

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

BIMERVAX XFG.1.1 emulsion for injection in pre-filled syringe
COVID-19 Vaccine (recombinant, adjuvanted)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a pre-filled syringe which contains 1 dose of 0.5 mL.

One dose (0.5 mL) contains 40 micrograms of SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion homodimer* (Omicron XFG.1.1 - XFG.1.1) adjuvanted with SQBA.

*Produced by recombinant DNA technology using a plasmid expression vector in a CHO cell line.

SQBA adjuvant containing per 0.5 mL dose: squalene (9.75 mg), polysorbate 80 (1.18 mg), sorbitan trioleate (1.18 mg), sodium citrate (0.66 mg), citric acid (0.04 mg) and water for injections.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection (injection)
White homogeneous emulsion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BIMERVAX XFG.1.1 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

A single intramuscular dose (0.5 mL) of BIMERVAX XFG.1.1 should be administered regardless of prior COVID-19 vaccination status (see section 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, BIMERVAX XFG.1.1 should be administered at least 6 months after the most recent dose of a COVID-19 vaccine.

Immunocompromised individuals

Additional doses may be administered to individuals who are severely immunocompromised in accordance with official recommendations, see section 4.4 and 5.1.

Elderly

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Paediatric population

The safety and efficacy of BIMERVAX XFG.1.1 in children aged less than 12 years have not yet been established. No data are available.

Method of administration

BIMERVAX XFG.1.1 is for intramuscular administration only, preferably into the deltoid muscle of the upper arm.

Do not administer this vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported with COVID-19 vaccines. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination.

No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of BIMERVAX.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a

psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia), because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

There are limited data available on immunogenicity and safety of the vaccine when administered to immunocompromised individuals, including those receiving immunosuppressant therapy (see section 5.1). The efficacy of BIMERVAX XFG.1.1 may be lower in immunocompromised individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with BIMERVAX XFG.1.1 may not protect all vaccine recipients.

Excipients with known effect

Potassium

This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

Sodium

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Polysorbate 80

This vaccine contains 1.18 mg of polysorbate 80 in each dose. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of BIMERVAX XFG.1.1 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no experience with the use of BIMERVAX XFG.1.1 in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development (see section 5.3).

Administration of BIMERVAX XFG.1.1 during pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether BIMERVAX XFG.1.1 is excreted in human milk.

No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to BIMERVAX XFG.1.1 is negligible.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, see section 5.3.

4.7 Effects on ability to drive and use machines

BIMERVAX XFG.1.1 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

BIMERVAX (original, heterodimer B.1.351 and B.1.1.7 strains)

Individuals 18 years of age and older

The most common adverse reactions reported after a booster dose with BIMERVAX in adult individuals who received a primary series with mRNA COVID-19 vaccine, were injection site pain (82.9%), headache (30.9%), fatigue (31.1%) and myalgia (20.7%). 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.

The most common adverse reactions reported after an additional booster dose of BIMERVAX as a fourth dose were injection site pain (79.9%), headache (25.0%) and fatigue (25.0%). 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.

Adolescents 12 through 17 years of age

The most common adverse reactions reported after a booster dose of BIMERVAX in adolescents were injection site pain (77.5%), headache (28.3%), fatigue (29.3%) and malaise (22.5%). The median duration of local and systemic adverse reactions was 1 to 3 days. Most adverse reactions occurred within 2 days following vaccination and were mild to moderate in severity.

BIMERVAX XBB.1.16 (Omicron XBB.1.16-adapted BIMERVAX)

The safety of BIMERVAX XBB.1.16 is inferred from the safety data of the BIMERVAX (original, heterodimer B.1.351 and B.1.1.7 strains) vaccine and the safety data from the clinical trial of the adapted BIMERVAX XBB.1.16 vaccine.

The overall safety profile for the BIMERVAX XBB.1.16 booster dose was similar to that seen after the BIMERVAX (original, heterodimer B.1.351 and B.1.1.7 strains) booster dose. The most common adverse reactions reported were injection site pain (68.11%), headache (23.42%), fatigue (19.60%) and myalgia (13.62%). Most adverse reactions were mild to moderate in severity. No new adverse reactions were identified for the BIMERVAX XBB.1.16 booster dose.

