17 October 2024
EMA/510906/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on group of an extension of marketing authorisation and variations

Bimervax XBB.1.16

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

Procedure No. EMEA/H/C/006058/X/0014/G

Note

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

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List of abbreviations

AE	Adverse event
% RP	Recovery percentage
AAE	Antibody Affinity Extraction
ACE2	Angiotensin-converting enzyme 2
ADE	Antibody-dependent enhancement
AE	Adverse event
AEMPs	*Agencia Española de Medicamentos y Productos Sanitarios* (Spanish Agency for Medicines and Health Products)
AESI	Adverse events of special interest
ANOVA	Analysis of variance
BAN	British Approved Name
BSE	Bovine spongiform encephalopathy
CAS	Chemical Abstracts Service
CDMO	Contract development manufacturing organization
CDP	Clinical development plan
cGMP	Current good manufacturing practices
CH	Central helix
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
COVID-19	Coronavirus disease 2019
Cp	Crossing point
CPP	Critical process parameter
CQA	Critical quality attributes
CV	Coefficient of variation
CYP	Cytochrome
DBL	Data base lock
DC	Dendritic cells
DG-R	Deglycosylated - reduced
dLNs	Draining lymph nodes
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug Substance
ECACC	European Collection of Authenticated Cell Cultures
ECB	Expanded cell bank
ECDC	European Centre for Disease Control
ECLIA	Electrochemiluminescence immunoassay
eCRF	electronic Case Report Form
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
EMA	European Medicines Agency
EP	Enrolled population
ERVs	Endogenous Retroviruses

AE	Adverse event
ES	Spain
ETF	Emergency Task force
EU	European Union
EU	Endotoxin unit
F	Fucosylated glycan family
FIH	First-in-human
G	Terminally Galactosylated glycan family
GCP	Good clinical practice
GMFR	Geometric mean fold rise
GMP	Good Manufacturing Practice
GMT	Geometric mean titre
HCP	Host cell protein(s)
HIV	Human immunodeficiency virus
HLA-I	Human leukocyte antigen class I
HRP	Horseradish peroxidase
i.m.	Intramuscular
IAP	Intracisternal Type-A ERVs Particles
IC_{50}	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Intracellular cytokine staining
ICU	Intensive care unit
ID_{50}	Half-infective dose
IFN	Interferon
Ig	Immunoglobulin
IgG	Immunoglobulin G
IL	Interleukin
IMP	Investigational medicinal product
INN	International non-proprietary name
IPC	In-process control
IRS	Interim reference standard
IRT	Interactive Response Technology
ITT	Intention-to-treat
JAN	Japanese Accepted Name
KPP	Key process parameter
LAL	Limulus amoebocyte lysate
LLOQ	Lower limit of quantification
LoD	Limit of detection
LOQ	Limit of quantification
LPLV	Last patient last visit
LS	Least square
MAA	Marketing authorisation application
MAAE	Medically attended adverse event
mAb	Monoclonal antibody

AE	Adverse event
MAP	Mouse antibody production
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed model repeated measures
mRNA	Messenger RNA
MW	Molecular weight
N/A	Not applicable
N/T	Not tested
nAb	Neutralising antibody
Nabs	Neutralising antibodies
NHP	Non-human primates
non-KPP	Non-key process parameter
NR	Non-reduced
NtA	Notice to Applicants
OD	Optical density
OOS	Out of specifications
pAPC	Antigen-presenting cell
PAR	Proven acceptable range
PBMC	Peripheral blood mononuclear cell
PBNA	Pseudovirus-based neutralisation assay
PBS	Phosphate-buffered saline
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PDCO	Paediatric Committee
PES	Polyethersulfone
Ph. Eur.	European Pharmacopoeia
PHEIC	Public Health Emergency of International Concern
PHH-1V	COVID-19 vaccine HIPRA
PHH-1V81	COVID-19 Vaccine HIPRA
PI	Principal investigator
PIP	Paediatric investigation plan
PK	Pharmacokinetic
PNGase	Peptide: N-glycosidase F
PP	Per-protocol population
PP	Process parameter
PRS	Primary reference standard
PRV	Pseudorabies Virus
PSUR	Periodic Safety Update Report
PT	Preferred term
QC	Quality control
qPCR	Quantitative polymerase chain reaction
QTPP	Quality target product profile
R	Correlation coefficient

AE	Adverse event
r^2	Determination coefficient
RBD	Receptor binding domain
RBM	Receptor Binding Motif
Reo3	Reovirus Type 3
RLU	Relative light units
RMP	Risk management plan
RP	Relative potency
RP-HPLC-UV	Reversed phase - high-performance liquid chromatography - ultraviolet
S	Syalilated glycan family
S protein	Spike protein
SA	Scientific Advice
SAE	Serious adverse events
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SEC-HPLC	Size-exclusion-high performance liquid chromatography
SEC-MALLS	Size-exclusion chromatography with multi angle laser light scattering
SIIV	Seasonal surface antigen inactivated adjuvanted influenza vaccine
SmPC	Summary of product characteristics
SOC	System Organ Class
SOP	Standard operating procedure
SP	Safety population
SUB	Single-use bioreactors
TAG-CO-VAC	Technical Advisory Group on COVID-19 Vaccine Composition
TBD	To be defined
$TCID_{50}$	Fifty-percent tissue culture infective doses
TFF	Tangential flow filtration
Tfh	Follicular T helper
Th	CD4 T helper
TLFs	Tables, listings and figures
TSA	Thermal shift stability assay
TSE	Transmissible spongiform encephalopathy
ULOQ	Upper limit of quantification
USAN	United States Adopted Name
UV	Ultraviolet
VAERD	Vaccine-associated enhanced respiratory disease
VLPs	Virus-like Particles
VNA	Virus neutralisation assay
VOC	Variant of concern
VOI	Variant of interest
VSV	Vesicular stomatitis virus
VUM	Variant under monitoring

AE	Adverse event
WCB	Working cell bank
WHO	World Health Organization
WRS	Working reference standard
WT	Wild type
X-MuLV	Xenotropic- Murine Leukaemia Virus
MAH	Marketing authorisation holder
MA	Marketing authorisation

1. Background information on the procedure

1.1. Submission of the dossier

Hipra Human Health S.L. submitted on 8 February 2024 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
B.I.a.6.a	B.I.a.6.a - Changes to the active substance of a vaccine against human coronavirus - Replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine	II
B.I.a.1.j	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	II
B.I.a.1.j	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	II

Extension application to modify the vector used to produce the antigen. To introduce adaptations to the active substance and finished product manufacturing processes and respective control strategies to accommodate those changes.

In addition, the MAH proposed:

Type II B.I.a.6.a - To modify the authorised human coronavirus vaccine Bimervax composition - to add SARS-CoV-2 S XBB.1.16 (damlecovatein) variant strain.

Type II B.I.a.1.j - To add an alternative site responsible for the detection of extraneous agents in cell cultures of the master cell bank (MCB) and working cell bank (WCB) used in the manufacturing process of the PHH-1V81 active substance (AS).

Type II B.I.a.1.j - To add an alternative site responsible for the testing of RBD purity and product-related substances/impurities performed in the PHH-1V81 active substance (AS) and finished product (FP) release and stability.

The MAH applied for the following indication for Bimervax XBB.1.16:

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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0465/2022 on the agreement of a paediatric investigation plan (PIP).

