Amsterdam, 25 June 2026
EMADOC-1700519818-3306580
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

BIMERVAX

COVID-19 vaccine (recombinant, adjuvanted)

Procedure no: EMA/PAM/0000331983

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start date	23 Feb 2026	23 Feb 2026
☐	CHMP Rapporteur AR	30 March 2026	30 March 2026
☐	CHMP comments	13 April 2026	8 April 2026
☐	Updated CHMP Rapporteur AR	16 April 2026	n/a
☐	Request for Supplementary Information	23 April 2026	23 April 2026
☐	Re-Start date	27 May 2026	27 May 2026
☐	CHMP Rapporteur AR	10 June 2026	10 June 2026
☐	CHMP comments	15 June 2026	n/a
☐	Updated CHMP Rapporteur AR	18 June 2026	n/a
☒	CHMP outcome	25 June 2026	25 June 2026

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1. Introduction

On 10 February 2026, the MAH submitted a completed paediatric study for BIMERVAX, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

HIPRA-HH-3 is a completed Phase II open-label, multi-centre, non-inferiority study of safety and immunogenicity of Bimervax as heterologous booster dose for the prevention of coronavirus disease (COVID-19) in adolescents from 12 years to less than 18 years of age. HIPRA-HH-3 is part of the clinical development plan required to comply with the EMA's paediatric Investigation Plan (PIP) as per the Decision dated 04 November 2022 (P/0465/2022).

The PIP was subsequently modified on 19 July 2024 (P/0253/2024) and on 4 December 2025 (EMA/PE/0000290050).

On 18 September 2025, a positive CHMP opinion for the extension of indication to include the use of BIMERVAX in adolescents aged 12 years and older was issued based on interim results of HIPRA-HH-3 study (Procedure No. EMA/VR/0000257408). Therefore, no amendments to be introduced in the current Product Information have been identified by the MAH as part of this submission. The current indication for these vaccines in the EU is following:

- BIMERVAX is indicated as a booster for active immunisation to prevent COVID-19 in individuals 12 years of age and older who have previously received a mRNA COVID- 19 vaccine.
- Adapted BIMERVAX (XBB.1.16 and LP.8.1) vaccines are indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

In addition, with the current submission, REC no. 1 (Submission of the final CSR for the study HIPRA-HH-3) issued on Procedure No. EMA/VR/0000257408 is fulfilled.

2.2. Information on the pharmaceutical formulation used in the study

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 12 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.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

HIPRA-HH-3 - 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.

2.3.2. Clinical 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)

Description

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 completed, the release date for the present final study report was on 22nd January 2026, the final study report presents Day 14-336 immunogenicity data of all enrolled participants in the Immunogenicity data set, and safety findings through Day 336 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 study release date (22nd January 2026), a total of 240 participants received a single BIMERVAX booster dose on Day 0. The immunogenicity was evaluated in 90 adolescents and the safety was evaluated in 240 adolescent participants.

Methods

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

1. Acute illness with fever ≥ 38.0°C at Screening or within 24 hours prior to vaccination.
2. 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.
3. Received medications intended to prevent or treat COVID-19 before Screening, except for Comirnaty vaccines.
4. Previous or current diagnosis of MIS-C.

5. 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.
6. 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).
7. 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.
8. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
9. Female who was pregnant or breastfeeding.
10. 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.
11. Participation in other studies involving study intervention within 28 days prior to Screening and/or during study participation.
12. Received any non-study vaccine (including seasonal Influenza vaccine) within 14 days before after Screening. For live or attenuated vaccines, 4 weeks before or after Screening.
13. History of illegal substance use or alcohol abuse within the past 2 years.
14. History of a diagnosis or other conditions that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant’s safety. 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.

Objective(s)

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 D614G 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 D614G 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 D614G 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.

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 planned 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 at Day 14 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

Table 1. Participants Enrolment and Disposition (Safety Population)

	Statistics	**Adolescents (12-17 years old)**
Enrolled population	n	242
Intention-to-treat (ITT)	n	240 (100.0)

	Statistics	Adolescents (12-17 years old)
Modified Intention-to-treat (mITT)	n (%)	238 (99.2)
Per-Protocol set (PP)	n (%)	228 (96.7)
Immunogenicity population (IGP)	n (%)	90 (37.5)
Safety population set (SP)	n (%)	240 (100.0)
Participants who completed the study	n (%)	238 (99.2)
Participants who prematurely discontinued study	n (%)	2 (0.8)
Reason for study withdrawal		
Other		2 (0.8)
Study duration (months)[a]	n	240
	Mean	11.00
	SD	0.86
	Minimum	4.04
	Median	11.07
	Interquartile Range	0.92
	Maximum	12.48

Abbreviations: EP = enrolled population; IGP = immunogenicity population; ITT = intent-to-treat; mITT = modified ITT;
PP = per-protocol; SP = safety population; n = the number of participants meeting the criterion; (%) = n/number of participants in the SP*100; SD = standard deviation.
[a]Study duration is based on ITT population. Study duration (months) = ([Date of study completion or early withdrawal - Date of booster vaccination + 1] / 30.4375).
Source: Table 14.1.1

Recruitment

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

Date first participant enrolled: 08 June 2023

Date last participant completed: 09 September 2025

Release date of the report: 22 January 2026

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 14 major protocol deviations (MPDs) were reported during Study HIPRA-HH-3, half (7 of 14) of them resulted from the collection of blood samples for immunogenicity analyses from participants not assigned to the immunogenicity cohort. Two 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. Two more patients received vaccines which had been subject to temperature deviations prior to administration. In such case, the CRO or the sponsor should have been contacted in order to decide whether or not the vaccines in question could be used for immunisation, however in case of the above two patients, CRO or sponsor was not informed. Minor PDs included missing biochemistry and/or haematology parameter assessments, as well as follow-up visits performed slightly out of window.

Baseline data

Table 2. Demographics and Baseline Characteristics (Safety Population)

	Statistics	Adolescents (12-17 years old) (N=240)	Young adults external 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	7 (2.9)	23 (27.7)	30 (9.3)
	Not Hispanic or Latino	233 (97.1)	60 (72.3)	293 (90.7)
	Not Reported	0	0	0
	Unknown	0	0	0
Height (cm) at Screening	n	240	83	323
	Mean	166.47	169.79	167.32
	SD	9.882	8.552	9.655
	Minimum	141.0	147.0	141.0
	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	240	83	323
	Mean	20.708	22.761	21.236
	SD	2.7393	2.8995	2.9185
	Minimum	14.67	18.17	14.67
	Median	20.545	22.590	20.990
	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	76.0
	SD	13.49	14.19	13.66
	Minimum	51	47	47
	Median	76.0	74.0	75.0
	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

Efficacy results

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 IC50 in Neutralising Antibody Titres Against Omicron BA.1 (Immunogenicity Population)

		Adolescents (12-17 years old) (N=90)	Young adults external control (18-25 years old) (N=81)	Overall (N=171)
Visit	**Statistics**	**Observed value**	**Observed value**	**Observed value**
Baseline	n	90	81	171
	Geometric mean	1271.52	48.48	270.57
	Geometric SD	3.37	3.19	7.54
	Minimum	1.34	1.30	1.30
	Q1	2.76	1.30	1.48
	Median	3.13	1.45	2.55
	Q3	3.47	1.86	3.18
	Maximum	4.69	3.47	4.69
Day 14	n	88	80	168
	Geometric mean	24081.34	2346.67	7945.90
	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. Raw data provided as >49220 have been imputed
as 49220 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.1.1.1.

A statistical analysis of neutralising antibody titres against Omicron BA.1 variant by MMRM at Baseline and Day 14 is presented in Table 4.

Table 4. Analysis of IC50 in Neutralising Antibody Titres Against Omicron BA.1 (Immunogenicity Population)

	Adolescents (12-17 years old) (N=90)	Young adults external control (18-25 years old) (N=81)
Baseline Visit		
Number of participants with data, n (%)	90 (100.0)	81 (100.0)
Adjusted group mean (LS Mean)[a]	3.10	1.69
Standard error	0.054	0.057
95% CI	3.00, 3.21	1.57, 1.80
GMT for adjusted group mean[b]	1271.52	48.48
95% CI	992.69, 1628.67	37.35, 62.94
GMT for group ratio (Young adults vs Adolescents)[b]		
Adjusted ratio	-	0.04
95% CI for adjusted ratio	-	0.03, 0.06
p-value for adjusted ratio = 1	-	<0.0001
Day 14 Visit		
Number of participants with data, n (%)	88 (97.8)	80 (98.8)
Adjusted group mean (LS Mean)[a]	4.38	3.37
Standard error	0.04	0.05
95% CI	4.29, 4.47	3.28, 3.46
GMT for adjusted group mean[b]	23940.91	2340.57
95% CI	19628.00, 29201.53	1900.25, 2882.92
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. (%) = Participants/N*100
[a]A 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.
[b]The 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. Raw data provided as >49220 have been imputed as 49220 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.1.2.1.