BIMERVAX XFG.1.1 (Omicron XFG.1.1-adapted BIMERVAX)

The safety of BIMERVAX XFG.1.1 is inferred from safety data of BIMERVAX (original, heterodimer B.1.351 and B.1.1.7 strains) vaccine and from the Omicron XBB.1.16-adapted BIMERVAX vaccine.

Tabulated list of adverse reactions

The safety profile presented below is based on pooled safety data generated in two phase 2b and phase 3 clinical trials with a total of 3 156 individuals 18 years of age and older, that received one booster dose of BIMERVAX at least 3 months after a previous COVID-19 vaccine. The median duration of the safety follow-up was 12 months for a 99.4% of the individuals, and 6 months for a 0.6% of the individuals.

The safety of an additional booster dose of BIMERVAX as a fourth dose was assessed in 288 individuals, 18 years of age and older, who had completed either 3 doses of COVID-19 mRNA vaccine (tozinameran) or 2 doses of COVID-19 mRNA vaccine (tozinameran) and 1 dose of BIMERVAX, and received an additional booster dose with BIMERVAX between 6 and 12 months after the third previous dose.

The safety of a booster dose of BIMERVAX in adolescents aged 12 through 17 years is based on safety data from the phase 3 clinical trial and the ongoing phase 2b clinical trial. A total of 276 participants, with and without medical history of prior SARS-CoV-2 infection, received a booster dose of BIMERVAX at least 3 months after the last dose of the primary series.

The safety of a booster dose of BIMERVAX XBB.1.16 was assessed in an ongoing phase 2b/3 clinical trial in individuals 18 years of age and older fully vaccinated against COVID-19 with a mRNA vaccine at least 6 months before receiving a booster dose with BIMERVAX XBB.1.16. From this study, safety data is available for 602 individuals who received a booster dose of BIMERVAX XBB.1.16 with a median follow-up time of 6 month.

Adverse reactions observed during clinical trials are listed below according to the following frequency categories: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1000$), very rare ($< 1/10\ 000$) and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions from BIMERVAX clinical trials in individuals 12 years of age and older

System class	organ	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			Lymphadenopathy ^a			
Nervous system disorders		Headache		Dizziness Somnolence	Paraesthesia Hypoaesthesia	
Cardiac disorders						Pericarditis ^c
Gastrointestinal disorders			Diarrhoea Vomiting Nausea		Odynophagia Abdominal pain ^b	
Skin and subcutaneous tissue disorders				Pruritus	Urticaria Cold sweats Rash Erythema	
Musculoskeletal and connective tissue disorders		Myalgia		Arthralgia		
General disorders and administration site conditions		Injection site pain Fatigue	Injection site swelling Injection site erythema Injection site induration Pyrexia Axillary pain	Asthenia Chills Malaise Injection site pruritus	Injection site bruising Injection site hypersensitivity	

^a This term also included events reported as lymphadenitis

^b This term also included events reported as upper and lower abdominal pain

^c Based on a single event during clinical trials

Paediatric population

Injection site induration, malaise, axillary pain and arthralgia occurred at higher frequencies in adolescents compared to adults, with the frequency being very common in adolescents.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Covid-19 vaccines, ATC code: J07BN04

Mechanism of action

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

Efficacy

The efficacy of BIMERVAX and BIMERVAX XBB.1.16 has been inferred by immunobridging of immune response to an authorised COVID-19 vaccine, for which efficacy is established. The efficacy of BIMERVAX XFG.1.1 is inferred from the immunogenicity data of prior BIMERVAX vaccines.

Immunogenicity

BIMERVAX XBB.1.16 (Omicron XBB.1.16-adapted BIMERVAX)

The immunogenicity of damlecovatein was evaluated in the clinical trial HIPRA-HH-14, a Phase 2b/3, double-blind, randomised, active-controlled, multi-centre, non-

inferiority clinical trial to assess the safety, tolerability and immunogenicity of a booster vaccination with damlecovatein compared to COVID-19 mRNA vaccine (raxtozinameran) adapted vaccine, in adults fully vaccinated against COVID-19 with a mRNA vaccine at least 6 months before enrolment.