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

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**ETF co-ordinator**
9 November 2023	EMA/SA/0000148115	Florian Klinglmueller

The Scientific advice pertained to the following quality, non-clinical and clinical aspects:

- *CMC development of the adapted PHH-1V81 vaccine*
- *Agreement with the selection of vaccine candidate XBB1.16*
- *Concurrence that Bimervax's recombination-based protein technology is a manufacturing platform*
- *Agreement that the two proposed non-clinical safety and immunogenicity studies in mice could support the approval of the adapted vaccine*
- *Design of the phase IIb/III safety and immunogenicity clinical trial to support approval of the adapted vaccine*

1.6. Steps taken for the assessment of the product

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

Rapporteur: Beata Maria Jakline Ullrich

The application was received by the EMA on	8 February 2024
The procedure started on	29 February 2024

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 May 2024
ETF discussion took place on	31 May 2024
BWP discussion took place on	19 June 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	27 June 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	19 July 2024
The CHMP Rapporteurs circulated the CHMP Rapporteurs Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	29 August 2024
BWP discussion took place on	11 September 2024
The CHMP agreed on the consolidated List of outstanding issues to be sent to the MAH during the meeting on	19 September 2024
The MAH submitted the responses to the CHMP consolidated List of outstanding issues on	25 September 2024
The CHMP Rapporteurs circulated the CHMP Rapporteurs Assessment Report on the responses to the List of Outstanding issues to all CHMP and PRAC members on	03 October 2024
BWP discussion took place on	09 October 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Bimervax on	17 October 2024

2. Scientific discussion

2.1. Problem statement

In December 2019, the World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020, the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally. On 30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. Four years later, SARS-CoV-2 strains are still circulating, and the COVID-19 infection might still be a concern, especially in vulnerable populations. COVID-19 infection has the risk of development of the long COVID condition even in non-vulnerable, otherwise healthy population.

The emergence of SARS-CoV-2 variants with multiple mutations have led MAHs to develop variant vaccine constructs. To assist in the continued management of the COVID-19 public health threat, a new updated vaccine XBB.1.16 is being introduced to the MAA as a new variant vaccine.

2.1.1. Disease or condition

COVID-19 is a disease caused by the novel coronavirus SARS-CoV-2. The clinical manifestation of COVID-19 is non-specific and variable. It can range from no symptoms (asymptomatic) to severe pneumonia and death. The disease burden is highest amongst subjects with increased age; however, all age groups are susceptible.

2.1.2. Epidemiology

The transmission characteristics of SARS-CoV-2 are very similar to those of SARS-CoV and pandemic influenza (Viner et al., 2020; Rahman et al., 2021) and SARS-CoV-2 presents a moderate to severe infectious threat with a mean R0 range of 2.24 to 3.58 (Rahman et al., 2021). As a respiratory infectious disease, the virus is transmitted primarily by droplets, respiratory secretions, and direct contact although viral particles have been isolated from faecal swabs and blood. The incubation period on average is 1–14 days, however, is generally 3–7 days.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer, and obesity are considered risk factors for developing severe COVID-19.

2.1.3. Aetiology and pathogenesis

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

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit of the spike protein catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

2.1.4. Clinical presentation, diagnosis

The most common symptoms of infection include headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhoea (60.1%), gustatory dysfunction (54.2%), sore throat (52.9%) and fever (45.4%).

Patients with COVID-19 experience varying degrees of severity. Some individuals may be asymptomatic, whereas around 80% of infected individuals have only mild infection (Viner et al., 2020; Rahman et al., 2021). Importantly, asymptomatic subjects may have viral loads similar to those of symptomatic patients and are thus possible sources of infection. Of the remaining cases, approximately 15% develop severe disease characterised by dyspnoea, hypoxia, and lung changes on imaging, and 5% are critically ill. The critical ill often include elderly and those with underlying disorders who may experience acute respiratory distress syndrome, septic shock, metabolic acidosis, and coagulation dysfunction, which may ultimately lead to multiple organ failure and even death. A small percentage of patients also manifest gastrointestinal symptoms, such as diarrhoea and vomiting.

Overall, poor clinical outcomes among adult COVID-19 patients are associated with a higher comorbidity burden.

In addition to the above, SARS-CoV-2 is also known to cause so-called "long COVID" or "post-COVID condition" which is generally defined as individuals with ongoing symptoms of COVID-19 that persist beyond four weeks from initial infection (World Health Organization (WHO), 2021). Older age, female sex, poor pre-pandemic mental or general health, asthma, smoking, vaping, hospitalisation, or being overweight or obese are factors associated with post COVID-19 condition. The following symptoms are considered to be the most common for long COVID: fatigue, dyspnoea, cough, sleep disturbances, anxiety, depression, cognitive impairment, and difficulty concentrating. Fatigue and concentration problems were noted to last beyond 12 weeks.

2.1.5. Management

At the time of authorisation of this vaccine, several products have received marketing authorisation for the treatment of COVID-19. These encompass antiviral therapy (PF-07321332 / ritonavir, remdesivir), anti-inflammatory therapy (dexamethasone), IL-6 inhibitor (tocilizumab), IL-1 inhibitor (anakinra) as well as monoclonal antibodies directed against the SARS-CoV-2 spike protein (casirivimab/imdevimab, regdanvimab, sotrovimab and tixagevimab / cilgavimab). These therapies have shown variable efficacy depending on the severity and duration of illness as well as against different variants of concern.

Besides Bimervax, there are three approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease: Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), and Nuvaxovid (EMEA/H/C/005808). The emergence of SARS-CoV-2 variants with multiple mutations have the MAHs to develop variant vaccine constructs. To assist in the continued management of the COVID-19 public health threat, the mRNA vaccines as well as Nuvaxovid include in their marketing authorisation adapted Omicron vaccines.

2.2. About the product

HIPRA has developed PHH-1V81, which is an adapted version of the parent vaccine Bimervax and contains a SARS-CoV-2 S protein RBD fusion homodimer (XBB.1.16 variants) as the antigen. With respect to the Bimervax antigen, the PHH-1V81 antigen has the same number of amino acids in the peptide sequence (438 amino acids, corresponding to amino acids 319 to 537 of the spike protein) and maintain the dual domain dimeric structure of the original Bimervax a SARS-CoV-2 S protein RBD fusion heterodimer (B.1.351-B.1.1.7 variants) as the antigen.

Bimervax XBB.1.16 is administered by a single i.m. injection. The administration volume is 0.5 mL per dose. The dose level of active substance is 40 µg per dose whereas the dose of SBQA adjuvant is 50% v:v (0.25 mL).

Bimervax XBB.1.16 is indicated for active immunisation to prevent COVID-19 in individuals 16 years of age and older.

2.3. Type of Application and aspects on development

2.4. Quality aspects

2.4.1. Introduction

This line extension (LE) for Bimervax was submitted to modify the vector used to produce the antigen. Some adaptations to the active substance and finished product manufacturing processes were introduced alongside respective control strategies to accommodate those changes.

A type II variation (B.I.a.6.a) was grouped with this line extension to modify the authorised human coronavirus vaccine Bimervax composition - to add SARS-CoV-2 Omicron XBB.1.16 variant strain as another presentation.

Two additional type II variations concerning manufacturing sites were also grouped and part of this LE as follows:

- Type II B.I.a.1.j - To add an alternative site responsible for the detection of extraneous agents in cell cultures of the master cell bank (MCB) and working cell bank (WCB) used in the manufacturing process of the PHH-1V81 active substance (AS).
- Type II B.I.a.1.j - To add an alternative site responsible for the testing of receptor-binding-domain (RBD) purity and product-related substances/impurities performed in the PHH-1V81 active substance (AS) and finished product (FP) release and stability.

Bimervax XBB.1.16 (PHH-1V81, COVID-19 Vaccine (recombinant, adjuvanted)) finished product (FP) is a sterile, white homogeneous emulsion for injection, recombinant protein-based vaccine for intramuscular use. One dose (0.5 mL) contains 40 micrograms (µg) of SARS-CoV-2 virus recombinant spike (S) protein RBD fusion homodimer comprised of Omicron XBB.1.16- XBB.1.16 strains, as active substance (INN: damlecovatein), adjuvanted with SQBA. Other ingredients are: disodium phosphate dodecahydrate, potassium dihydrogen phosphate, sodium chloride, potassium chloride and water for injections. The SQBA adjuvant contains squalene, polysorbate 80, sorbitan trioleate, sodium citrate, citric acid and water for injections. The product will be available in 1 dose of 0.5 mL and pack sizes of 5, 10 and 20 single dose vials.

2.4.2. Active Substance

2.4.2.1. General information

The subunit antigen of the PHH-1V81 vaccine is a SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion homodimer – Omicron XBB.1.16-XBB.1.16 variant.