Secondary immunogenicity endpoints

Neutralising antibodies against Omicron BA.1

A summary of log10-transformed neutralising antibody titres against Omicron BA.1 variant at all study timepoints is presented in Table 5

The results for neutralising antibodies against Omicron BA.1 at Baseline and Day 14 are presented both in the primary endpoint section, where they are analysed through statistical comparison with young adults from study HIPRA-HH-2, and in this secondary endpoint section, where they are shown descriptively for all study timepoints. Minor differences could be expected between the two presentations reflecting the distinct analytical approaches: inferential testing in the primary endpoint versus descriptive reporting in the secondary endpoint.

Table 5. Summary of IC50 in Neutralising Antibody Titres Against Omicron BA.1 (Immunogenicity Population)

		Adolescents (12-17 years old) (N=90)
Visit	**Statistics**	**Observed value**
Baseline	n	90
	Geometric mean	1271.52
	Geometric SD	3.37
	Minimum	1.34
	Q1	2.76
	Median	3.13
	Q3	3.47
	Maximum	4.69
Day 14	n	88
	Geometric mean	24081.34
	Geometric SD	2.45
	Minimum	2.91
	Q1	4.13
	Median	4.63
	Q3	4.69
	Maximum	4.69
Day 84	n	88
	Geometric mean	9466.56
	Geometric SD	2.14
	Minimum	2.35
	Q1	3.82
	Median	4.05
	Q3	4.19
	Maximum	4.54
Day 168	n	89
	Geometric mean	5692.44
	Geometric SD	2.16
	Minimum	2.56
	Q1	3.59
	Median	3.75
	Q3	3.94
	Maximum	4.49
Day 336	n	88
	Geometric mean	3362.36
	Geometric SD	2.34
	Minimum	2.27
	Q1	3.29
	Median	3.53
	Q3	3.75
	Maximum	4.30

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. Raw data provided as >49220 have been imputed as 49220 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.1.1.2.

Table 6. Analysis of IC50 in Neutralising Antibody Titres Against Omicron BA.1 (Immunogenicity Population)

Visit	Adolescents (12-17 years old) (N=90)
Baseline	
Number of participants with data, n (%)	90 (100.0)
Adjusted mean (LS Mean)[a]	3.10
Standard error	0.05
95% CI	3.00, 3.21
Adjusted GMT[b]	1271.52
95% CI	992.69, 1628.67
Day 14	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	4.38
Standard error	0.04
95% CI	4.30, 4.47
Adjusted GMT[b]	24109.57
95% CI	19774.18, 29395.49
Day 84	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.98
Standard error	0.04
95% CI	3.91, 4.05
Adjusted GMT[b]	9497.55
95% CI	8067.64, 11180.90
Day 168	
Number of participants with data, n (%)	89 (98.9)
Adjusted mean (LS Mean)[a]	3.75
Standard error	0.04
95% CI	3.68, 3.82
Adjusted GMT[b]	5670.53
95% CI	4823.21, 6666.70
Day 336	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.53
Standard error	0.04
95% CI	3.45, 3.61
Adjusted GMT[b]	3371.72
95% CI	2816.89, 4035.85

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. (%) = Participants/N*100

[a]A Mixed-Effects Model for Repeated Measures was fitted to assess the endpoint on the log10 scale. In the model, the visit (Baseline, Days 14, 84, 168 and 336) was included as fixed effect. An unstructured covariance matrix was used to model the within-participant error and Kenward-Roger approximation was employed to estimate the degrees of freedom.
[b]The 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. Raw data provided as >49220 have been imputed as 49220 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.1.2.2.

Neutralising Antibodies Against Beta

Table 7. Summary of IC50 in Neutralising Antibody Titres Against Beta (Immunogenicity Population)

		Adolescents (12-17 years old) (N=90)
Visit	**Statistics**	**Observed value**
Baseline	n	90
	Geometric mean	1731.99
	Geometric SD	3.10
	Minimum	1.86
	Q1	2.91

	Median	3.30
	Q3	3.67
	Maximum	4.15
Day 14	n	88
	Geometric mean	16529.01
	Geometric SD	1.91
	Minimum	3.37
	Q1	4.06
	Median	4.21
	Q3	4.44
	Maximum	4.59
Day 84	n	88
	Geometric mean	8568.31
	Geometric SD	2.25
	Minimum	2.71
	Q1	3.71
	Median	4.02
	Q3	4.22
	Maximum	4.59

		Adolescents (12-17 years old) (N=90)
Visit	**Statistics**	**Observed value**
Day 168	n	89
	Geometric mean	6204.37
	Geometric SD	2.24
	Minimum	2.60
	Q1	3.62
	Median	3.79
	Q3	4.09
	Maximum	4.31
Day 336	n	88
	Geometric mean	4557.50
	Geometric SD	2.33
	Minimum	2.64
	Q1	3.42
	Median	3.67
	Q3	3.92
	Maximum	4.31

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. Raw data provided as >39020 have been imputed as 39020 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.1.1.2.

Table 8. Analysis of IC50 in Neutralising Antibody Titres Against Beta (Immunogenicity Population)

Visit	Adolescents (12-17 years old) (N=90)
Baseline	
Number of participants with data, n (%)	90 (100.0)
Adjusted mean (LS Mean)[a]	3.24
Standard error	0.05
95% CI	3.14, 3.34
Adjusted GMT[b]	1731.99
95% CI	1366.19, 2195.73
Day 14	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	4.21
Standard error	0.03
95% CI	4.15, 4.27
Adjusted GMT[b]	16279.89
95% CI	14187.44, 18680.95
Day 84	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.92
Standard error	0.04
95% CI	3.85, 4.00
Adjusted GMT[b]	8400.41
95% CI	7069.30, 9982.15
Day 168	
Number of participants with data, n (%)	89 (98.9)
Adjusted mean (LS Mean)[a]	3.79
Standard error	0.04
95% CI	3.72, 3.86
Adjusted GMT[b]	6161.97
95% CI	5203.65, 7296.78
Day 336	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.65
Standard error	0.04
95% CI	3.57, 3.73
Adjusted GMT[b]	4449.30
95% CI	3717.43, 5325.25

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. (%) = Participants/N*100
[a]A Mixed-Effects Model for Repeated Measures was fitted to assess the endpoint on the log10 scale. In the model, the visit (Baseline, Days 14, 84, 168 and 336) was included as fixed effect. An unstructured covariance matrix was used to model the within-participant error and Kenward-Roger approximation was employed to estimate the degrees of freedom.

[b]The 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. Raw data provided as >39020 have been imputed as 39020 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.1.2.2.

Neutralising Antibodies Against Delta

Table 9. Summary of IC50 in Neutralising Antibody Titres Against Delta (Immunogenicity Population)

		Adolescents (12-17 years old) (N=90)
Visit	**Statistics**	**Observed value**
Baseline	n	90
	Geometric mean	645.84
	Geometric SD	3.11
	Minimum	1.36
	Q1	2.52
	Median	2.89
	Q3	3.13
	Maximum	3.89
Day 14	n	88
	Geometric mean	9781.04
	Geometric SD	2.22
	Minimum	3.09
	Q1	3.78
	Median	4.00
	Q3	4.18
	Maximum	4.71
Day 84	n	88
	Geometric mean	5053.95
	Geometric SD	2.13
	Minimum	2.47
	Q1	3.48
	Median	3.74
	Q3	3.93
	Maximum	4.31
Day 168	n	89
	Geometric mean	2379.90
	Geometric SD	2.33
	Minimum	2.38
	Q1	3.16
	Median	3.40
	Q3	3.58
	Maximum	4.29
Day 336	n	88
	Geometric mean	1624.55
	Geometric SD	2.18
	Minimum	2.17
	Q1	3.00
	Median	3.19
	Q3	3.44
	Maximum	3.90

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. Raw data provided as >50848 have been imputed as 50848 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.1.1.2.

Table 10. Analysis of IC50 in Neutralising Antibody Titres Against Delta (Immunogenicity Population)

Visit	Adolescents (12-17 years old) (N=90)
Baseline	
Number of participants with data, n (%)	90 (100.0)
Adjusted mean (LS Mean)[a]	2.81
Standard error	0.05
95% CI	2.71, 2.91
Adjusted GMT[b]	645.84
95% CI	509.39, 818.84
Day 14	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.98
Standard error	0.04
95% CI	3.91, 4.06
Adjusted GMT[b]	9647.94
95% CI	8142.57, 11431.63
Day 84	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.70
Standard error	0.04
95% CI	3.63, 3.77
Adjusted GMT[b]	4954.91
95% CI	4215.25, 5824.36
Day 168	
Number of participants with data, n (%)	89 (98.9)
Adjusted mean (LS Mean)[a]	3.37
Standard error	0.04
95% CI	3.30, 3.45
Adjusted GMT[b]	2356.26
95% CI	1973.02, 2813.93
Day 336	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.20
Standard error	0.04
95% CI	3.13, 3.27
Adjusted GMT[b]	1581.98
95% CI	1339.10, 1868.91

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. (%) = Participants/N*100

[a]A Mixed-Effects Model for Repeated Measures was fitted to assess the endpoint on the log10 scale. In the model, the visit (Baseline, Days 14, 84, 168 and 336) was 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.
[b]The 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. Raw data provided as >50848 have been imputed as 50848 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.1.2.2.