This phase 2b/3 clinical trial excluded individuals who were pregnant, individuals who were immunocompromised or had received immunosuppressants within 90 days, received any previous Omicron XBB adapted vaccine as well as individuals with COVID-19 infection diagnosed in the previous 6 months. Individuals were also required a minimum interval of 3 months after receipt of any immunotherapy (monoclonal antibodies, plasma) prior to the study.

At the cut-off date of the Interim Analysis, a total of 800 individuals had been vaccinated. A total of 599 subjects were included in the immunogenicity analysis (406 subjects vaccinated with damlecovatein and 193 subjects vaccinated with COVID-19 mRNA vaccine (raxtozinameran). Participants were stratified before randomisation by age group and by number of doses previously received (3 or $\geq$ 4 doses). The median age was 45 years (range: 18 to 88 years), with similar age ranges in both vaccine arms, including 13.6% and 11.7% of subjects 60 years of age and older in the damlecovatein and COVID-19 mRNA vaccine (raxtozinameran) groups, respectively. Most subjects had received either 3 (66.9%) or 4 (33.0%) previous mRNA COVID-19 vaccine doses.

Immunogenicity of a booster dose of damlecovatein was based on an assessment of geometric mean titres (GMT) of neutralising antibodies, measured by a pseudovirion-based neutralisation assay (PBNA), against SARS-CoV-2 Omicron XBB.1.16 (primary endpoint of efficacy) and Omicron XBB.1.5, and binding antibodies at Baseline and at Day 14. GMT ratio is the result of the GMT values (ID_{50}) of COVID-19 mRNA vaccine (raxtozinameran) / damlecovatein. Non-inferiority of damlecovatein to COVID-19 mRNA vaccine (raxtozinameran) is concluded if the upper limit of the 2-sided 95% Confidence Interval of the GMT ratio is < 1.5 . Superiority of damlecovatein to COVID-19 mRNA vaccine (raxtozinameran) is concluded if the upper limit of the 2-sided 95% Confidence Interval of the GMT ratio is < 1.0 (see Table 2, GMT ratio column). Superiority of damlecovatein was met for all the variants tested.

Table 2: Post-booster GMT ratio for BIMERVAX XBB.1.16 (damlecovatein) versus COVID-19 mRNA vaccine (raxtozinameran) with neutralisation titres (PBNA) against SARS-CoV-2 Omicron XBB.1.16 and XBB.1.5 at Baseline and at Day 14 post-booster dose

	BIMERVAX XBB.1.16 (damlecovatein) N=406		COVID-19 mRNA vaccine (raxtozinameran) N=193		COVID-19 mRNA vaccine (raxtozinameran) / BIMERVAX XBB.1.16
	GMT	95% CI	GMT	95% CI	GMT Ratio; (95% CI)
Baseline					
Omicron XBB.1.16	152.46	134.72 - 172.54	161.57	136.40 - 191.37	1.06 (0.87 - 1.29)

Omicron XBB.1.5	151.93	134.89 - 171.13	167.89	142.04 - 198.44	1.11 (0.90 - 1.35)
Day 14 post-booster					
Omicron XBB.1.16	1 946.38	1 708.44 – 2 217.46	1 512.21	1 261.72 – 1 812.44	0.78 (0.63 - 0.96)
Omicron XBB.1.5	1 888.89	1 676.98 – 2 127.57	1 486.03	1 257.25 – 1 756.45	0.79 (0.64 - 0.96)

N: number of participants in the mITT population

Abbreviations: GMT = Geometric Mean Titre; CI: Confidence intervals; PBNA = pseudovirion-based neutralisation assay

BIMERVAX (original, heterodimer B.1.351 and B.1.1.7 strains)

Individuals 16 years of age and older

The immunogenicity of BIMERVAX was evaluated in one pivotal phase 2b multi-centre clinical trial (Study HIPRA-HH-2) and in one phase 3 multi-centre clinical trial (Study HIPRA-HH-5).

