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 XBB.1.16 emulsion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose vial which contains 1 dose of 0.5 mL.

One dose (0.5 mL) contains 40 micrograms of damlecovatein adjuvanted with SQBA.

Damlecovatein is a SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion homodimer (Omicron XBB.1.16 - XBB.1.16 strain) 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 XBB.1.16 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

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

4.2 Posology and method of administration

Posology

Individuals 16 years of age and older
A single intramuscular dose (0.5 mL) of BIMERVAX XBB.1.16 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 XBB.1.16 should be administered at least 6 months after the most recent dose of a COVID-19 vaccine.

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

Paediatric population
The safety and efficacy of BIMERVAX XBB.1.16 in children and adolescents less than 16 years of age have not been established yet. No data are available.

Method of administration

BIMERVAX XBB.1.16 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

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of BIMERVAX XBB.1.16 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 XBB.1.16 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 XBB.1.16 with other vaccines has not been studied.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There is no experience with the use of BIMERVAX XBB.1.16 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 XBB.1.16 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 XBB.1.16 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 XBB.1.16 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 XBB.1.16 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)
The most common adverse reactions reported after a booster dose with BIMERVAX in individuals 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.

The most common adverse reactions reported 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.

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.

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 3 192 individuals 16 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 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 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 and BIMERVAX XBB.1.16 clinical trials in individuals 16 years of age and older

System organ class	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

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 at 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

Damlecovatein is a recombinant protein vaccine whose active substance (antigen) is SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion homodimer - Omicron XBB.1.16 - XBB.1.16 strain. 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, damlecovatein induces antigen-specific T-cell immune response, which may contribute to protection to COVID-19.

Efficacy

Efficacy of damlecovatein has been inferred by immunobridging of immune responses to an authorised XBB adapted COVID-19 vaccine, for which vaccine efficacy has been established.

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 ≥ 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	1946.38	1708.44 - 2217.46	1512.21	1261.72 - 1812.44	0.78 (0.63 - 0.96)
Omicron XBB.1.5	1888.89	1676.98 - 2127.57	1486.03	1257.25 - 1756.45	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)
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	1949.44	1696.03, 2240.72	3302.34	2793.60, 3903.73	1.69 (1.44, 2.00)
Beta	4268.18	3701.04, 4922.21	2608.59	2188.98, 3108.63	0.61 (0.51, 0.73)
Delta	1459.98	1282.22, 1662.37	1473.73	1253.18, 1733.10	1.01 (0.85, 1.20)
Omicron BA.1	2032.63	1773.66, 2329.40	1209.23	1019.34, 1434.50	0.59 (0.50, 0.71)
Day 28 post-booster					
D614G strain	2241.24	1949.80, 2576.24	2947.35	2494.84, 3481.94	1.32 (1.12, 1.55)
Beta	3754.90	3255.80, 4330.50	2437.02	2046.38, 2902.22	0.65 (0.54, 0.78)
Delta	1706.85	1498.96, 1943.58	1508.08	1283.26, 1772.30	0.88 (0.74, 1.05)
Omicron BA.1	1516.12	1322.89, 1737.58	987.53	833.05, 1170.66	0.65 (0.54, 0.78)
Day 98 post-booster (N: BIMERVAX: 78; N: tozinameran: 42 as per protocol subset)					
D614G strain	1193.17	931.14, 1528.94	1054.61	761.88, 1459.83	0.88 (0.60, 1.30)
Beta	1980.37	1526.63, 2568.98	1150.92	815.99, 1623.32	0.58 (0.39, 0.88)
Delta	1981.10	1547.00, 2537.02	1014.07	730.25, 1408.20	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	1213.44	1055.38, 1395.17	752.09	636.46, 888.74	0.62 (0.53, 0.73)
Beta	2554.58	2214.40, 2947.01	1774.54	1489.68, 2113.88	0.69 (0.58, 0.83)
Delta	2306.86	2025.18, 2627.72	1256.46	1068.85, 1477.02	0.54 (0.46, 0.65)
Omicron BA.1	882.67	769.93, 1011.91	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.

Immunogenicity of BIMERVAX as an additional booster dose was based on an assessment of geometric mean titres (GMT) of neutralising antibodies, measured by a pseudovirion-based neutralisation assay (PBNA) against Beta, Delta, Omicron BA.1 and Omicron BA.4/5 variants. GMT ratio is the result of the GMT values (ID_{50}) of 3 doses of COVID-19 mRNA vaccine (tozinameran)/an additional booster dose of BIMERVAX administered after 3 doses of COVID-19 mRNA vaccine (tozinameran) or administered after 2 doses of COVID-19 mRNA and one dose of BIMERVAX. Superiority of the additional booster dose with BIMERVAX was met if the upper limit of the 2 sided 95% Confidence Interval (CI) of the GMT ratio was < 1 (see Table 4, GMT ratio column).