This antigen is expressed in the same Chinese Hamster Ovary (CHO) cell line as the parent vaccine (PHH-1V, B.1.351-B.1.1.7 variants)) but PHH-1V81 contains two RBD monomers derived from the Omicron XBB.1.16 variant from SARS-CoV-2.

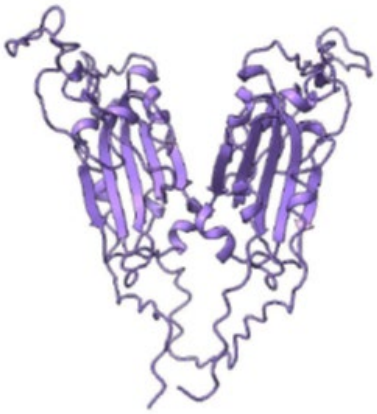


Figure 1: Structure of XBB.1.16-XBB.1.16 homodimer receptor-binding domain (RBD) immunogen of PHH-1V81

With respect to the parent heterodimer vaccine (PHH-1V), PHH-1V81 antigen has the same number of amino acids in the peptide sequence (438 amino acids, corresponding to amino acids 319 to 537 of the spike protein) and maintains the dual domain dimeric structure of the original parent antigen: positions 319-537 of the XBB.1.16 variant, duplicated to form the RBD homodimer.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturers

PHH-1V81 active substance (AS) is manufactured by Laboratorios Hipra, S.A., Ctra. C-63, Km 48,300. Polígono, Industrial El Rieral, 17170 Amer (Girona), Spain.

All the manufacturing sites involved in the manufacture of the active substance are appropriately authorised and hold valid GMP certification.

Description of manufacturing process and process controls

As the parent vaccine PHH-1V, the PHH-1V81 AS manufacturing process starts with a CHO suspension cell line stably transfected however, with a new vector expressing the active substance antigen.

The manufacturing process starts with thawing of a single working cell bank (WCB) vial followed by serial cell culture expansion steps to the final bioreactor (upstream process). The material from the production bioreactor is harvested and clarified followed sequentially by concentration and diafiltration, chromatography, viral clearance, precipitation, chromatography, concentration and diafiltration, viral clearance by nanofiltration and final sterile filtration (downstream process).

Adjustments have been made to the AS manufacturing process, due to the intrinsic characteristics of the protein compared to the parent antigen PHH-1V. Hence, a dedicated control strategy has been developed for the adapted antigen.

For each new strain introduced in the active substance manufacturing process, an extended comparability exercise should be performed, to ensure that the process remains valid and that the active substance maintain the same quality. Such full comparability assessment was not submitted in the initial submission. Therefore, a Major Objection was initially raised about the analytical comparability of the active substance batches from XBB.1.16-XBB.1.16 strain variant (PHH-1V81) vs the active substance parent vaccine (PHH-1V). The complete analytical comparability exercise of PHH-1V81 vs PHH-1V was further provided. With the full comparability exercise, it was demonstrated that the process design, process performance, and analytical attributes for PHH-1V81 were similar to PHH-

1V, and that the strain-specific differences observed are not expected to impact Bimervax efficacy and safety. Therefore, the Major Objection initially raised concerning the comparability to the active substance parent vaccine has been satisfactorily solved.

Control of materials

Raw materials

For the strain update, the only data of the new raw materials used in the manufacture of the AS PHH-1V81 were provided.

Source, history and generation of the cell substrate:

The host cell line of origin was the same CHO cells used for the parent antigen. However, for transfection to form PHH-1V81, a new vector was used.

The MCB and WCB were established and duly controlled.

Genetic stability of the cell line has been demonstrated. For the XBB.1.16 strain update, an alternative site responsible for the detection of extraneous agents in cell cultures of the MCB and WCB was approved.

Control of critical steps and intermediates

The critical quality attributes (CQAs) established for the adapted antigen PHH-1V81 are the same as those defined for the parent antigen PHH-1V. However, the risk assessment performed to define the CQAs for the RBD fusion heterodimer (parent antigen) has been reviewed for PHH-1V81 based on the previous knowledge acquired from the parent antigen PHH-1V.

A process control strategy based on previous knowledge and experience gained from the parent antigen PHH-1V has been established to consistently ensure the required quality of PHH-1V81 DS. The different elements that form the control strategy of the manufacturing process of the PHH-1V81 DS are: material attributes, process controls (which includes the process parameters and in-process controls, IPCs), and release controls.

Process validation and/or evaluation

PHH-1V81 AS manufacturing process validation was performed with 3 consecutive GMP commercial scale batches.

The 3 consecutive batches tested met the pre-determined process validation acceptance criteria. No deviation was observed during the study. Nevertheless, for the process validation data provided, some clarifications concerning holding time were required and satisfactorily solved. The data demonstrate that the manufacturing process produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

Material attributes used for the manufacturing process of the adapted antigen PHH-1V81 are the same as those used for the parent antigen PHH-1V. Laboratory development studies were performed to justify some of the process parameters and the IPC performed in the manufacture of the PHH-1V81 AS. These studies were complete with data obtained at commercial scale.

PHH-1V81 AS specifications mostly follow the specifications established and approved for the PHH-1V AS.

Overall, the manufacturing process development is considered adequate. In addition, batch release data of the PHH-1V81 batches have been compared to historical data for all PHH-1V batches and the differences observed have been evaluated in relation to their potential clinical relevance.

Comparability stability studies show improved stability for the adapted active substance PHH-1V81 versus the parent AS PHH-1V.

Small scale manufacturing processes were used for initial development of PHH-1V81 AS. Batch release data of the AS batches used during the different phases of the development were provided and comparability to the commercial batches demonstrated.

Characterisation

The same orthogonal assays used for the in-depth characterisation of the RBD fusion heterodimer of the parent vaccine PHH-1V, has been applied to the new RBD fusion homodimer of the adapted vaccine, PHH-1V81.

The techniques and tests used for characterization of PHH-1V81 active substance generated relevant information on the primary, secondary and higher-order structure including post-translational (e.g. glycoforms) and other modifications (amino acid oxidation and deamidation, charge heterogeneity, secondary and higher-order structure, and product-related substances/impurities of the RBD fusion protein) as well as the biological activity of the active substance. Data from one pre-clinical batch and 3 PPQ batches were presented.

Overall, the combination of orthogonal physicochemical and biological methods used, allows adequate characterisation of PHH-1V81 active substance and results show consistency between the batches used for the characterisation. It is also noted that the commercial batch used in clinical trials was used for characterisation studies of PHH-1V81 active substance.

The characterisation of PHH-1V81 AS was also compared to historical data of PHH-1V AS. The strain-specific differences observed are not expected to impact efficacy and safety.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The release and shelf-life specifications for the active substance include appropriate general tests (for appearance, pH and thermal shift assay (TSA)), tests for identity, heterogeneity, purity and impurities, biological activity (potency), quantity, sterility and endotoxins.

The tests proposed for PHH-1V81 AS release and shelf-life are the same as the ones approved for the parent vaccine PHH-1V. PHH-1V81 AS specifications limits mostly follow the specifications established and approved for the parent PHH-1V AS.

As no data related to PHH-1V81 was provided to demonstrate that the changes proposed in the acceptance criteria for PHH-1V81 for product-related substances/impurities will not negatively affect the safety and efficacy of the Bimervax vaccine, the same acceptance criteria for product-related substances/impurities by SEC-HPLC of the parent vaccine was requested to be applied to the AS/FP PHH-1V81.

The initial proposed specification of the AS were therefore revised for the new variant PHH-1V81 as they were not representative of the current manufacturing process neither were they warranted from the stability profile. It is recognised that more manufacturing experience is needed to understand if the specifications require further amendment, nonetheless the revised proposed limits are suitable to guarantee the quality attributes of the final vaccine since they have been clinically qualified.

The applicant is recommended to submit the reassessment of the active substance specification after 20 AS batches are produced at commercial scale, and if applicable submit variation(s) to revise the PHH-1V81 AS specifications (Recommendation 3).