HIPRA-HH-2

Study HIPRA-HH-2 is a phase 2b, double-blind, randomised, active-controlled, multi-centre, non-inferiority clinical trial to assess immunogenicity and safety of a booster vaccination with BIMERVAX compared to COVID-19 mRNA (tozinameran) vaccine, in adults fully vaccinated against COVID-19 with a mRNA vaccine at least 6 months before enrolment. This phase 2b clinical trial excluded individuals who were pregnant, individuals who were immunocompromised or had received immunosuppressants within 12 weeks, as well as individuals with previous COVID-19 infection. Individuals were also required a minimum interval of 3 months after receipt of any immunotherapy (monoclonal antibodies, plasma) prior to the study.

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

Immunogenicity of a booster dose of BIMERVAX was based on an assessment of geometric mean titres (GMT) of neutralising antibodies, measured by a pseudovirion-based neutralisation assay (PBNA) against SARS-CoV-2 (D614G) strain, Beta, Delta and Omicron BA.1 variants. GMT ratio is the result of the GMT values (ID_{50}) of COVID-19 mRNA vaccine (tozinameran)/BIMERVAX. Non-inferiority of BIMERVAX to COVID-19 mRNA vaccine (tozinameran) is concluded if the upper limit of the 2 sided 95% Confidence Interval (CI) of the GMT ratio is < 1.4 . Superiority of BIMERVAX to COVID-19 mRNA vaccine (tozinameran) is concluded if the upper limit of the 2-sided 95% Confidence Interval of the GMT ratio is < 1.0 (see Table 3, GMT ratio column).

Table 3: Post-booster GMT ratio for BIMERVAX versus COVID-19 mRNA vaccine (tozinameran) with neutralisation titres (PBNA) against SARS-CoV-2 (D614G strain), Beta, Delta and Omicron BA.1 at days 14, 28, 98 and 182 post-booster dose (per protocol population)

	BIMERVAX N=504		COVID-19 mRNA vaccine (tozinameran) N=247		COVID-19 mRNA vaccine (tozinameran) / BIMERVAX
	GMT	95% CI	GMT	95% CI	GMT Ratio; (95% CI)
Day 14 post-booster					
D614G strain	1 949.44	1 696.03, 2 240.72	3 302.34	2 793.60, 3 903.73	1.69 (1.44, 2.00)
Beta	4 268.18	3 701.04, 4 922.21	2 608.59	2 188.98, 3 108.63	0.61 (0.51, 0.73)
Delta	1 459.98	1 282.22, 1 662.37	1 473.73	1 253.18, 1 733.10	1.01 (0.85, 1.20)
Omicron BA.1	2032.63	1773.66, 2329.40	1 209.23	1 019.34, 1 434.50	0.59 (0.50, 0.71)
Day 28 post-booster					
D614G strain	2 241.24	1 949.80, 2 576.24	2 947.35	2 494.84, 3 481.94	1.32 (1.12, 1.55)
Beta	3 754.90	3 255.80, 4 330.50	2 437.02	2 046.38, 2 902.22	0.65 (0.54, 0.78)
Delta	1 706.85	1 498.96, 1 943.58	1 508.08	1 283.26, 1 772.30	0.88 (0.74, 1.05)
Omicron BA.1	1 516.12	1 322.89, 1 737.58	987.53	833.05, 1 170.66	0.65 (0.54, 0.78)
Day 98 post-booster (N: BIMERVAX: 78; N: tozinameran: 42 as per protocol subset)					
D614G strain	1 193.17	931.14, 1 528.94	1 054.61	761.88, 1 459.83	0.88 (0.60, 1.30)
Beta	1 980.37	1 526.63, 2 568.98	1 150.92	815.99, 1 623.32	0.58 (0.39, 0.88)
Delta	1 981.10	1 547.00, 2 537.02	1 014.07	730.25, 1 408.20	0.51 (0.35, 0.76)
Omicron BA.1	668.25	514.73, 867.56	400.71	283.27, 566.83	0.60 (0.40, 0.91)
Day 182 post-booster					
D614G strain	1 213.44	1 055.38, 1 395.17	752.09	636.46, 888.74	0.62 (0.53, 0.73)
Beta	2 554.58	2 214.40, 2 947.01	1 774.54	1 489.68, 2 113.88	0.69 (0.58, 0.83)
Delta	2 306.86	2 025.18, 2 627.72	1 256.46	1 068.85, 1 477.02	0.54 (0.46, 0.65)
Omicron BA.1	882.67	769.93, 1 011.91	667.30	562.74, 791.28	0.76 (0.63, 0.91)

N: number of participants in the population per-protocol.