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)

	Cohort 1 2 doses COVID-19 mRNA+2 doses of BIMERVAX			**Cohort 2 3 doses COVID-19 mRNA+1 dose of BIMERVAX**		
	Post-dose 3 GMT (95% CI) N=38	**Post-dose 4 GMT (95% CI) N=80**	**GMT Ratio (95%CI)**	**Post-dose 3 GMT (95% CI) N=38**	**Post-dose 4 GMT (95% CI) N=110**	**GMT Ratio (95%CI)**
Day 14 post-booster						
Beta	2547.34 (1741.36, 3726.35)	5790.20 (4371.05, 7670.09)	0.44 (0.28, 0.68)	2783.85 (1975.09, 3923.79)	6383.89 (5057.19, 8058.64)	0.44 (0.31, 0.62)
Delta	1565.21 (1041.33, 2352.66)	5199.90 (3752.82, 7204.97)	0.30 (0.20, 0.46)	1637.19 (1130.5, 2370.9)	4085.85 (3057.24, 5460.52)	0.40 (0.28, 0.57)
Omicron BA.1	1528.68 (970.94, 2406.80)	3580.61 (2492.90, 5142.92)	0.43 (0.27, 0.69)	1739.02 (1121.56, 2696.41)	4049.01 (2795.38, 5864.84)	0.43 (0.28, 0.65)
Omicron BA.4/5	1094.55 (720.53, 1662.72)	2945.40 (2216.80, 3913.50)	0.37 (0.22, 0.62)	1295.76 (845.10, 1986.75)	2506.46 (1849.64, 3396.52)	0.52 (0.34, 0.78)
Day 98 post-booster						
Beta	1544.65 (773.99, 3082.64)	4609.95 (3474.24, 6116.91)	0.34 (0.16, 0.69)	1601.47 (849.42, 3019.37)	3743.39 (2951.87, 4747.14)	0.43 (0.23, 0.81)
Delta	1330.09 (672.40, 2631.08)	1864.55 (1343.99, 2586.73)	0.71 (0.36, 1.43)	1102.65 (569.19, 2136.06)	1746.82 (1305.89, 2336.63)	0.63 (0.33, 1.22)
Omicron BA.1	461.12 (214.68, 990.45)	2110.41 (1467.27, 3035.45)	0.22 (0.10, 0.48)	520.63 (242.27, 1118.79)	1980.84 (1371.69, 2860.50)	0.26 (0.12, 0.56)
Omicron BA.4/5	ND	1886.95 (1418.08, 2510.85)	ND	ND	1574.26 (1156.85, 2142.28)	ND
Day 182 post-booster						
Beta	809.61 (555.69, 1179.56)	2415.77 (1814.55, 3216.20)	0.34 (0.22, 0.52)	890.39 (633.9, 1250.6)	2088.80 (1643.29, 2655.08)	0.43 (0.30, 0.60)
Delta	732.92 (489.25, 1097.95)	1309.33 (941.50, 1820.86)	0.56 (0.37, 0.85)	771.85 (534.93, 1113.71)	1337.38 (999.37, 1789.72)	0.58 (0.40, 0.83)
Omicron BA.1	357.34 (227.83, 560.47)	1756.94 (1218.19, 2533.97)	0.20 (0.13, 0.33)	404.87 (262.13, 625.33)	1900.74 (1315.82, 2745.67)	0.21 (0.14, 0.32)
Omicron BA.4/5	ND	1836.26 (1373.92, 2454.19)	ND	ND	1604.42 (1179.06, 2183.22)	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: ID_{50}) 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 (ChAd=x1-S recombinant) ≥ 18 years old N=40**		**mRNA primed (elasomeran) ≥ 18 years old N=171**	
	Pre-booster					
	GMT	95% CI	GMT	95% CI	GMT	95% CI
D614G strain	720.10	356.96; 1452.64	288.58	194.56; 428.02	657.49	499.52; 865.43
Beta	471.68	208.39; 1067.60	539.49	345.97; 841.26	497.77	376.98; 657.26
Delta	803.84	376.27; 1717.26	283.75	182.43; 441.35	914.68	657.97; 1271.55
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	4753.65	2356.45; 9589.48	2298.81	1549.89; 3409.63	4437.27	3371.158; 5840.55
Beta	8820.74	3897.14; 19964.72	5009.47	3212.53; 7811.54	6857.95	5193.76; 9055.38
Delta	7564.79	3541.05; 16160.76	2600.31	1671.78; 4044.56	5811.47	4180.44; 8078.87
Omicron BA.1	5757.43	2231.25; 14856.19	1847.41	1090.05; 3131.00	4379.81	3073.24; 6241.85

N: Number of participants with available data for the relevant endpoint
Abbreviations: GMT = Geometric Mean Titre; CI: Confidence intervals

Elderly population

The immunogenicity of BIMERVAX XBB.1.16 has been shown in the elderly population (≥ 65 years old).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with BIMERVAX and BIMERVAX XBB.1.16 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 XBB.1.16 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

9 months at 2 ºC – 8 ºC.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

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

6.5 Nature and contents of container

0.5 mL of emulsion in a single dose vial (type I glass) closed with a type I elastomeric stopper and an aluminium seal fitted with a plastic flip-off cap.

Each single dose vial contains 1 dose of 0.5 mL.

Pack sizes: 5, 10 or 20 single dose vials.

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 in a single dose vial.
- Unopened vaccine should be stored at 2 ºC to 8 ºC and kept within the outer carton to protect from light.
- Immediately prior to use, remove the vaccine vial from the outer carton.

Inspect the vial
- Gently swirl the vial before the dose withdrawal. Do not shake.
- Each vial 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.

Administer the vaccine
- An overfill is included in each vial to ensure that a 0.5 mL dose can be extracted. Discard any remaining vaccine in the vial after a 0.5 mL dose has been extracted.
- One 0.5 mL dose is withdrawn into a sterile needle and sterile syringe to be administered by intramuscular injection, preferably in the deltoid muscle of the upper arm.
- Do not mix the vaccine in the same syringe with any other vaccines or medicinal products.
- Do not pool excess vaccine from multiple vials.

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)

PLGB 56346/0004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/12/2024

10. DATE OF REVISION OF THE TEXT

27/12/2024