Analytical procedures

Considering that the RBD amino acid sequence differs between PHH-1V and PHH-1V81 variants, the AS analytical procedures which are intrinsic or specific to the antigen, have been adapted and validated to confirm the validity of the analytical methods for the new antigen. Summaries of analytical methods have been provided and descriptions of the in-house methods are considered satisfactory. The in-house analytical procedures used for AS testing were validated as per ICH Q2 (R2) guidelines.

Approved protocols and validation reports for each analytical method were provided. The relevant parameters have been assessed and the presented verification and validation reports indicate suitability of the analytical procedures for their intended use.

Overall, the new and revised methods for PHH-1V81 AS batch release and their validation are endorsed. The relevance of the TSA in stability studies should be demonstrated in future new strains. Therefore, for future strain updates the applicant is recommended to demonstrate that the TSA is able to detect progressive degradation of the RBD active substance and RBD finished product (Recommendation 2).

Batch analysis

Batch release data from consecutive commercial batches have been provided (one batch was used in the clinical trial). The batches comply with the release specifications. Overall, the data from these consecutive commercial batches demonstrate good manufacturing consistency for PHH-1V81 AS.

Reference standards

A two-tiered system for the reference standard (RS) is used. A development reference standard, and subsequently primary reference standard and working reference standard were established.

Container closure system

The primary packaging system for the adapted recombinant protein RBD fusion homodimer (PHH-1V81) active substance is the same as the one used for the parent recombinant protein RBD fusion heterodimer (PHH-1V) AS.

A toxicological risk assessment has been performed with the PHH-1V81 antigen The information provided in this section is acceptable.

2.4.2.4. Stability

A shelf-life of 6 months is claimed for the active substance when stored at 2 ºC – 8 ºC.

Six months data from ICH stability studies have been completed for four active substance PHH-1V81 commercial batches at long-term (5 ºC ± 3 ºC) and at accelerated conditions (25 ºC ± 2 ºC). The 6 months comparability stability data generated under accelerated conditions (25 ºC ± 2 ºC), show an improved stability for the adapted active substance PHH-1V81 versus the parent active substance PHH-1V.

The approved AS shelf-life for the parent vaccine PHH-1V is 5 months at 5 ºC ± 3 ºC in the proposed primary packaging. However, for the strain adapted vaccine PHH-1V81, all tested parameters remained within the established acceptance criteria after 6 months of storage at 5ºC ± 3ºC, e.g. one month more than the shelf-life for the PHH-1V vaccine.

The PHH-1V AS has shown susceptibility to elevated temperature, oxidising agents, and low pH conditions in the parental vaccine, consistent with the expectations for a biological entity of proteinaceous nature. PHH-1V AS has demonstrated stability under other stressed conditions such as mechanical agitation or fluorescent light.

In conclusion, based on the results, a shelf-life of 6 months for the active substance at 5ºC ± 3ºC, with no temperature excursion, is considered acceptable for the strain adapted vaccine PHH-1V81.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description and composition of the finished product

The adaptation of the vaccine against new emerging COVID-19 variants involves replacing the RBD strain/s in the adapted vaccine composition, while the rest of vaccine components remain unchanged.

The FP COVID-19 Vaccine HIPRA (PHH-1V81) contains 40 µg/dose of the active substance SARS-CoV-2 virus (recombinant spike (S) protein receptor binding domain (RBD) fusion homodimer – Omicron XBB.1.16-XBB.1.16 variant. Other ingredients are: disodium phosphate dodecahydrate, potassium dihydrogen phosphate, sodium chloride, potassium chloride and water for injections. The SQBA adjuvant contains squalene, polysorbate 80, sorbitan trioleate, sodium citrate, citric acid and water for injections.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

The adjuvanted vaccine is presented as a sterile, preservative-free white homogeneous emulsion for injection for intramuscular use and supplied in one pack sizes of 5, 10 and 20 PHH-1V81 40 µg/0.5 mL single-dose vials.

The active substance, the antigen, is formulated with a phosphate-buffered saline (PBS) solution and with SQBA adjuvant (main components are: squalene, polysorbate 80 and sorbitan trioleate).

Overfilling is carried out to ensure that the correct volume of the appropriate dose (0.5 mL) can be extracted from the vials. No overages are included in the product formulation.

The primary packaging and secondary packaging material for the PHH-1V81 FP are the same as the one used for the parent PHH-1V FP in single-dose container.

Finished Medicinal Product - SQBA adjuvant, emulsion for injection

Description and composition of the finished product

The SQBA adjuvant for Bimervax XBB.1.16 is described as an oil-in water emulsion for intramuscular use containing squalene as the internal oil phase, sodium citrate-citric acid buffer as the external aqueous phase and polysorbate 80 and sorbitan trioleate as emulsifiers. There have been no changes

to the SQBA adjuvant from the parent vaccine and the information provided in relation to the SQBA adjuvant is adequate.

Pharmaceutical development

HIPRA developed an adapted vaccine (PHH-1V81) containing an RBD fusion homodimer based on the XBB.1.16 strain. The ECDC-EMA statement on updating COVID-19 vaccines composition for 2 variants of 7th June 2023, stated that adapted COVID-19 vaccines should have a monovalent composition with the inclusion of a strain belonging to the XBB family of Omicron subvariants.

The amount defined for PHH-1V81 AS in PHH-1V81 FP is 40 µg/dose and is the same as that established for the parent vaccine (PHH-1V FP), which has a demonstrated efficacy and safety profile in different clinical trials.

After confirming the immunogenicity of the adapted vaccine, the manufacturing process of PHH-1V81, was developed.

The manufacturing process for the FP COVID-19 Vaccine HIPRA (PHH-1V81; homodimer - XBB.1.16-XBB.1.16 variant) in single-dose container is essentially identical to that of the parent vaccine, PHH-1V. The main difference in the manufacturing process involves the replacement of the RBD strains (fusion homodimer – XBB.1.16-XBB.1.16 variants (PHH-1V81) vs heterodimers – B.1.351-B.1.1.7 variants (PHH-1V)) in the adapted vaccine composition.

The quality target product profile (QTPP) of PHH-1V81 FP is similar to that of PHH-1V FP, and is designed to be manufactured at the same manufacturing sites with the same batch size range and using the same industrial equipment as established for the parent vaccine. The development of the PHH-1V81 FP manufacturing process has been based on assessing the impact of a) the change in protein on the established manufacturing process of the parent vaccine and b) the implementation of the necessary adaptations, including those in the control strategy.

An appropriate process control strategy for PHH-1V81 FP has been established based on knowledge and previous experience with parent vaccine PHH-1V, to consistently ensure the required quality of PHH-1V81 FP. The same critical process parameters (CPPs), key process parameters (KPPs) and non-key process parameters (non-KPPs) used for the parent vaccine are applicable for the vaccine PHH-1V81.

For each new strain introduced in the finished product manufacturing process, an extended comparability exercise should be performed, to ensure that the process remains valid and that the finished product maintain the same quality. Such full comparability assessment was not submitted in the initial submission. Therefore, a Major Objection was initially raised about the analytical comparability of the finished product batches from XBB.1.16-XBB.1.16 strain variant (PHH-1V81) vs finished product parent vaccine (PHH-1). A complete analytical comparability exercise of PHH-1V81 vs PHH-1 was further provided. With the full comparability exercise, it was demonstrated that the process design, process performance, and analytical attributes for PHH-1V81 were similar to PHH-1, and that the strain-specific differences observed are not expected to impact Bimervax efficacy and safety. Therefore the Major Objection initially raised concerning the comparability of PHH-1V81 to finished product parent vaccine has been satisfactorily solved.

The primary packaging materials for the PHH-1V81 vaccine is the same as the ones approved for parent PHH-1V vaccine in single dose container.

The microbiological attributes are controlled by several sterile filtrations as well as finished product batch release specification for sterility and endotoxins.

2.4.3.2. Manufacture of the product and process controls

Manufacturers

All the manufacturing sites involved in the manufacturing process of the finished product have been clearly indicated, as well as the compliance with GMP adequately demonstrated.