Neutralising Antibodies Against D614G

Table 11. Summary of IC50 in Neutralising Antibody Titres Against D614G (Immunogenicity Population)

		Adolescents (12-17 years old) (N=90)
Visit	**Statistics**	**Observed value**
Baseline	n	90
	Geometric mean	747.63
	Geometric SD	2.62
	Minimum	1.89
	Q1	2.59
	Median	2.82
	Q3	3.19
	Maximum	3.85
Day 14	n	88
	Geometric mean	9831.03
	Geometric SD	2.11
	Minimum	2.70
	Q1	3.85
	Median	4.08
	Q3	4.25
	Maximum	4.31
Day 84	n	88
	Geometric mean	4370.50
	Geometric SD	2.27
	Minimum	2.56
	Q1	3.40
	Median	3.66
	Q3	3.91
	Maximum	4.31
Day 168	n	89
	Geometric mean	3330.14
	Geometric SD	2.13
	Minimum	2.55
	Q1	3.28
	Median	3.54
	Q3	3.73
	Maximum	4.25

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. Raw data provided as >20480 have been imputed as 20480 for the purposes of analysis. Transformations have been made on the imputed data. Source: Table 14.2.1.1.2.

Table 12. Analysis of IC50 in Neutralising Antibody Titres Against D614G (Immunogenicity Population)

Visit	Adolescents (12-17 years old) (N=90)
Baseline	
Number of participants with data, n (%)	90 (100.0)
Adjusted mean (LS Mean)[a]	2.87
Standard error	0.04
95% CI	2.79, 2.96
Adjusted GMT[b]	747.63
95% CI	611.04, 914.75
Day 14	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.99
Standard error	0.04
95% CI	3.92, 4.05
Adjusted GMT[b]	9673.68
95% CI	8256.10, 11334.66
Day 84	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.63
Standard error	0.04
95% CI	3.56, 3.71
Adjusted GMT[b]	4278.94
95% CI	3594.70, 5093.43
Day 168	
Number of participants with data, n (%)	89 (98.9)
Adjusted mean (LS Mean)[a]	3.52
Standard error	0.04
95% CI	3.45, 3.59
Adjusted GMT[b]	3306.79
95% CI	2821.33, 3875.78
Day 336	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	3.42
Standard error	0.03
95% CI	3.35, 3.48
Adjusted GMT[b]	2611.10
95% CI	2238.25, 3046.07

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. (%) = Participants/N*100
[a]A Mixed-Effects Model for Repeated Measures was fitted to assess the endpoint on the log10 scale. In the model, the visit (Baseline, Days 14, 84, 168 and 336) was 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.
[b]The 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. Raw data provided as >20480 have been imputed as 20480 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.1.2.2.

Geometric Mean Fold Rise in Neutralising Antibodies

Geometric Mean Fold Rise in Neutralising Antibodies Against Omicron BA.1

Table 13. Summary of Fold Rise in Neutralising Antibody Titres Against Omicron BA.1 (Immunogenicity Population)

Visit	Statistics	Adolescents (12-17 years old) (N=90)
Day 14	n	88
	Geometric mean	18.47
	Geometric SD	3.23
	Minimum	−0.02
	Q1	0.94
	Median	1.25
	Q3	1.59
	Maximum	2.37

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. Raw data provided as >49220 have been imputed as 49220 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.2.1.

Table 14. Analysis of GMFR in Neutralising Antibody Titres Against Omicron BA.1 (Immunogenicity Population)

	Adolescents (12-17 years old) (N=90)
Day 14	
Number of participants included in the analysis, n (%)	88 (97.8)
Fold rise group mean	1.27
Standard error	0.05
95% CI	1.16, 1.37
GMFR group mean[a]	18.47
95% CI	14.41, 23.69

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; N = number of participants in the population; n = number of participants included in the analysis. (%) = n/N*100
[a]The GMFR for group mean was estimated on the log10 scale and back-transformed.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Raw data provided as >49220 have been imputed as 49220 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.2.2.

Geometric Mean Fold Rise in Neutralising Antibodies Against Beta

Table 15. Summary of Fold Rise in Neutralising Antibody Titres Against Beta (Immunogenicity Population)

Visit	Statistics	Adolescents (12-17 years old) (N=90)
Day 14	n	88
	Geometric mean	9.11
	Geometric SD	2.86
	Minimum	0.03
	Q1	0.66
	Median	0.85
	Q3	1.21
	Maximum	2.12

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. Raw data provided as >39020 have been imputed as 39020 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.2.1.

Table 16. Analysis of GMFR in Neutralising Antibody Titres Against Beta (Immunogenicity Population)

	Adolescents (12-17 years old) (N=90)
Day 14	
Number of participants included in the analysis, n (%)	88 (97.8)
Fold rise group mean	0.96
Standard error	0.05
95% CI	0.86, 1.06
GMFR group mean[a]	9.11
95% CI	7.29, 11.38

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; N = number of participants in the population; n = number of participants included in the analysis. (%) = Participants/N*100
[a]The GMFR for group mean was estimated on the log10 scale and back-transformed.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Raw data provided as >39020 have been imputed as 39020 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.2.2.

Geometric Mean Fold Rise in Neutralising Antibodies Against Delta

Table 17. Summary of Fold Rise in Neutralising Antibody Titres Against Delta (Immunogenicity Population)

Visit	Statistics	Adolescents (12-17 years old) (N=90)
Day 14	n	88
	Geometric mean	14.24
	Geometric SD	3.26
	Minimum	0.09
	Q1	0.79
	Median	1.12
	Q3	1.53
	Maximum	2.76

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. Raw data provided as >50848 have been imputed as 50848 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.2.1.

Table 18. Analysis of GMFR in Neutralising Antibody Titres Against Delta (Immunogenicity Population)

	Adolescents (12-17 years old) (N=90)
Day 14	
Number of participants included in the analysis, n (%)	88 (97.8)
Fold rise group mean	1.15
Standard error	0.06
95% CI	1.05, 1.26
GMFR group mean[a]	14.24
95% CI	11.09, 18.29

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; N = number of participants in the population; n = number of participants included in the analysis. (%) = Participants/N*100
[a]The GMFR for group mean was estimated on the log10 scale and back-transformed.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Raw data provided as >50848 have been imputed as 50848 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.2.2.

Geometric Mean Fold Rise in Neutralising Antibodies Against D614G

Table 19. Summary of Fold Rise in Neutralising Antibody Titres Against D614G (Immunogenicity Population)

Visit	Statistics	Adolescents (12-17 years old) (N=90)
Day 14	n	88
	Geometric mean	12.75
	Geometric SD	2.77
	Minimum	−0.145
	Q1	0.83
	Median	1.13
	Q3	1.37
	Maximum	2.42

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. Raw data provided as >20480 have been imputed as 20480 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.2.1.

Table 20. Analysis of GMFR in Neutralising Antibody Titres Against D614G (Immunogenicity Population)

	Adolescents (12-17 years old) (N=90)
Day 14	
Number of participants included in the analysis, n (%)	88 (97.8)
Fold rise group mean	1.11
Standard error	0.05
95% CI	1.01, 1.20
GMFR group mean[a]	12.75
95% CI	10.27, 15.81

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; N = number of participants in the population; n = number of participants included in the analysis. (%) = Participants/N*100
[a]The GMFR for group mean was estimated on the log10 scale and back-transformed.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Raw data provided as >20480 have been imputed as 20480 for the purposes of analysis. Transformations have been made on the imputed data.
Source: Table 14.2.2.2.

Binding Antibody Titres

Table 21. Summary of Binding Antibody Titres (Immunogenicity Population)

		Adolescents (12-17 years old) (N=90)
Visit	**Statistics**	**Observed value**
Baseline	n	89
	Geometric mean	7714.55
	Geometric SD	2.87
	Minimum	2.20
	Q1	3.64
	Median	3.97
	Q3	4.18
	Maximum	4.71
Day 14	n	88
	Geometric mean	98038.63
	Geometric SD	1.88
	Minimum	4.27
	Q1	4.83
	Median	5.05
	Q3	5.20
	Maximum	5.35
Day 84	n	88
	Geometric mean	71169.43
	Geometric SD	1.97
	Minimum	3.97
	Q1	4.70
	Median	4.85
	Q3	5.08
	Maximum	5.35
Day 168	n	89
	Geometric mean	47943.53
	Geometric SD	1.94
	Minimum	3.80
	Q1	4.53
	Median	4.68
	Q3	4.87
	Maximum	5.32
Day 336	n	87
	Geometric mean	32713.52
	Geometric SD	1.99
	Minimum	3.64
	Q1	4.35
	Median	4.50
	Q3	4.75
	Maximum	5.23

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. Raw data provided as >225000 have been imputed as 225000 for the purposes of analysis for binding antibodies.
Transformations have been made on the imputed data.
Source: Table 14.2.3.1.