Abbreviations: GMT = Geometric Mean Titre; CI: Confidence intervals; PBNA = pseudovirion-based neutralisation assay

The immunogenicity of an additional booster dose of BIMERVAX was assessed in a total of 288 individuals 18 years of age and older. Individuals had previously completed either a series of 2 doses of COVID-19 mRNA (tozinameran) vaccine and one dose of BIMERVAX (Cohort 1) or 3 doses of COVID-19 mRNA (tozinameran) vaccine (Cohort 2), and received an additional booster dose with BIMERVAX between 6 and 12 months after the previous dose. Of these, 190 subjects were analysed in the efficacy population (80 subjects in Cohort 1 and 110 subjects in Cohort 2). The median age was 49 years (range: 20 to 82 years), with similar age ranges in both Cohorts, including 11.5% of subjects 65 years of age and older.

Table 4: Neutralising antibody levels (PBNA) and GMT ratio after an additional booster dose with BIMERVAX, administered either after a primary series with mRNA COVID-19 vaccine and a booster dose of BIMERVAX (cohort 1) or after a primary series with mRNA COVID-19 vaccine and a booster dose of mRNA COVID-19 vaccine (cohort 2), against Beta, Delta, Omicron BA.1 and Omicron BA.4/5 at days 14, 98 and 182 post-booster dose (per protocol population)

Day 14 post-booster						
Beta	2 547.34 (1 741.36, 3 726.35)	5 790.20 (4 371.05, 7 670.09)	0.44 (0.28, 0.68)	2 783.85 (1 975.09, 3 923.79)	6 383.89 (5 057.19, 8 058.64)	0.44 (0.31, 0.62)
Delta	1 565.21 (1 041.33, 2 352.66)	5 199.90 (3 752.82, 7 204.97)	0.30 (0.20, 0.46)	1 637.19 (1 130.5, 2 370.9)	4 085.85 (3 057.24, 5 460.52)	0.40 (0.28, 0.57)
Omicron BA.1	1 528.68 (970.94, 2 406.80)	3 580.61 (2 492.90, 5 142.92)	0.43 (0.27, 0.69)	1 739.02 (1 121.56, 2 696.41)	4 049.01 (2 795.38, 5 864.84)	0.43 (0.28, 0.65)
Omicron BA.4/5	1 094.55 (720.53, 1 662.72)	2 945.40 (2 216.80, 3 913.50)	0.37 (0.22, 0.62)	1 295.76 (845.10, 1 986.75)	2 506.46 (1 849.64, 3 396.52)	0.52 (0.34, 0.78)
Day 98 post-booster						