Description of manufacturing process and process controls

The finished product (PHH-1V81) is manufactured using standard manufacturing steps. Briefly, the Bimervax XBB.1.16 finished product manufacturing process starts with the addition of the active substance RBD fusion homodimer to the container containing the SQBA adjuvant and stirred until complete homogenisation. In parallel, the buffer solution is prepared by dissolving the components, stirred until complete homogenisation, sterile filtered and the filtrate collected on the container containing the mixture of antigen and adjuvant. The emulsion is further homogenised and filtered to obtain the vaccine bulk. The filtered vaccine bulk is sterile filtered followed by immediate aseptic filling under inert atmosphere.

Once the vials are filled and capped, vaccine vials are tested, visually inspected, labelled, packed and released.

No reprocessing activities are considered for the finished product production.

Process validation

The process validation study included manufacture of 3 consecutive batches The 3 batches comply with the specifications established for in-process controls and batch release. It is therefore concluded that the PHH-1V81 FP manufacturing process has been duly validated and that it is consistent.

2.4.3.3. Product specification, analytical procedures, batch analysis

The release and shelf-life specifications for the finished product include appropriate general tests, tests for identity, heterogeneity, purity and impurities, biological activity (potency), quantity, sterility, endotoxins, visible and sub-visible particles and extractable volume.

Analytical methods

Considering that the RBD amino acid sequence differs between the parent PHH-1V and PHH-1V81 variants, the finished product analytical procedures which are intrinsic or specific to the antigen, have been adapted and validated to confirm the validity of the analytical methods for the new antigen. Adequate summaries of analytical methods have been provided and descriptions of the in-house methods are considered satisfactory. The in-house analytical procedures used were validated as per ICH Q2 (R2) guidelines. Validation reports for each analytical method were provided. The relevant parameters have been assessed and the presented verification and validation reports indicate suitability of the analytical procedures for their intended use.

Other analytical methods not affected by the intrinsic or specific characteristics of the adapted antigen, have been minimally adapted and revalidated.

Finally, general tests and analytical procedures linked to the excipients remain identical as no impact is expected.

Overall, the analytical methods are considered suitable for their intended use and sufficient information was provided.

Batch analysis

PHH-1V81 FP GMP batches were manufactured at commercial scale and filled. Each PHH-1V81 FP batch has been produced with different batches of PHH-1V81 AS.

All these FP batches comply with batch release specifications. One of these batches has been used in the clinical trial (HIPRA-HH-14) and in the pre-clinical study EIDHH-2023-023-PHH-1V81. Three batches were used for manufacturing process validation. No data have been provided about some batches used in the first non-clinical studies. This is acceptable since data of batches for the relevant pre-clinical and clinical studies were available. The risk analysis of potential elemental impurities in PHH-1V81 show that there is no risk. In addition, based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The Applicant states that, given the limited manufacturing experience with the adapted FP, there may be a need to revise the current specifications in the future when data on an additional 15 commercial batches are available. This proposal is acknowledged and endorsed therefore the applicant is recommended to submit the reassessment of the finished product specification after 15 additional batches are produced at commercial scale, and if applicable submit the revision of the finished product specifications (Recommendation 5).

2.4.3.4. Stability of the product

A shelf-life of 9 months when stored at 2 ºC – 8 ºC is claimed for the PHH-1V81 vaccine.

Stability studies in line with ICH were conducted on batches of PHH-1V81 FP filled in single-dose containers.

Theresults under real time and accelerated conditions are in line with the ones obtained for batches from the parent vaccine packaged in single-dose and multidose containers.

Based on the provided stability data, a shelf-life of 9 months at 2 ºC – 8 ºC for the PHH-1V81 vaccine is acceptable. If future data support longer stability, the shelf-life of the PHH-1V81 vaccine may be extended accordingly through the appropriate variation.

2.4.3.5. Adventitious agents

During the manufacture of the active substance, the only material that has an animal or human origin is the CHO cells used as starting material for the expression of the RBD protein. Apart from the CHO cells, none of the raw materials is of direct animal or human origin or have been produced using animal-origin components. Taking into account the information provided, it is concluded that the risk for TSE/BSE contamination do not exist or is very low. Other than the CHO cell line expressing the active substance and squalene (fish origin) contained in SQBA adjuvant, no animal or human derived materials are used in the manufacturing process of the vaccine. Therefore, there is no concern about TSE safety.

Data on viral clearance for PHH-1V81 AS/FP were extrapolated from the PHH-1V AS/FP manufacturing process, which is considered acceptable since minor changes, not impacting the steps of viral inactivation or removal, were made to the AS purification and FP manufacturing process.

Nevertheless, a confirmatory viral clearance run has been conducted for the adapted vaccine PHH-1V81.

The information provided regarding adventitious agents evaluation is sufficient and adequate.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance of Bimervax vaccine is a SARS-CoV-2 virus recombinant Spike (S) protein RBD fusion heterodimer – B.1.351-B.1.1.7 variant (PHH-1V), which was authorised on 30 March 2023.

With this line extension, HIPRA has developed Bimervax XBB.1.16 (PHH-1V81), which is an adapted version of the parent vaccine Bimervax and contains a SARS-CoV-2 S protein RBD fusion homodimer (Omicron XBB.1.16-XBB.1.16 variant) as the antigen. With respect to the Bimervax antigen, the PHH-1V81 antigen has the same number of amino acids in the peptide sequence (438 amino acids, corresponding to amino acids 319 to 537 of the spike protein) and maintains the dual domain dimeric structure of the original Bimervax antigen.

The formulation, dose level and intended clinical route of administration for PHH-1V81 are the same as the parent vaccine Bimervax. This recombinant subunit antigen is expressed in the same CHO cell line as the Bimervax parent vaccine. This new antigen is a purified fusion protein (single polypeptide) in which the two RBD chains have the same peptide sequence (i.e. single chain homodimer).

An adapted manufacturing process, including an adapted control strategy, has been developed and validated for PHH-1V81 AS and FP. The previous experience and knowledge acquired for PHH-1V (the parent vaccine) has been used as the foundation of the updated vaccine. The comparability of the PHH-1V and PHH-1V81 manufacturing processes has been shown with expected exceptions linked to the strain adaptation. The development batch used in the non-clinical study, the batch for the clinical study manufactured at commercial scale and the two other batches manufactured at commercial scale were found comparable.

A shelf-life of 6 months for the PHH-1V81 AS at 2-8ºC is approvable. Nine months stability data (real time and accelerated) were provided for PHH-1V81 FP and show a comparable stability profile as the parent vaccine. Therefore, a shelf-life of 9 months at 2-8ºC for the finished product as proposed by the applicant is endorsed.

A comprehensive risk assessment on elemental impurities and nitrosamine impurities were provided and found acceptable.

For each new strain introduced in the AS/FP manufacturing process, an extended comparability exercise should normally be performed, to ensure that the process remains valid and that the AS/FP maintain the same quality. Such full comparability assessment was not submitted in the initial submission. Therefore, Major Objections were initially raised about the analytical comparability of the AS and FP batches from XBB.1.16-XBB.1.16 strain variant (PHH-1V81) vs AS and FP parent vaccine (PHH-1). The complete analytical comparability exercise of PHH-1V81 vs PHH-1 was subsequently provided. With the full comparability exercise, it was demonstrated that the process design, process performance, and analytical attributes for PHH-1V81 were similar to PHH-1, and that the strain-specific differences observed are not expected to impact Bimervax XBB.1.16 efficacy and safety. Therefore, the Major Objections initially raised concerning the comparability of Bimervax XBB.1.16 to parent vaccine at the AS and FP level have been satisfactorily solved.