Table 22. Analysis of Binding Antibody Titres (Immunogenicity Population)

Visit	Adolescents (12-17 years old) (N=90)
Baseline	
Number of participants with data, n (%)	89 (98.9)
Adjusted mean (LS Mean)[a]	3.89
Standard error	0.05
95% CI	3.79, 3.98
Adjusted GMT[b]	7676.04
95% CI	6173.31, 9544.57
Day 14	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	4.99
Standard error	0.03
95% CI	4.93, 5.05
Adjusted GMT[b]	96994.65
95% CI	84107.10, 111856.93
Day 84	
Number of participants with data, n (%)	88 (97.8)
Adjusted mean (LS Mean)[a]	4.85
Standard error	0.03
95% CI	4.79, 4.91
Adjusted GMT[b]	70399.62
95% CI	61203.57, 80977.41
Day 168	
Number of participants with data, n (%)	89 (98.9)
Adjusted mean (LS Mean)[a]	4.68
Standard error	0.03
95% CI	4.62, 4.74
Adjusted GMT[b]	47547.67
95% CI	41344.10, 54682.06

Visit	Adolescents (12-17 years old) (N=90)
Day 336	
Number of participants with data, n (%)	87 (96.7)
Adjusted mean (LS Mean)[a]	4.51
Standard error	0.03
95% CI	4.45, 4.57
Adjusted GMT[b]	32522.89
95% CI	28202.58, 37505.04

Abbreviations: CI = confidence interval; GMT = geometric mean titre; N = number of participants in the population; n = number of participants with data. (%) = Participants/N*100
[a]A Mixed-Effects Model for Repeated Measures was fitted to assess the endpoint on the log10 scale. In each model, the visit (Baseline, Day 14, 84, 168 and 336) was 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.
[b]The GMT for means was 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. Raw data provided as >225000 have been imputed as 225000 for the purposes of analysis for binding antibodies. Transformations have been made on the imputed data.
Source: Table 14.2.3.2.

Geometric Mean Fold Rise in Binding Antibody Titres

Table 23. Summary of Fold Rise in Binding Antibody Titres (Immunogenicity Population)

Visit	Statistics	Adolescents (12-17 years old) (N=90)
Day 14	n	87
	Geometric mean	12.39
	Geometric SD	3.01
	Minimum	0.05
	Q1	0.75
	Median	1.08
	Q3	1.33
	Maximum	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. Raw data provided as >225000 have been imputed as 225000 for the purposes of analysis for binding antibodies.
Transformations have been made on the imputed data.
Source: Table 14.2.4.1.

Table 24. Analysis of GMFR in Binding Antibody Titres (Immunogenicity Population)

	Adolescents (12-17 years old) (N=90)
Day 14	
Number of participants included in the analysis, n (%)	87 (96.7)
Fold rise group mean	1.09
Standard error	0.05
95% CI	0.99, 1.20
GMFR group mean[a]	12.39
95% CI	9.80, 15.67

Abbreviations: N = number of participants in the population; n = number of participants with data; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation. (%) = Participants/N*100
[a]The GMFR for group mean was estimated on the log10 scale and back-transformed.
Raw data provided as <0.4 have been imputed as 0.4 for the purposes of analysis. Raw data provided as >225000 have been imputed as 225000 for the purposes of analysis for binding antibodies. Transformations have been made on the imputed data.
Source: Table 14.2.4.2.

Fold Change Analysis in Binding Antibodies

The percentage of individuals that achieved ≥4-fold change in binding antibody titres from Baseline to Days 14, 84, 168 and 336, after a BIMERVAX booster dose are presented in Table 25.

Table 25. Analysis of Fold Change in Binding Antibody Titres (Immunogenicity Population)

	Adolescents (12-17 years old) (N=90)
Day 14	
Number of participants included in the analysis, n (%)	87 (96.7)
Number of participants with ≥ 4-fold change from baseline, n (%)[a]	73 (83.9)
95% CI[b]	74.5, 90.9
Adjusted odds (Back-transformed LS Mean)[c]	5.31
Standard error (log scale)	0.30
95% CI	2.98, 9.46
Day 84	
Number of participants included in the analysis, n (%)	87 (96.7)
Number of participants with ≥ 4-fold change from baseline, n (%)[a]	68 (78.2)
95% CI[b]	68.0, 86.3
Adjusted odds (Back-transformed LS Mean)[c]	3.70
Standard error (log scale)	0.26
95% CI	2.22, 6.18
Day 168	
Number of participants included in the analysis, n (%)	88 (97.8)
Number of participants with ≥ 4-fold change from baseline, n (%)[a]	58 (65.9)
95% CI[b]	55.0, 75.7
Adjusted odds (Back-transformed LS Mean)[c]	1.97
Standard error (log scale)	0.23
95% CI	1.27, 3.07

	Adolescents (12-17 years old) (N=90)
Day 336	
Number of participants included in the analysis, n (%)	86 (95.6)
Number of participants with ≥ 4-fold change from baseline, n (%)[a]	40 (46.5)
95% CI[b]	35.7, 57.6
Adjusted odds (Back-transformed LS Mean)[c]	0.85
Standard error (log scale)	0.22
95% CI	0.55, 1.31

Abbreviations: CI = confidence interval; LS mean = least square mean; N = number of participants in the population; n = number of participants meeting the criterion. (%) = Participants/N*100
[a]% = n / number of participants in the analysis. Fold rise is calculated as post-baseline titre/baseline titre.
[b]Exact CI for the proportion of participants with ≥ 4-fold change from baseline has been calculated using the Clopper-Pearson method.
[c]A generalised estimating equations model for repeated measures was fitted to assess the endpoint. The model assumed a binomial family with logit link and employed an unstructured covariance matrix. The odds were estimated using the LS Means from the fitted model and back-transformed.
Source: Table 14.2.5.

Cellular immunity

Table 26. Descriptive and paired t-test contrast summary of T-cell response by IFN-γ ELISpot after RBD Beta and RBD Omicron BA.1 stimulation

Visit	Statistics	RBD Beta (N=16)	RBD Omicron BA.1 (N=16)
Baseline	Number of subjects with data	16	16
	Mean	61.693	55.977
	Standard deviation	59.734	46.086
	Minimum	2.500	2.500
	Q1	33.438	18.750
	Median	42.500	48.750
	Q3	57.500	66.875
	Maximum	215.000	160.000
Day 14	Number of subjects with data	16	16
	Mean	402.734	339.609
	Standard deviation	217.147	190.831
	Minimum	87.500	90.000
	Q1	233.438	185.938
	Median	382.500	308.125
	Q3	559.375	475.938
	Maximum	777.500	681.250
Difference Day 14 - Baseline	Number of subjects with data	16	16
	Mean difference	12.2257	10.8481
	95% CI	9.9784 ; 14.4731	8.8179 ; 12.8782
	p-value	<0.0001	<0.0001

Safety results

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 were also included in the final CSR. All laboratory data from Baseline and Day 14 including pregnancy test results were 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 were 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 after vaccination with Bimervax. Each participant was to be followed for 12 months after the administration of the booster vaccination on Day 0. The mean study duration for participants in the SP was 11.00 months (range: 4.04-12.48).

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 17 years is presented in Table 27.

Table 27. Overall safety of Bimervax in adolescents (Study HIPRA-HH-3, Safety Population)

	Adolescents (12-17 years old) (N=240)	
	Events	**Participants (%)**
Total number of TEAEs	871	206 (85.8)
Total number of serious TEAEs	0	0
Total number of participants with TEAEs leading to death		0
TEAE intensity[a]		
Grade 1	737	150 (62.5)
Grade 2	115	48 (20.0)
Grade 3	19	8 (3.3)
Relationship to study treatment[a]		
Unrelated[b]	121	8 (3.3)
Related[c]	750	198 (82.5)
Maximum intensity of solicited local reactions and solicited systemic events[a]	781	200 (83.3)
Grade 1	653	146 (60.8)
Grade 2	109	46 (19.2)
Grade 3	19	8 (3.3)
Relationship of solicited local reactions and solicited systemic events to study treatment[a]	781	200 (83.3)
Unrelated[b]	37	2 (0.8)
Related[c]	744	198 (82.5)
Maximum intensity of solicited systemic events[a]	421	136 (56.7)
Grade 1	347	102 (42.5)
Grade 2	62	28 (11.7)
Grade 3	12	6 (2.5)
Relationship of solicited systemic events to study treatment[a]	421	136 (56.7)
Unrelated[b]	36	6 (2.5)
Related[c]	385	130 (54.2)
Maximum intensity of solicited local reactions[a]	360	192 (80.0)
Grade 1	306	157 (65.4)
Grade 2	47	31 (12.9)
Grade 3	7	4 (1.7)
Relationship of solicited local reactions to study treatment[a]	360	192 (80.0)
Unrelated[b]	1	0
Related[c]	359	192 (80.0)
Maximum intensity of unsolicited adverse events[a]	90	60 (25.0)
Grade 1	84	54 (22.5)
Grade 2	6	6 (2.5)
Relationship of unsolicited adverse events to study treatment[a]	90	60 (25.0)
Unrelated[b]	84	54 (22.5)
Related[c]	6	6 (2.5)
Maximum intensity of treatment-emergent MAAEs[a]	23	20 (8.3)
Grade 1	20	17 (7.1)
Grade 2	3	3 (1.3)
Relationship of treatment-emergent MAAEs to study treatment[a]	23	20 (8.3)
Unrelated[b]	23	20 (8.3)

TEAEs reported by MedDRA SOC and PT are presented in Table 28.