Beta	1 544.65 (773.99, 3 082.64)	4 609.95 (3 474.24, 6 116.91)	0.34 (0.16, 0.69)	1 601.47 (849.42, 3 019.37)	3 743.39 (2 951.87, 4 747.14)	0.43 (0.23, 0.81)
Delta	1 330.09 (672.40, 2 631.08)	1 864.55 (1 343.99, 2 586.73)	0.71 (0.36, 1.43)	1 102.65 (569.19, 2 136.06)	1 746.82 (1 305.89, 2 336.63)	0.63 (0.33, 1.22)
Omicron BA.1	461.12 (214.68, 990.45)	2 110.41 (1 467.27, 3 035.45)	0.22 (0.10, 0.48)	520.63 (242.27, 1 118.79)	1 980.84 (1 371.69, 2 860.50)	0.26 (0.12, 0.56)
Omicron BA.4/5	ND	1 886.95 (1 418.08, 2 510.85)	ND	ND	1 574.26 (1 156.85, 2 142.28)	ND
Day 182 post-booster						
Beta	809.61 (555.69, 1 179.56)	2 415.77 (1 814.55, 3 216.20)	0.34 (0.22, 0.52)	890.39 (633.9, 1 250.6)	2 088.80 (1 643.29, 2 655.08)	0.43 (0.30, 0.60)
Delta	732.92 (489.25, 1 097.95)	1 309.33 (941.50, 1 820.86)	0.56 (0.37, 0.85)	771.85 (534.93, 1 113.71)	1 337.38 (999.37, 1 789.72)	0.58 (0.40, 0.83)
Omicron BA.1	357.34 (227.83, 560.47)	1 756.94 (1 218.19, 2 533.97)	0.20 (0.13, 0.33)	404.87 (262.13, 625.33)	1 900.74 (1 315.82, 2 745.67)	0.21 (0.14, 0.32)
Omicron BA.4/5	ND	1 836.26 (1 373.92, 2 454.19)	ND	ND	1 604.42 (1 179.06, 2 183.22)	ND

N: Number of participants with available data for the relevant endpoint

Abbreviations: GMT = Geometric Mean Titre; CI: Confidence intervals; ND: not determined

HIPRA-HH-5

This study is an ongoing open label, single arm, multicentre, phase 3 clinical trial to assess the safety and immunogenicity of a booster vaccination with BIMERVAX for the prevention of COVID-19 in subjects vaccinated with several primary vaccine schedules, with or without previous non-severe COVID-19 infections. BIMERVAX was administered at least 91 days after the last dose or at least 30 days after the COVID-19 infection. This phase 3 clinical trial excluded individuals who were pregnant as well as individuals who were immunocompromised or had received immunosuppressants within 12 weeks. Individuals were also required a minimum interval of 3 months after receipt of any immunotherapy (monoclonal antibodies, plasma) prior to the study.

The interim report includes data from a total of 2 646 subjects who were vaccinated with BIMERVAX as a booster dose in healthy individuals (at least 16 years old) previously vaccinated with different COVID-19 vaccines (mRNA COVID-19 vaccines: tozinameran and elasomeran, and adenovirus-vector vaccines (COVID-19 Vaccine (ChAdOx1-S [recombinant]) and COVID-19 vaccine (Ad26.COV2-S [recombinant])). Of these, 230 (8%) subjects were included in the immunogenicity population. In the immunogenicity analysis, the population of the COVID-19 mRNA vaccine (tozinameran)/COVID-19 mRNA vaccine (tozinameran) vaccine group were all subjects between 16-17 years old.

Overall, the median age was 34.4 years (range: 16 to 85 years of age). Subjects were balanced between genders, 52.49% male and 47.47% female.

Immunogenicity was measured by Pseudovirion-based neutralisation assay (PBNA) against SARS-CoV-2 (D614G) strain and against Beta, Delta and Omicron BA.1. Data on GMT (geometric mean titre: ID₅₀) at baseline (prior to the administration of the booster dose) and at Day 14 (2 weeks after the administration of the booster dose) are provided in the following table.

Table 5: Neutralising antibody Geometric Mean Titres (GMT) at 14 days post-booster with BIMERVAX in individuals 16 years of age and older-per protocol analysis

	mRNA primed (tozinameran) 16-17 years old N=11		Ad-vector primed (ChAdOx1-S recombinant) ≥ 18 years old N=40		mRNA primed (elasomeran) ≥ 18 years old N=171	
	GMT	95% CI	GMT	95% CI	GMT	95% CI
Pre-booster						
D614G strain	720.10	356.96; 1 452.64	288.58	194.56; 428.02	657.49	499.52; 865.43
Beta	471.68	208.39; 1 067.60	539.49	345.97; 841.26	497.77	376.98; 657.26
Delta	803.84	376.27; 1 717.26	283.75	182.43; 441.35	914.68	657.97; 1 271.55
Omicron BA.1	257.99	99.98; 665.71	159.34	94.02; 270.05	221.62	155.51; 315.84
Day 14 post-booster						
D614G strain	4 753.65	2 356.45; 9 589.48	2 298.81	1 549.89; 3 409.63	4437.27	3 371.158; 5 840.55
Beta	8 820.74	3 897.14; 19 964.72	5 009.47	3 212.53; 7 811.54	6857.95	5 193.76; 9 055.38
Delta	7 564.79	3 541.05; 16 160.76	2 600.31	1 671.78; 4 044.56	5811.47	4 180.44; 8 078.87
Omicron BA.1	5 757.43	2 231.25; 14 856.19	1 847.41	1 090.05; 3 131.00	4379.81	3 073.24; 6 241.85

