ≥ 4-fold change in nAb from baseline to Day 14, against variant Omicron BA.1	n (%) (95% CI)	54 (88.5) (77.8; 95.3)	27 (100) (87.2; 100)	same as for GMT	Study HH-3
Unfavourable Effects						
		%	**12-15 yoa Study HH-3 (n=148)**	**Pooled Safety Data for Bimervax (n=3192)**		
Safety (SP)	Injection site pain	Percent of participants with event	77.7	82.83	Unc: Limited sample size of safety population.c External control.c	
	Headache		26.4	31.42		
	Fatigue		26.4	31.20		
	Malaise		24.3	21.55		
	Axillary pain		12.2	1.25		
	Myalgia[b]		13.5			

		%	12-15 yoa Study HH-3 (n=148)	Pooled Safety Data for Bimervax (n=3192)		
	Arthralgia		15.5	0.63		
	Lymphadenopathy		6.1	1.35		

Notes:
[b] in the pooled safety population, Myalgia was not presented as a separate PT.
[c] Applies for all unfavourable effects
All neutralisation titres were measured as IC50 by PBNA

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The paramount shortcoming of the data provided for this procedure is that the comparison of results from a single-arm trial to an external control group carries substantial risks for biases. Even though measures to mitigate potential sources of bias had been implemented, baseline immunogenicity differed greatly, most likely because enrolment of adolescent subjects (12-17 years of age, Study HH-3) was approximately 2 years after that of the young adults (18-25 years of age, Study HH-2) and thus at a time when an increased number of people had baseline immunity, in general, against SARS-CoV-2 due to natural exposure.

Although the Day 14 neutralising and binding antibodies GMTs were significantly higher in the adolescents compared to those of the external young adults group, the informative value of the sole comparison of GMTs across studies and across populations with considerable different baseline values is strongly impaired. It is, however, reassuring that results indicate that Day 14 (i.e., post-booster) GMTs in adolescents reach levels comparable or higher (absolute) than post-booster GMTs in young adults, which were considered acceptable to infer efficacy at the time of authorisation of Bimervax. Comparison of GMFRs may be more informative and serve as a suitable measure to evaluate and compare changes in immunogenicity and be of use as success criterion in absence of a defined GMT threshold, however, no corresponding success criteria were predefined. Moreover, it is unclear whether GMFRs starting from different baseline levels are comparable. Nevertheless, GMFR results demonstrated a rise in titres from baseline until Day 14, and taken together with Day 14 GMT data, are indicative of an anamnestic immune response. This holds also true for study subjects 12 to 15 yoa, which constitute the most relevant age group for the current procedure as BIMERVAX is already indicated for individuals 16 yoa and older.

Due to recruitment challenges, instead of planned 154 subjects, only 88 subjects were included in the Immunogenicity Population of Study HH-3. The sample size of the most relevant age group (i.e., 12 to 15 yoa) was even lower (n=61), however, the reported data are still deemed being sufficient to conclude on immunogenicity.

Long-term effect of the BIMERVAX booster in the adolescent population is still unknown since the study is ongoing and only Day 14 data have been submitted yet.

The vaccine is mildly reactogenic and generally well-tolerated in the intended target population. The lack of AESIs and study vaccine related serious AEs is reassuring. The indirect comparison to the established safety profile in subjects ≥16 years suggests a higher rate in solicited systemic events (especially driven by malaise, joint pain, axillary pain and enlarged lymph nodes). Local reactions seem comparable or partly less frequent in the adolescent population and only a few of the reported events

were of grade 3 (all recovered/resolved). Therefore, the safety profile is acceptable, although the safety population is limited and there is a lack of an in- or external study control.

3.7.2. Balance of benefits and risks

The available immunogenicity data is deemed adequate to conclude on a sufficient anamnestic immune response to Bimervax in individuals 12 to 15 years of age.

The vaccine is mildly reactogenic and generally well-tolerated in the intended target population. No direct control was provided for safety data, but no safety concern is observed from the data submitted. The comparison to the established safety profile in subjects ≥16 years suggests a higher rate in solicited systemic events, but otherwise a comparable rate of unwanted effects seems reported.

3.8. Conclusions

The overall B/R of Bimervax in the adolescent population from 12 yoa to less than 16 yoa is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include the use of Bimervax in adolescents aged between 12 years to 15 years of age, based on interim results from the ongoing study HIPRA-HH-3. HIPRA-HH-3 is an open-label, multi-centre, non-inferiority study to assess the 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. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is updated to include editorial changes and it is brought in line with the latest QRD template version 10.4.

The variation leads amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation amendments to Annexes I, II, and IIIB are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0253/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Bimervax-VR-0000257408'