Table 28. TEAEs by SOCs and PTs – Study HH-3 (Safety Population)

	Adolescents (12-17 years old) (N=240)	
System organ class Preferred term	**Events**	**Participants (%)**
Total number of TEAEs	871	206 (85.8)
General disorders and administration site conditions	560	195 (81.3)
Injection site pain	313	187 (77.9)
Fatigue	82	73 (30.4)
Malaise	74	67 (27.9)
Axillary pain	29	28 (11.7)
Injection site induration	26	26 (10.8)
Injection site erythema	19	18 (7.5)
Pyrexia	9	9 (3.8)
Discomfort	3	3 (1.3)
Vessel puncture site pain	2	2 (0.8)
Asthenia	1	1 (0.4)
Injection site swelling	1	1 (0.4)
Secretion discharge	1	1 (0.4)
Nervous system disorders	98	79 (32.9)
Headache	92	77 (32.1)
Presyncope	2	2 (0.8)
Syncope	2	2 (0.8)
Dizziness	1	1 (0.4)
Migraine	1	1 (0.4)

	Adolescents (12-17 years old) (N=240)	
System organ class Preferred term	**Events**	**Participants (%)**
Musculoskeletal and connective tissue disorders	81	52 (21.7)
Myalgia	41	39 (16.3)
Arthralgia	38	35 (14.6)
Pain in extremity	1	1 (0.4)
Synovial cyst	1	1 (0.4)
Gastrointestinal disorders	44	33 (13.8)
Diarrhoea	21	18 (7.5)
Vomiting	14	14 (5.8)
Nausea	6	6 (2.5)
Odynophagia	2	2 (0.8)
Abdominal pain	1	1 (0.4)
Infections and infestations	24	23 (9.6)
Pharyngitis	5	5 (2.1)
Nasopharyngitis	3	3 (1.3)
Viral infection	3	3 (1.3)
Upper respiratory tract infection	2	2 (0.8)
Bronchitis	1	1 (0.4)
Chlamydial infection	1	1 (0.4)
Conjunctivitis	1	1 (0.4)
Gastroenteritis	1	1 (0.4)
Otitis externa	1	1 (0.4)
Pharyngotonsillitis	1	1 (0.4)
Pneumonia	1	1 (0.4)
Postoperative wound infection	1	1 (0.4)
Pustule	1	1 (0.4)
Rhinitis	1	1 (0.4)
Tonsillitis bacterial	1	1 (0.4)
Blood and lymphatic system disorders	24	21 (8.8)
Lymphadenopathy	20	19 (7.9)
Anaemia	1	1 (0.4)
Mesenteric lymphadenitis	1	1 (0.4)
Neutropenia	1	1 (0.4)
Splenomegaly	1	1 (0.4)
Respiratory, thoracic and mediastinal disorders	13	13 (5.4)
Cough	5	5 (2.1)
Bronchospasm	3	3 (1.3)
Oropharyngeal pain	2	2 (0.8)
Asthma	1	1 (0.4)
Epistaxis	1	1 (0.4)
Rhinitis allergic	1	1 (0.4)
Reproductive system and breast disorders	7	6 (2.5)

	Adolescents (12-17 years old) (N=240)	
System organ class **Preferred term**	**Events**	**Participants (%)**
Premenstrual pain	5	5 (2.1)
Intermenstrual bleeding	1	1 (0.4)
Menstruation irregular	1	1 (0.4)
Investigations	5	5 (2.1)
Blood bilirubin increased	4	4 (1.7)
Neutrophil count increased	1	1 (0.4)
Congenital, familial and genetic disorders	4	4 (1.7)
Gilberts syndrome	3	3 (1.3)
Congenital scoliosis	1	1 (0.4)
Injury, poisoning and procedural complications	3	3 (1.3)
Ligament sprain	2	2 (0.8)
Craniocerebral injury	1	1 (0.4)
Psychiatric disorders	3	3 (1.3)
Anxiety	1	1 (0.4)
Initial insomnia	1	1 (0.4)
Insomnia	1	1 (0.4)
Skin and subcutaneous tissue disorders	3	3 (1.3)
Erythema	1	1 (0.4)
Hyperhidrosis	1	1 (0.4)
Rash	1	1 (0.4)
Ear and labyrinth disorders	1	1 (0.4)
Ear pain	1	1 (0.4)
Social circumstances	1	1 (0.4)
Menarche	1	1 (0.4)

Solicited adverse events

Solicited Systemic Events by time

Table 29. Summary of Solicited Systemic Events from Day 0 Through Day 7 (Safety Population)

		Adolescents (12-17 years old) (N=240)	
Timepoint	**Events**	**Events**	**Participants (%)**
Cumulative events from Day 0 to Day 7	Total number of events	382	136 (56.7)
	Malaise	70	70 (29.2)
	Fatigue	73	73 (30.4)
	Headache	77	77 (32.1)
	Muscle pain	39	39 (16.3)
	Joint pain	35	35 (14.6)
	Axillary pain	27	27 (11.3)
	Enlarged lymph nodes (lymphadenopathy)	18	18 (7.5)
	Nausea/vomiting	18	18 (7.5)
	Fever	8	8 (3.3)
	Diarrhoea	17	17 (7.1)
Day 0	Total number of events	176	80 (33.3)
	Malaise	35	35 (14.6)
	Fatigue	32	32 (13.3)
	Headache	31	31 (12.9)
	Muscle pain	25	25 (10.4)
	Joint pain	21	21 (8.8)
	Axillary pain	11	11 (4.6)
	Enlarged lymph nodes (lymphadenopathy)	7	7 (2.9)
	Nausea/vomiting	7	7 (2.9)
	Fever	4	4 (1.7)
	Diarrhoea	3	3 (1.3)
Day 1	Total number of events	244	105 (43.8)
	Malaise	48	48 (20.0)
	Fatigue	49	49 (20.4)
	Headache	47	47 (19.6)
	Muscle pain	31	31 (12.9)
	Joint pain	25	25 (10.4)
	Axillary pain	17	17 (7.1)
	Enlarged lymph nodes (lymphadenopathy)	12	12 (5.0)
	Nausea/vomiting	8	8 (3.3)
	Fever	4	4 (1.7)
	Diarrhoea	3	3 (1.3)

		Adolescents (12-17 years old) (N=240)	
Timepoint	**Events**	**Events**	**Participants (%)**
Day 2	Total number of events	139	65 (27.1)
	Malaise	22	22 (9.2)
	Fatigue	26	26 (10.8)
	Headache	30	30 (12.5)
	Muscle pain	17	17 (7.1)
	Joint pain	9	9 (3.8)
	Axillary pain	16	16 (6.7)
	Enlarged lymph nodes (lymphadenopathy)	8	8 (3.3)
	Nausea/vomiting	4	4 (1.7)
	Fever	1	1 (0.4)
	Diarrhoea	6	6 (2.5)
Day 3	Total number of events	59	34 (14.2)
	Malaise	8	8 (3.3)
	Fatigue	12	12 (5.0)
	Headache	14	14 (5.8)
	Muscle pain	2	2 (0.8)
	Joint pain	3	3 (1.3)
	Axillary pain	9	9 (3.8)
	Enlarged lymph nodes (lymphadenopathy)	6	6 (2.5)
	Nausea/vomiting	1	1 (0.4)
	Fever	0	0
	Diarrhoea	4	4 (1.7)
Day 4	Total number of events	39	23 (9.6)
	Malaise	9	9 (3.8)
	Fatigue	5	5 (2.1)
	Headache	10	10 (4.2)
	Muscle pain	1	1 (0.4)
	Joint pain	1	1 (0.4)
	Axillary pain	2	2 (0.8)
	Enlarged lymph nodes (lymphadenopathy)	5	5 (2.1)
	Nausea/vomiting	1	1 (0.4)
	Fever	0	0
	Diarrhoea	5	5 (2.1)

		Adolescents (12-17 years old) (N=240)	
Timepoint	**Events**	**Events**	**Participants (%)**
Day 5	Total number of events	47	24 (10.0)
	Malaise	10	10 (4.2)
	Fatigue	6	6 (2.5)
	Headache	13	13 (5.4)
	Muscle pain	3	3 (1.3)
	Joint pain	1	1 (0.4)
	Axillary pain	0	0
	Enlarged lymph nodes (lymphadenopathy)	5	5 (2.1)
	Nausea/vomiting	4	4 (1.7)
	Fever	0	0
	Diarrhoea	5	5 (2.1)
Day 6	Total number of events	36	20 (8.3)
	Malaise	6	6 (2.5)
	Fatigue	7	7 (2.9)
	Headache	8	8 (3.3)
	Muscle pain	2	2 (0.8)
	Joint pain	2	2 (0.8)
	Axillary pain	0	0
	Enlarged lymph nodes (lymphadenopathy)	3	3 (1.3)
	Nausea/vomiting	1	1 (0.4)
	Fever	2	2 (0.8)
	Diarrhoea	5	5 (2.1)
Day 7	Total number of events	31	17 (7.1)
	Malaise	3	3 (1.3)
	Fatigue	4	4 (1.7)
	Headache	10	10 (4.2)
	Muscle pain	1	1 (0.4)
	Joint pain	1	1 (0.4)
	Axillary pain	0	0
	Enlarged lymph nodes (lymphadenopathy)	3	3 (1.3)
	Nausea/vomiting	2	2 (0.8)
	Fever	1	1 (0.4)
	Diarrhoea	6	6 (2.5)