Some recommendations (related to TSA; comparability exercise update; AS and FP specifications and Module 2 and 3 updates) were set. The applicant is recommended to update Module 2 and 3 concerning the internal term "mg of activity" (mga) which should be replaced by mg of "RBD fusion homodimer" (Recommendation 4). For future strain updates, it is also recommended to submit accelerated stability data in order to allow better extrapolation of the new strain AS/FP shelf-life (Recommendation 1). It is also assumed that the recommendations about the revision of AS/FP specification after production of additional batches at commercial scale will not be applied for the PHH-1V81 vaccine because it will not be commercialised. Nevertheless, these recommendations should be

followed for future new strain updates (Recommendation 3 & 5). Furthermore, for future strain updates the applicant is also recommended to demonstrate that the TSA is able to detect progressive degradation of the RBD AS and RBD FP (Recommendation 2).

This line extension is approved to support future strain variants of the vaccine. All the recommendations listed in this report should be considered and addressed for the approval of future new strain variants of Bimervax. Should the PHH-1V81 vaccine be commercialised, the recommendations should be appropriately addressed.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. This line extension to register Bimervax XBB.1.16 is approvable from the quality point of view.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends several points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

The MAH submitted new non-clinical data in support of the authorisation of the updated monovalent Bimervax XBB.1.16 vaccine, with PHH-1V81, the homodimeric form of RBD domain of Omicron XBB.1.16 SARS-CoV-2 variant, as vaccine antigen.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Table 1 presents an overview of the five non-clinical pharmacology studies that have been submitted in support of this application. The studies evaluated the safety and immunogenicity of PHH-1V81 vaccine administered intramuscularly as a primary or booster vaccination after a mRNA vaccine in mice (BALB/c).

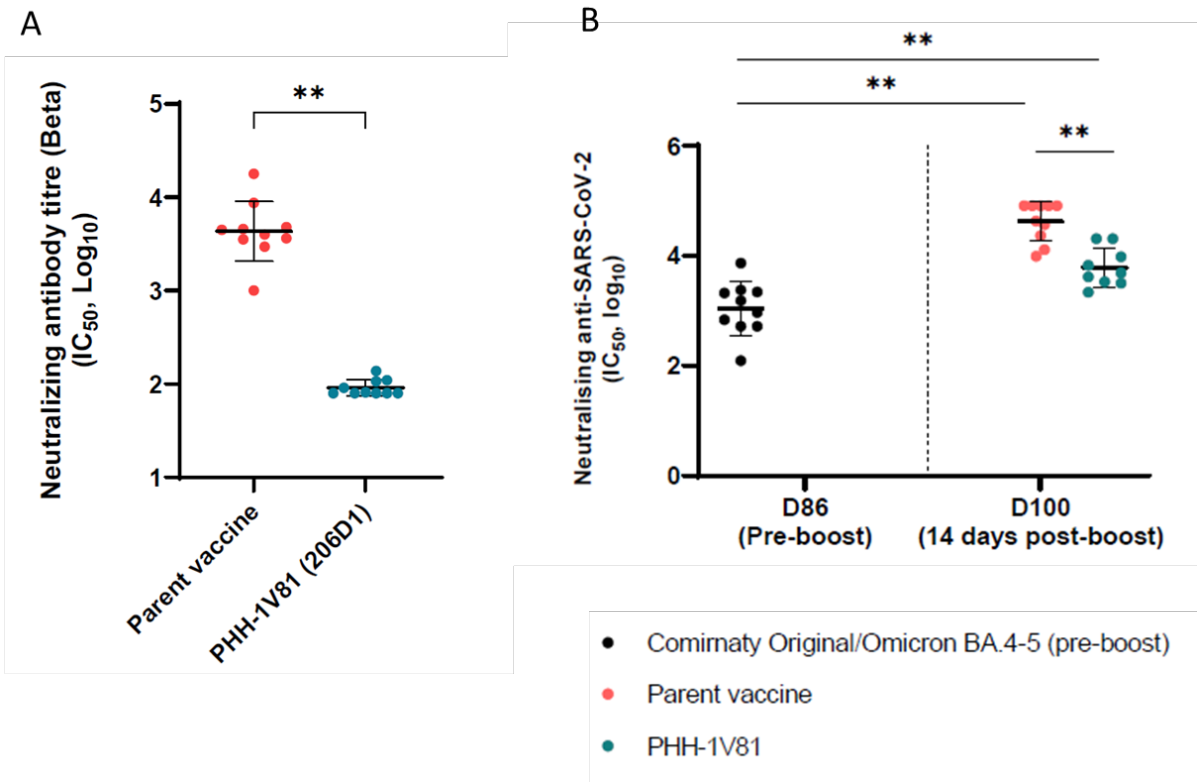
Table 1: Non-clinical pharmacology studies – PHH-1V81

Study ID	Bimervax vaccination	Vaccination and sampling schedules	age at D0 (weeks)
EIDHH-2023-00**9**-PHH1V81	primary	D0: 1st dose of Bimervax + wm D14: 2nd dose of Bimervax + wm D28: wm and PBNA	10

EIDHH-2023-0**10**-PHH1V81	booster	D0: 1st dose of Comirnaty D14: 2nd dose of Comirnaty D70: Bimervax + wm D84: wm and PBNA	9
EIDHH-2023-0**11**-PHH1V81	booster	D0: 1st dose of Comirnaty D14: 2nd dose of Comirnaty D86: Bimervax + wm D100: wm, PBNA and total IgG	9
EIDHH-2023-0**15**-PHH1V81	primary	D0: 1st dose of Bimervax + wm D14: 2nd dose of Bimervax + wm D28: wm and PBNA and total IgG	10
EIDHH-2023-0**23**-PHH1V81	primary	D0: 1st dose of Bimervax + wm D14: 2nd dose of Bimervax + wm D28: wm and PBNA	8-9

In all non-clinical studies the parent vaccine Bimervax PHH-1V elicited significantly higher neutralizing activity against the Beta variant than PHH-1V81, as expected (Figure 2), This could be observed when PHH-1V was used as primary vaccine (Figure 2A) and as booster as well (Figure 2B).

Figure 2: Neutralising antibody responses against SARS-CoV-2 Beta variant by PBNA.

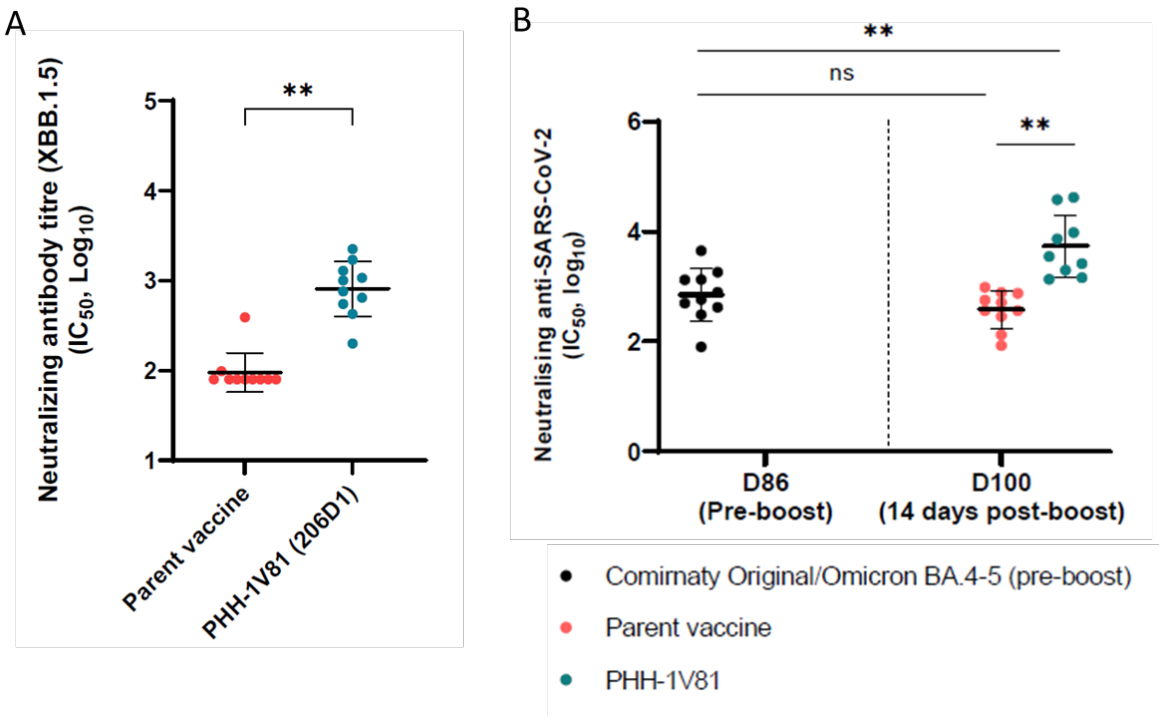


A. Primary vaccination with the parent and adapted Bimervax vaccines. Sera from mice collected on D28 in study EIDHH-2023-023-PHH1V81. **B.** Booster vaccination with Bimervax parent and adapted vaccines after priming with bivalent Comirnaty vaccine. Sera from mice collected on D86 and D100 in study EIDHH-2023-011-PHH1V81. Titres are expressed as $\log_{10}$ IC_{50}. Each data point represents an individual mouse serum with bars denoting the mean titre per group and the standard deviation. Statistically significant differences between groups are indicated with a line on top of each group: ** $p<0.01$. The representation of axes *y* is different. Results described in study