N: Number of participants with available data for the relevant endpoint

Abbreviations: GMT = Geometric Mean Titre; CI: Confidence intervals

Adolescents 12 through 17 years of age

The immunogenicity of BIMERVAX in individuals 12 through 17 years of age was evaluated in the ongoing phase 2b multi-centre clinical trial (Study HIPRA-HH-3).

HIPRA-HH-3

This study is an ongoing open label, uncontrolled, single-arm, multicentre, non-inferiority, phase 2b clinical trial to assess the safety and immunogenicity of a booster vaccination with BIMERVAX in adolescents 12 through 17 years of age. BIMERVAX was administered at least 6 months after the last dose of the primary series. HIPRA-HH-3 study excluded adolescents who were pregnant as well as adolescents who were immunocompromised or who have received immunosuppressants within 90 days. Participants with known history of SARS-CoV-2 infection were excluded from the immunogenicity analysis.

At the time of the interim analysis a total of 240 adolescent participants were vaccinated with a booster dose of BIMERVAX. Of these, 88 individuals were eligible for the immunogenicity analysis. The primary immunogenicity analysis, measured by Pseudovirion-based neutralisation assay (PBNA), compared geometric mean titres (GMT) of neutralising antibodies against Omicron BA.1 with those observed in young adult participants (aged 18 to 25 years) from the pivotal phase 2b study in adults (HIPRA-HH-2) at Baseline and at Day 14 (2 weeks after the administration of the booster dose). Both groups of participants included in the analysis had no previous documented medical history of SARS-CoV-2 infection.

Data on neutralising antibody titres against Omicron BA.1 at Baseline (prior to the administration of the booster dose) and at Day 14 after vaccination are provided in the following table.

Table 6: Neutralising antibody titres against Omicron BA.1 at day 14 post-booster with BIMERVAX in adolescents aged 12 to 17 years (immunogenicity population)

	Statistics	Adolescents (12-15 years old) N = 61	Adolescents (16-17 years old) N = 27	Total (12-17 years old) N= 88
Baseline	Geometric mean	1 240.77	1 457.30	1 303.54
	95 % CI	894.78; 1 720.55	984.9; 2 156.3	1 016.05; 1 672.39
Day 14	Geometric mean	22 970.81	26 792.00	24 081.34
	95 % CI	18 033.27; 29 260.25	20 150.31; 35 622.86	19 741.36; 29 375.43
	GMFR	18.51	18.38	18.47
	95 % CI	13.28; 25.81	13.15; 25.71	14.41; 23.69
	≥ 4- fold change from baseline, n (%)	54 (88.5)	27 (100)	81 (92)
	95 % CI	77.8; 95.3	87.2; 100	84.3; 96.7

N: Number of participants with available data for the relevant endpoint

Abbreviations: GMFR= Geometric Mean Fold Rise; CI: Confidence intervals

Elderly population

The immunogenicity of BIMERVAX was shown in the elderly population (≥ 65 years old).

Immunocompromised population

The immunogenicity and safety of a booster dose of BIMERVAX were evaluated in a phase 2b/3, open label, single arm, multi-centre clinical trial (HIPRA-HH-4) in adults with pre-existing immunosuppressive conditions, including people living with human immunodeficiency virus (HIV) infection with persistent CD4 T-cell counts $< 400/\text{mm}^3$ within last 6 months, kidney transplant on maintenance immunosuppressive therapy, haemodialysis/peritoneal dialysis, primary antibody deficiencies on IgG replacement therapy and auto-immune disease on treatment with rituximab/ocrelizumab. The booster dose of BIMERVAX was administered at least 91 days after 3 previous doses of COVID-19 vaccine or after 2 doses plus a documented history of COVID-19. Participants with history of COVID-19 disease were allowed to be included if diagnosed at least 91 days before enrolment.