Solicited Local Reactions by time

Table 30. Summary of Solicited Local Reactions from Day 0 through Day 7 (Safety Population)

		Adolescents (12-17 years old) (N=240)	
Timepoint	**Events**	**Events**	**Participants (%)**
Cumulative events from Day 0 to Day 7	Total number of events	357	192 (80.0)
	Pain	177	177 (73.8)
	Tenderness	134	134 (55.8)
	Induration/swelling	27	27 (11.3)
	Erythema/redness	19	19 (7.9)
Day 0	Total number of events	285	161 (67.1)
	Pain	142	142 (59.2)
	Tenderness	117	117 (48.8)
	Induration/swelling	19	19 (7.9)
	Erythema/redness	7	7 (2.9)
Day 1	Total number of events	284	162 (67.5)
	Pain	146	146 (60.8)
	Tenderness	105	105 (43.8)
	Induration/swelling	18	18 (7.5)
	Erythema/redness	15	15 (6.3)
Day 2	Total number of events	115	73 (30.4)
	Pain	51	51 (21.3)
	Tenderness	48	48 (20.0)
	Induration/swelling	11	11 (4.6)
	Erythema/redness	5	5 (2.1)
Day 3	Total number of events	43	29 (12.1)
	Pain	18	18 (7.5)
	Tenderness	19	19 (7.9)
	Induration/swelling	4	4 (1.7)
	Erythema/redness	2	2 (0.8)
Day 4	Total number of events	18	12 (5.0)
	Pain	7	7 (2.9)
	Tenderness	8	8 (3.3)
	Induration/swelling	2	2 (0.8)
	Erythema/redness	1	1 (0.4)
Day 5	Total number of events	10	5 (2.1)
	Pain	3	3 (1.3)
	Tenderness	5	5 (2.1)
	Induration/swelling	1	1 (0.4)

		Adolescents (12-17 years old) (N=240)	
Timepoint	**Events**	**Events**	**Participants (%)**
	Erythema/redness	1	1 (0.4)
Day 6	Total number of events	11	5 (2.1)
	Pain	3	3 (1.3)
	Tenderness	5	5 (2.1)
	Induration/swelling	1	1 (0.4)
	Erythema/redness	2	2 (0.8)
Day 7	Total number of events	5	4 (1.7)
	Pain	2	2 (0.8)
	Tenderness	3	3 (1.3)
	Induration/swelling	0	0
	Erythema/redness	0	0

Unsolicited Adverse Events

Table 31. Unsolicited AEs – Study HIPRA-HH-3 (Safety Population)

	Adolescents (12-17 years old) (N=240)	
Unsolicited Adverse Event	**Events**	**Participants (%)**
Total number of events	90	60 (25.0)
Cough	5	5 (2.1)
Dysmenorrhoea	5	5 (2.1)
Pharyngitis	5	5 (2.1)
Blood bilirubin increased	4	4 (1.7)
Bronchospasm	3	3 (1.3)
Gilbert's syndrome	3	3 (1.3)
Nasopharyngitis	3	3 (1.3)
Viral infection	3	3 (1.3)
Ligament sprain	2	2 (0.8)
Lymphadenopathy	2	2 (0.8)
Odynophagia	2	2 (0.8)
Oropharyngeal pain	2	2 (0.8)
Presyncope	2	2 (0.8)

Syncope	2	2 (0.8)
Upper respiratory tract infection	2	2 (0.8)
Vessel puncture site pain	2	2 (0.8)
Vomiting	2	2 (0.8)
Abdominal pain	1	1 (0.4)
Anaemia	1	1 (0.4)
Anxiety	1	1 (0.4)
Arthralgia	1	1 (0.4)
Asthenia	1	1 (0.4)
Asthma	1	1 (0.4)
Axillary pain	1	1 (0.4)
Bronchitis	1	1 (0.4)
Chlamydial infection	1	1 (0.4)
Congenital scoliosis	1	1 (0.4)
Conjunctivitis	1	1 (0.4)
Craniocerebral injury	1	1 (0.4)
Diarrhoea	1	1 (0.4)
Dizziness	1	1 (0.4)
Ear pain	1	1 (0.4)
Epistaxis	1	1 (0.4)
Gastroenteritis	1	1 (0.4)
Hyperhidrosis	1	1 (0.4)
Initial insomnia	1	1 (0.4)
Insomnia	1	1 (0.4)
Intermenstrual bleeding	1	1 (0.4)
Menarche	1	1 (0.4)
Menstruation irregular	1	1 (0.4)
Mesenteric lymphadenitis	1	1 (0.4)
Migraine	1	1 (0.4)
Neutropenia	1	1 (0.4)
Neutrophil count increased	1	1 (0.4)

	Adolescents (12-17 years old) (N=240)	
Unsolicited Adverse Event	**Events**	**Participants (%)**
Otitis externa	1	1 (0.4)
Pain in extremity	1	1 (0.4)
Pharyngotonsillitis	1	1 (0.4)
Pneumonia	1	1 (0.4)
Postoperative wound infection	1	1 (0.4)
Pustule	1	1 (0.4)
Pyrexia	1	1 (0.4)
Rash	1	1 (0.4)
Rhinitis	1	1 (0.4)
Rhinitis allergic	1	1 (0.4)
Secretion discharge	1	1 (0.4)
Splenomegaly	1	1 (0.4)
Synovial cyst	1	1 (0.4)
Tonsillitis bacterial	1	1 (0.4)

Serious adverse event/deaths/other significant events/AESIs

Deaths

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 (0.4%) 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 study.

Medically Attended Adverse Events (MAAEs)

No related MAAEs were reported during the study.

For the total safety population of study HH-3 (i.e. 12 to <18 years of age), there were 171 MAAEs in 88 (36.7%) participants which were deemed unrelated to the study drug. Of these, 150 events occurred in 72 (30.0%) participants which were Grade 1 in intensity and 21 events occurred in 16 (6.7%) participants which were Grade 2 in intensity.

COVID-19 infections

In the mITT population, 3 (1.3%) participants were reported to have microbiologically confirmed COVID-19 infections ≥14 days after study treatment administration throughout the study duration, occurring approximately 10 months after vaccination. No severe COVID-19 cases were reported.

MIS-C cases as per the WHO criteria

No participant reported to have MIS-C as per the WHO criteria.

Laboratory findings

Haematology

Among the 240 participants in the SP, Grade 2, 3 or 4 changes from Baseline for haematology parameters were observed for 1 participant on Day 14, specifically a 2-grade increase in haemoglobin compared to Baseline.

A participant had a grade 2 change in haemoglobin level as per CTCAE v5.0 classification (CTCAE term: Anemia). His baseline haemoglobin level was 105 g/L (normal range: 100-135 g/L), which decreased to 98 g/L at Day 14 (Grade 2 range, according to CTCAE: 80-100 g/dL). This event was considered not clinically significant by the PI and was not reported as an AE.

There were no Grade 3 and 4 haematology changes in this study.

Clinical chemistry

Among the 240 participants in the SP, Grade 2, 3 or 4 changes from Baseline for biochemistry parameters were observed for 1 participant on Day 14, specifically a 2-grade increase in glucose compared to Baseline.

A participant had a grade 2 change in glucose level as per CTCAE v5.0 classification (CTCAE term: Hypoglycemia). Her baseline glucose level was 4.66 mmol/L (normal range: 3.89-6.11 mmol/L), which decreased to 2.78 mmol/L at Day 14 (Grade 2 range, according to CTCAE: 2.2-3.0 mmol/L). This event was considered not clinically significant by the PI and was not reported as an AE.

There were no Grade 3 and 4 biochemistry changes in this study.

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

Four participants reported abnormal but not clinically significant physical examination findings at Day 14, and 2 participants at Day 84.

Discontinuation due to adverse events

There was no discontinuation due to AEs from HIPRA-HH-3.

2.3.3. Discussion on clinical aspects

2.3.3.1. Clinical efficacy

Design and conduct of clinical studies

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 completed, the first participant was enrolled on June 8th 2023, the date of final study report serving as the basis of the present submission was 22nd January 2026. The final study report presents Day 14-366 immunogenicity data of all enrolled participants in the Immunogenicity data set, and safety findings through Day 366 of participants in the safety population (refer to safety

section). 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 90 (37.5% 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 had justified the reduced sample size during the previous VR/257408 variation procedure. Study participants received their dose at least 6 months after primary vaccination with Comirnaty. This interval is considered acceptable as it is the approved BIMERVAX posology.

Objectives and endpoints

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, and as it was concluded in the previous VR/257408 procedure, the primary immunogenicity objective of the study was 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 was misleading as the trial did 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 could 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.