EIDHH-2023-009-PHH1V81, EIDHH-2023-010-PHH1V81, and EIDHH-2023-015-PHH1V81 are similar and not shown here.

In contrast, PHH-1V81 lead to significantly higher amount of neutralizing antibodies against Omicron XBB.1.5 than the parent vaccine Bimervax PHH-1V both as primary (Figure 3A) and booster vaccination (Figure 3B).

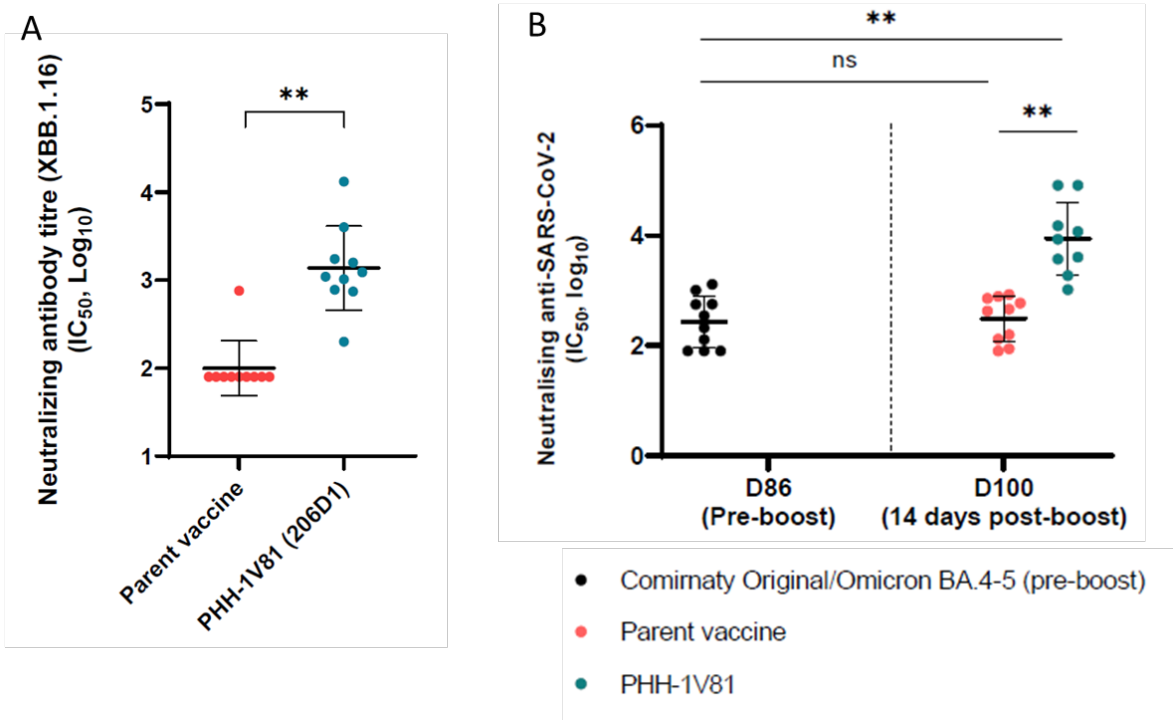
Figure 3: Neutralising antibody responses against SARS-CoV-2 XBB.1.5 variant by PBNA



A. Primary vaccination with the parent and adapted Bimervax vaccines. Sera from mice collected on D28 were assessed by pseudovirus neutralising activity in study EIDHH-2023-023-PHH1V81. **B.** Booster vaccination with Bimervax parent and adapted vaccines after priming with bivalent Comirnaty vaccine. Sera from mice collected on D86 and D100 in study EIDHH-2023-011-PHH1V81.
Titres are expressed as $\log_{10}$ IC_{50}. Each data point represents an individual mouse serum with bars denoting the mean titre per group and the standard deviation. Statistically significant differences between groups are indicated with a line on top of each group: ** p<0.01. The representation of axes *y* is different. Results described in study EIDHH-2023-009-PHH1V81, EIDHH-2023-010-PHH1V81, and EIDHH-2023-015-PHH1V81 are similar and not shown here.

PHH-1V81 also caused significantly higher amount of neutralizing antibodies against Omicron XBB.1.16 than the parent vaccine Bimervax PHH-1V (Figure 4) both as primary (Figure 4A) and booster vaccination (Figure 4B).

Figure 4: Neutralising antibody responses SARS-CoV-2 XBB.1.16 variant by PBNA

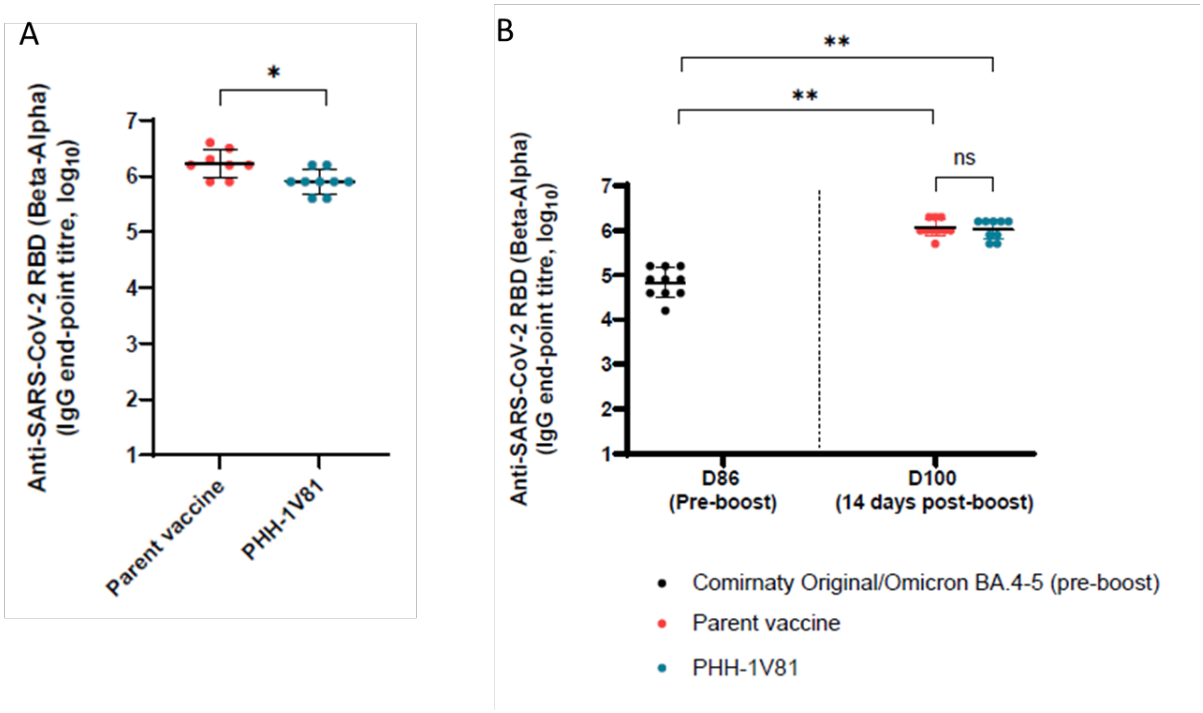


A. Primary vaccination with the parent and adapted Bimervax vaccines. Sera from mice collected on D28 were assessed in EIDHH-2023-023-PHH1V81. **B.** Booster vaccination with Bimervax parent and adapted vaccines after priming with bivalent Comirnaty vaccine. Sera from mice collected on D86 and D100 in study EIDHH-2023-011-PHH1V81. Titres are expressed as $\log_{10}$ IC_{50}. Each data point represents an individual mouse serum with bars denoting the mean titre per group and the standard deviation. Statistically significant differences between groups are indicated with a line on top of each group: ** p<0.01. The representation of axes *y* is different. Results described in study EIDHH-2023-009-PHH1V81, EIDHH-2023-010-PHH1V81, and EIDHH-2023-015-PHH1V81 are similar and not shown here.