A total of 238 individuals were vaccinated with a booster dose of BIMERVAX and a total of 228 participants were analysed excluding those who tested positive for COVID-19 within 14 days of the booster. The median age was 56 years old (range: 21 to 90 years of age).

Immunogenicity was measured by pseudovirion-based neutralisation assay (PBNA) against SARS-CoV-2 (D614G) strain and against Beta, and Omicron BA.1 and BA.4/5 up to 12 months post-booster dose in all immunosuppressive conditions studied, except in individuals living with confirmed HIV infection in which immunogenicity was measured by virus neutralisations assay (VNA) against SARS-CoV-2 (D614G) strain and against Omicron BA.2. A booster dose of BIMERVAX enhanced humoral immune response in all immunosuppressive conditions, except in individuals with auto-immune disease on rituximab/ocrelizumab therapy. However, a comparison to immunocompetent individuals to inform about the magnitude of the potential difference as regards immune responses was not conducted. Therefore, the clinical relevance of the reported immune responses in immunocompromised individuals is unknown.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with BIMERVAX in one or more subsets of the paediatric population in the prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Genotoxicity and carcinogenicity

BIMERVAX XFG.1.1 has not been evaluated for its genotoxic or carcinogenic potential. The components of the vaccine are not expected to have genotoxic or carcinogenic potential.

Reproductive toxicity

A developmental and reproductive toxicity study was performed in female and male rats prior to mating and during gestation. BIMERVAX was administered intramuscularly (equivalent to a full human dose) to female rats in four occasions, 21 and 14 days prior to mating and on gestation days 9 and 19. Males received three administrations, 35, 28 and 6 days prior to mating. No vaccine-related adverse effects on fertility, pregnancy/lactation, or development of the embryo/foetus and offspring were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dodecahydrate

Potassium dihydrogen phosphate

Sodium chloride

Potassium chloride

Water for injections

For adjuvant, see section 2.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

6.3 Shelf life

1 year at 2 °C – 8 °C.

Before use, the vaccine may be taken out of the refrigerator once for a maximum period of 24 hours at temperature not above 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the product in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.5 mL of emulsion in a pre-filled syringe (type I glass) with a plunger stopper (chlorobutyl rubber) and an integrated tip cap (polyisoprene rubber) without needle.

Each pre-filled syringe contains 1 dose of 0.5 mL.

Pack sizes: 1 or 10 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Handling instructions and administration

The vaccine should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose.

Preparation for use

- The vaccine comes ready to use.
- Unopened vaccine should be stored at 2 °C to 8 °C and kept within the outer carton to protect from light.
- Immediately prior to use, remove the pre-filled syringe from the outer carton.

Inspect the pre-filled syringe

- Gently swirl the pre-filled syringe. Do not shake.
- Before use, check the tightness of the closing system.
- Each pre-filled syringe contains a white and homogeneous emulsion.
- Visually inspect the vaccine for particulate matter and/or discolouration prior to administration. Do not administer the vaccine if any of these are present.
- Do not administer the vaccine if the pre-filled syringe is damaged.

Administer the vaccine

- Needles are not included in the pre-filled syringe cartons.
- Use a sterile needle for intramuscular injection.
- With the tip cap upright, remove the tip cap by twisting counterclockwise until it releases. Remove the cap in a slow, steady motion. Do not pull on it while turning.
- Attach the needle by twisting in a clockwise direction until the needle locks on the syringe.
- Uncap the needle when ready for administration.
- Administer the entire dose intramuscularly.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Hipra Human Health, S.L.U.
Avda. la Selva, 135
17170 Amer (Girona)
SPAIN

8 MARKETING AUTHORISATION NUMBER(S)

PL 56346/0011

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

16/09/2026

10 DATE OF REVISION OF THE TEXT

16/09/2026