As exploratory endpoints, 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 were provided in the final CSR.

Efficacy data and additional analyses

Protocol deviations

The MAH provided the list of protocol deviations (minor and major issues) known during Study HH-3. Half (7 of 14) of major protocol deviations (MPDs) resulted from the collection of blood samples for immunogenicity analyses from participants not assigned to the immunogenicity cohort. Two 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. Two more patients received vaccines which had been subject to temperature deviations prior to administration. In such case, the CRO or the sponsor should have been contacted in order to decide whether or not the vaccines in question could be used for immunisation, however in case of the above two patients, CRO or sponsor was not informed. 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 was investigated in a considerably limited subset of approximately 10% of the IGP and thus it is not very informative.

As it was discussed in details during the assessment and in the CHMP AR of procedure VR/257408, the most critical issue was the remarkable difference between baseline titre values for 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*) between adolescent group of Study HH-3 and young adults external control from Study HH-2, which hampered the comparison of GMT and also GMFR results. Saturation effect observed during the PBNA assays as well as the lack of predefined success criteria for GMFR change from baseline brought further uncertainties in the B/R decision. Despite all the above, these results did not challenge the result that adolescents experienced substantial increases in titre levels compared to baseline measurements.

In the present submission, the Applicant provided the final results of Study HIPRA-HH-3. Besides the D14 binding and neutralising immune responses, longer term immunogenicity data were provided.

Regarding the durability of the humoral immune response against Omicron BA.1, a progressive decline in neutralising antibody titres was observed over time (Days 84, 168 and 336 post-vaccination). However, levels remained above Baseline throughout the follow-up period. At Day 336, the GMT [95% CI] was 3371.72 [2816.89, 4035.85] compared to 1271.52 [992.69, 1628.67] at Baseline, suggesting persistence of the immune response throughout the follow-up period.

Immunogenicity against Beta, Delta, and D614G variants was evaluated at Baseline and at Days 14, 84, 168 and 336 after Bimervax vaccination. At Day 14, a substantial increase in the GMT [95% CI] for adjusted group mean was observed for all variants, indicating a remarkable initial humoral response. Over subsequent study timepoints, adjusted GMT [95% CI] declined progressively at Days 84, 168 and 336, consistent with the expected gradual decrease of neutralising antibody levels over time. However, titres remained above Baseline values across all variants at Day 336, suggesting persistence of the immune response throughout the follow-up period.

Cellular immune response, measured by means of ELISpot and ICS, was assessed at Baseline and Day 14 after Bimervax vaccination on a small subset of 16 subjects from the IGP. This makes the

conclusion on cellular immune response very uncertain. It can only conclude that some T-cell immune response occurred after immunisation with Bimervax most likely.

2.3.3.2. Clinical safety

HIPRA-HH-3 is a completed 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, and was conducted in 7 centres in Spain and completed. This submission is based on the final CSR released on 22nd January 2025. The respective final 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 recorded through the study duration.

In total 240 participants were followed for a mean duration of 11.00 months (range: 4.04-12.48; median age 15 years, maximum age 17 years) after vaccination with Bimervax, but n=300 subjects were planned to be enrolled. In the previous paediatric indication extension procedure VR/257408 the MAH justified 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) was considered to be sufficient to support an extension of indication to individuals 12 to <16 years of age.

It was also critically noted in procedure VR/257408 that interpretation of data is compromised as no internal control was included in the study. For contextualisation, the safety profile reported in procedure VR/257408 was compared to the available data as reported in the EPAR of Bimervax (in subjects ≥16 years). Still, this approach left considerable uncertainty.

As for overall safety of Bimervax in adolescent population of Study HH-3, the majority (85.8% for the total population) 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 Study HH-3. The majority of TEAEs were considered to be related to study treatment. AESIs have not been observed during the study HH-3. Discontinuation due to AEs have not occurred either. Overall, 172 MAAEs were reported in 88 (36.7%) participants. The most frequently reported MAAEs belonged to the Infections and Infestations SOC and Injury, Poisoning and Procedural Complications SOC.

Summary of Treatment-related Emergent Adverse Events by MeDRA System Organ Class and Preferred Term was not provided, relationship data were provided for SAEs only. Upon request, Applicant provided the tabulated summary of treatment related Emergent Adverse Events by MeDRA SOC and PT. Majority of treatment related AEs corresponds to solicited local reactions or solicited systemic AEs, as it is expected for a vaccine. No changes can be found in the frequencies and the reported PTs compared to the interim analysis of Study HIPRA-HH-3, submitted in the previous VR/257408 variation procedure.

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. Since they represent solicited AEs for the majority of cases, frequency data for the 12-16 year age range provided during the previous VR/257408 procedure are also presented here for totality's sake.

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 (16.3% 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.

As for AE intensity, 19 Grade 3 events were reported in 3.3% of subjects, all were solicited reactions (n=7 local and n=12 systemic).

Of the 871 TEAEs listed by the MAH, 781 events were solicited local or solicited systemic events and 90 were unsolicited AEs.

A total of 23 treatment-emergent MAAEs, all considered unrelated to the vaccine administration, were reported in 20 (8.3%) participants. Of these, 20 MAAEs were reported as Grade 1 intensity in 17 (7.1%) participants and 3 MAAEs were reported as Grade 2 intensity in 3 (1.3%) participants. No Grade 3 or Grade 4 MAAEs were reported.

Frequencies and time course of solicited systemic and local AEs seems to be similar to those provided during procedure VR/257408. Clarification on inconsistencies between event numbers of solicited local and systemic reactions in Table 27, (overall safety) and in Table 29 and Table 30 (tables presenting the time course of solicited local and systemic AEs, respectively) was requested. These inconsistencies were based on the differences in data sources and counting methodologies applied in the respective tables.

Most PTs within the **unsolicited AEs** by PT were experienced by one or two participants. Unsolicited AEs were lead by Cough, Pharyngitis, Dysmenorrhoea (2.1% each), Blood bilirubin increased (1.7%), Nasopharyngitis, Viral infection, Bronchospasm and Gilbert syndrome (1.3% each) AEs.

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.

There was no other **serious AEs** than the two SAEs have already been reported in the interim analysis (appendicitis and knee operation), and 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 36.7% of paediatric subjects (172 MAAEs in 88 subjects of the total population, one of them a back pain PT was erroneously assigned as related). Of the 171 unrelated MAAEs, 150 events occurred in 72 (30.0%) participants which were Grade 1 in intensity and 21 events occurred in 16 (6.7%) participants which were Grade 2 in intensity. No Grade 3 or Grade 4 MAAEs were reported.

The most frequently reported MAAEs belonged to the Infections and Infestations SOC (22.9% of the total population), the most common event within this SOC was bronchitis (3.8% of the total population). Other frequently reported MAAEs belonged to Injury, Poisoning and Procedural Complications SOC (8.8% of the total population) with ligament sprain (2.9% of the total population) as the most frequent event within this SOC. All MAAEs have recovered/resolved during the study 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 36.7%, respectively).

In the mITT population, 3 (1.3%) participants were reported to have microbiologically confirmed COVID-19 infections ≥14 days after study treatment administration throughout the study duration, occurring approximately 10 months after vaccination. No severe COVID-19 cases were reported.

In conclusion, no new safety concern seems apparent for the vaccination of adolescent subjects with Bimervax.

3. CHMP overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Frequencies and time course of solicited systemic and local AEs seems to be similar to those provided during procedure VR/257408. However, event numbers of solicited local and systemic reactions seem to be different in Table 27, where the overall safety is presented and in Table 29 and Table 30 where the time course of solicited local and systemic AEs are presented. Applicant is asked to clarify and provide corrected solicited AE number data, if necessary.
2. Summary of Treatment-related Emergent Adverse Events by MeDRA System Organ Class and Preferred Term was not provided, relationship data were provided for SAEs only. Applicant is asked to submit tabulated summary of treatment related Emergent Adverse Events by MeDRA SOC and PT.

The timetable was a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

Question 1

Frequencies and time course of solicited systemic and local AEs seems to be similar to those provided during procedure VR/257408. However, event numbers of solicited local and systemic reactions seem to be different in Table 27, where the overall safety is presented and in Table 29 and Table 30 where the time course of solicited local and systemic AEs are presented. Applicant is asked to clarify and provide corrected solicited AE number data, if necessary.

MAH's response

Differences in the total number of solicited systemic and solicited local adverse events (AEs) are observed between Table 27 (Treatment-Emergent Adverse Events (TEAEs) - Overall safety) and Tables 29 and 30 (solicited AEs - time course of solicited systemic and solicited local adverse events, respectively) of the Assessment Report (EMADOC-1700519818-2919735), corresponding to Table 32 and Tables 34 and 35 of the Clinical Study Report (CSR) of HIPRA-HH-3 study, respectively.

A summary of these differences is presented in Table 32 below:

Table 32. Summary of differences in solicited adverse events across tables (Safety population – HIPRA-HH-3)

Category	Table 27 (TEAEs - Overall safety)	Tables 29/30 (Solicited AEs - Cumulative events from Day 0 to Day 7)
Solicited systemic AEs	421 events in 136 (56.7%) participants	Table 29: 382 events in 136 (56.7%) participants
Solicited local AEs	360 events in 192 (80.0%) participants	Table 30: 357 events in 192 (80.0%) participants

Abbreviations: AE = adverse event; 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.
Source: Clinical Study Report – HIPRA-HH-3, version 1.0, 22 January 2026 – Table 32, Table 34 and Table 35.

Following further data review, it is confirmed that these differences do not represent data inconsistencies or errors but are a consequence of different data sources and counting methodologies applied in the respective tables.

Specifically, Table 27 (TEAEs - Overall safety, corresponding to Table 32 of the CSR) displays solicited adverse events within the summary of TEAEs and is based on data recorded in the general AE page of the electronic Case Report Form (eCRF). In this dataset, each adverse event is recorded as an individual AE entry with its own start and end dates. Therefore, if the same event occurs in separate time periods, it may be entered as multiple AE records and counted multiple times in the TEAE summary.

In contrast, Tables 29 and 30 (time course of solicited systemic and local AEs, respectively, corresponding to Tables 34 and 35 of the CSR) are based on solicited AEs recorded in the participant diary section of the eCRF, where events are captured on a daily basis from Day 0 to Day 7 following vaccination. For the cumulative summaries presented in these tables, each solicited event is counted once per participant, regardless of the number of days on which it is reported. As a result, a single event reported across multiple days is represented as one event in the cumulative analysis.

Accordingly, a single solicited event reported over multiple, non-consecutive days may correspond to more than one AE entry in the general AE dataset. For example, a solicited AE reported on Days 0–1 and again on Days 3–4 would be entered as two independent AEs in the general AE page of the eCRF and, therefore, counted twice in the TEAE summary. In contrast, in the participant diary section of the eCRF, the event would be entered on a daily basis and counted only once per participant in the cumulative diary-based analysis.

This difference in recording and counting explains why a single event may contribute multiple times to Table 27 but only once to Tables 29 and 30, resulting in a higher number of events in the TEAE

summary compared to the cumulative solicited event tables (421 vs 382 for systemic events and 360 vs 357 for local reactions). Importantly, the number of participants experiencing solicited events is consistent across tables, confirming that there are no discrepancies at subject level and no missing data.

To support interpretation, a clarifying footnote was included in the solicited systemic and solicited local AE tables (Tables 29 and 30, corresponding to Tables 34 and 35 in the CSR), describing the counting methodology applied in both the by-day and cumulative analyses: "*If a participant experienced more than one event, the participant is counted once for each type of event. An event is counted on each day it is reported in the by-day analysis and counted once in the cumulative analysis.*"

It is therefore confirmed that these differences are expected given the predefined data sources, counting rules and reporting processes (participant diary versus general AE page of the eCRF), and that they do not impact the overall safety evaluation or the conclusions of the study. The TEAE summary reflects all recorded AE occurrences, while the diary-based summaries provide a participant-level representation of solicited reactogenicity over the predefined post-vaccination period.

In conclusion, the Applicant confirms that the solicited AE data are correctly presented. Both counting approaches are standard, methodological and appropriate for their respective analyses. For this reason, no corrections to the solicited AE numbers are deemed necessary.

Rapporteur's assessment

Applicant confirmed that the above mentioned differences do not represent data inconsistencies or errors. They are a consequence of different data sources and counting methodologies applied in the respective tables.

Table 27, presenting the overall safety of Bimervax in Study HIPRA-HH-3 was based on data recorded in the general AE page of the electronic Case Report Form (eCRF). In this dataset, each adverse event is recorded as an individual AE entry with its own start and end dates. Therefore, if the same event occurs in separate time periods, it may be entered as multiple AE records and counted multiple times in the TEAE summary.

However, Tables 29 and 30 (time course of solicited systemic and local AEs, respectively, corresponding to Tables 34 and 35 of the CSR) were based on solicited AEs recorded in the participant diary section of the eCRF, where events are captured on a daily basis from Day 0 to Day 7 following vaccination. For the cumulative summaries presented in these tables, each solicited event is counted once per participant, regardless of the number of days on which it is reported. As a result, a single event reported across multiple days is represented as one event in the cumulative analysis.

To support interpretation, a clarifying footnote was included in the solicited systemic and solicited local AE tables (Tables 29 and 30, corresponding to Tables 34 and 35 in the CSR), describing the counting methodology applied in both the by-day and cumulative analyses: "*If a participant experienced more than one event, the participant is counted once for each type of event. An event is counted on each day it is reported in the by-day analysis and counted once in the cumulative analysis.*"

Applicant's response is acceptable.

Conclusion

Issue considered resolved.

Question 2

Summary of Treatment-related Emergent Adverse Events by MeDRA System Organ Class and Preferred Term was not provided, relationship data were provided for SAEs only. Applicant is asked to submit tabulated summary of treatment related Emergent Adverse Events by MeDRA SOC and PT.

MAH's response

In study HIPRA-HH-3 a total of 871 Treatment-Emergent Adverse Events (TEAEs) were reported in 206 (85.8%) participants. Among these, a total of 750 TEAEs were considered related in 198 (82.5%) participants.

In response to this request, a tabulated summary of the 750 related TEAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) is provided in the table below.

The most frequently reported related TEAEs were within the General Disorders and Administration Site Conditions SOC, with 538 TEAEs reported in 194 (80.8%) participants. The most common events (≥10%) within this SOC were injection site pain (313 events in 187 [77.9%] participants), followed by fatigue (76 events in 70 [29.2%] participants), malaise (67 events in 62 [25.8%] participants), axillary pain (28 events in 27 [11.3%] participants) and injection site induration (26 events in 26 [10.8%] participants). Injection site erythema, pyrexia, discomfort and injection site swelling were less frequently reported.

Other frequently reported (≥5%) related TEAEs belonged to the Nervous System Disorders SOC (81 TEAEs in 71 [29.6%] participants), Musculoskeletal and Connective Tissue Disorders SOC (77 TEAEs in 50 [20.8%] participants), Gastrointestinal Disorders SOC (34 TEAEs in 26 [10.8%] participants) and Blood and Lymphatic System Disorders SOC (16 TEAEs in 15 [6.3%] participants).

Within the Nervous System Disorders SOC, headache was the only related TEAE reported, with 81 events in 71 (29.6%) participants. Within the Musculoskeletal and Connective Tissue Disorders SOC, myalgia and arthralgia were the reported related TEAEs, with 41 events in 39 (16.3%) participants and 36 events in 34 (14.2%) participants, respectively. Within the Gastrointestinal Disorders SOC, diarrhoea was the most common related TEAE, with 17 events in 14 (5.8%) participants. Within the Blood and Lymphatic System Disorders SOC, 16 lymphadenopathy TEAEs were reported in 15 (6.3%) participants. Other related TEAEs by SOC occurred with lesser frequency.

As shown below, most related TEAEs correspond to solicited local and systemic AEs and represent most of the events observed.

Table 33: Summary of related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety population – HIPRA-HH-3)

	Adolescents (12-17 years old) (N=240)	
System Organ Class Preferred Term	**Events**	**Participants (%)**
Total number of related TEAEs	750	198 (82.5)
General disorders and administration site conditions	**538**	**194 (80.8)**
Injection site pain	313	187 (77.9)
Fatigue	76	70 (29.2)
Malaise	67	62 (25.8)
Axillary pain	28	27 (11.3)
Injection site induration	26	26 (10.8)
Injection site erythema	18	17 (7.1)
Pyrexia	6	6 (2.5)
Discomfort	3	3 (1.3)
Injection site swelling	1	1 (0.4)
Nervous system disorders	**81**	**71 (29.6)**
Headache	81	71 (29.6)
Musculoskeletal and connective tissue disorders	**77**	**50 (20.8)**
Myalgia	41	39 (16.3)
Arthralgia	36	34 (14.2)
Gastrointestinal disorders	**34**	**26 (10.8)**
Diarrhoea	17	14 (5.8)
Vomiting	10	10 (4.2)
Nausea	6	6 (2.5)
Odynophagia	1	1 (0.4)
Blood and lymphatic system disorders	**16**	**15 (6.3)**
Lymphadenopathy	16	15 (6.3)
Respiratory, thoracic and mediastinal disorders	**2**	**2 (0.8)**
Oropharyngeal pain	2	2 (0.8)
Skin and subcutaneous tissue disorders	**1**	**1 (0.4)**
Erythema	1	1 (0.4)
Psychiatric disorders	**1**	**1 (0.4)**
Initial insomnia	1	1 (0.4)

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: Clinical Study Report - HIPRA-HH-3, version 1.0, 22 January 2026 – Listing 16.2.7.1.

Rapporteur's assessment

Frequencies of treatment-related AEs have been provided by PT and SOC as requested

The majority of treatment related AEs corresponds to solicited local reactions or solicited systemic AEs, as it is expected for a vaccine. No changes can be found in the frequencies and the reported PTs compared to the interim analysis of Study HIPRA-HH-3, submitted in the previous VR/257408 variation procedure. Applicant's response is acknowledged and accepted.

Conclusion

Issue resolved.