When Bimervax vaccines were applied as booster doses, PHH-1V81 was able to lead significantly higher neutralizing activity against all tested SARS-CoV-2 variants compared to what was observed after Comirnaty Original/Omicron BA.4-5 primary vaccination (Figure 3B and Figure 4B). The only exception was against Beta variant in study EIDHH-2023-010-PHH1V81 in which $0.05 < p < 0.1$ (Figure 2B). In contrary, Bimervax parent vaccine PHH-1V failed to cause higher neutralizing activity against the studied Omicron variants when it was used as booster (Figure 3B and Figure 4B).

Primary vaccination with the PHH-1V parent vaccine led to higher titres of total receptor binding domain (RBD) specific IgGs compared with PHH-1V81 as detected by ELISA coated with Beta-Alpha dimer (Figure 5A). When Bimervax vaccines were administered as booster both vaccines elevated the level of the RBD specific IgGs, however, no such difference could be observed between the effect of Bimervax vaccines like in the case of primary vaccination (Figure 5B).

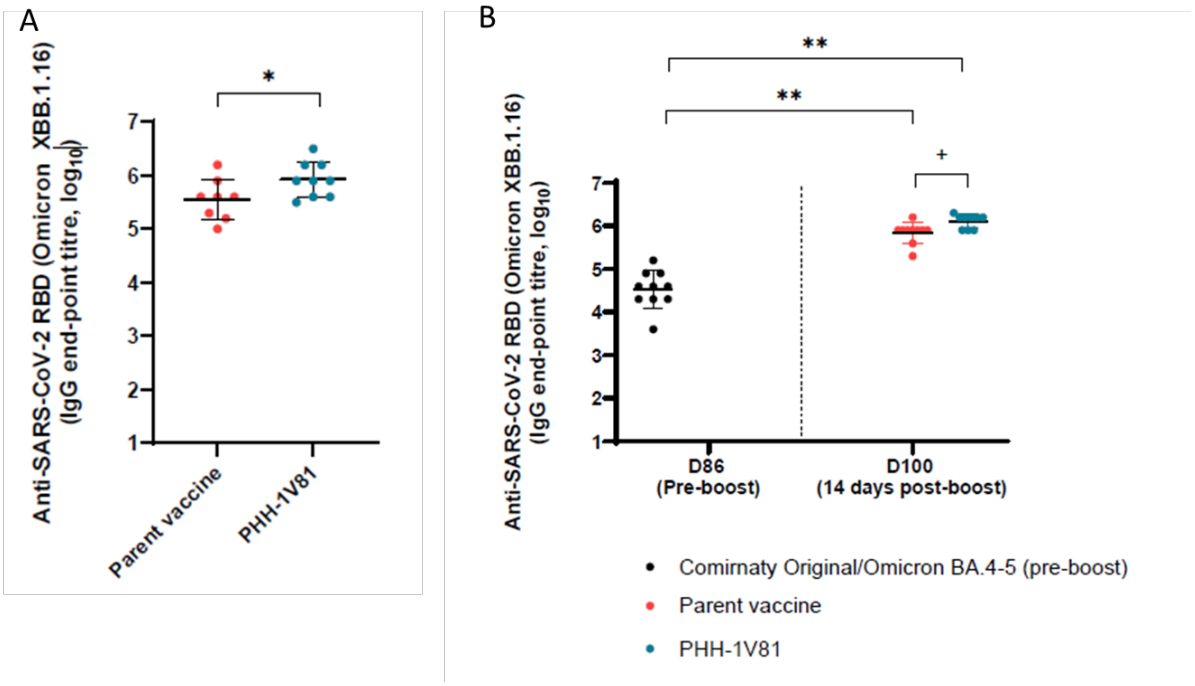
Figure 5: SARS-CoV-2 Alpha-Beta-RBD-specific IgG responses.



A. Primary vaccination with the parent and adapted Bimervax vaccines. End-point antibody titres were determined by ELISA on day D28. From study EIDHH-2023-015-PHH1V81. **B.** SARS-CoV-2 Alpha-Beta RBD-specific IgG responses on days D86 (Pre-boost) and D100 (14 days post-boost) in study EIDHH-2023-011-PHH1V81. Booster vaccination with Bimervax parent and adapted vaccines after priming with bivalent Comirnaty vaccine. End-point antibody titres determined by ELISA are shown.
Each data point represents an individual mouse serum with bars denoting the mean titre per group and the standard deviation. Statistically significant differences between groups are indicated with a line on top of each group: * $p<0.05$; ** $p<0.01$. The representation of axes *y* is different.

The PHH-1V81 vaccine led to more RBD specific IgG in the case of Omicron XBB.1.16 based coat on ELISA plates compared with PHH-1V parent vaccine (Figure 6A). When Bimervax vaccines were administered as booster this difference was also existing but less expressed ($0.05<p<0.1$), while both vaccines elevated the level of the RBD specific IgGs, compared with the level before the booster administration (Figure 6B).

Figure 6: SARS-CoV-2 XBB.1.16-RBD-specific IgG responses.

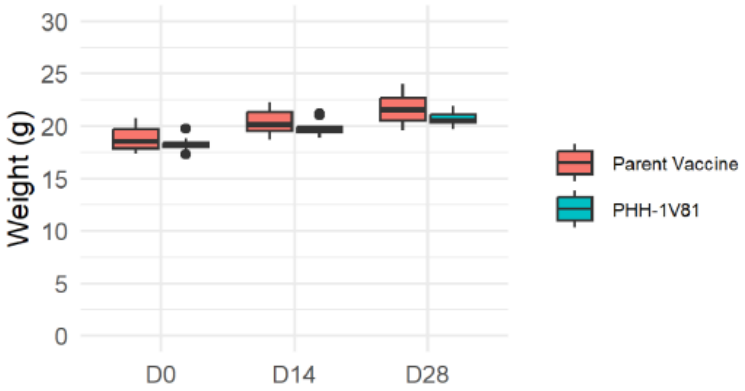


A. Primary vaccination with the parent and adapted Bimervax vaccines. End-point antibody titres were determined by ELISA on day D28. From study EIDHH-2023-015-PHH1V81. **B.** SARS-CoV-2 XBB.1.16-RBD-specific IgG responses on days D86 (Pre-boost) and D100 (14 days post-boost) in study EIDHH-2023-011-PHH1V81. Booster vaccination with Bimervax parent and adapted vaccines after priming with bivalent Comirnaty vaccine. End-point antibody titres determined by ELISA are shown.
Each data point represents an individual mouse serum with bars denoting the mean titre per group and the standard deviation. Statistically significant differences between groups are indicated with a line on top of each group: + 0.05<p<0.1; * p<0.05; ** p<0.01. The representation of axes *y* is different.

The safety evaluation of PHH-1V81 included mice's weight measurements and the assessment of clinical sings compared to PHH-1V. Weight measurements were done on the day of vaccination with Bimervax vaccines and before blood extraction. There were no significant differences in the weight of PHH-1V81 vaccinated animals compared to PHH-1V vaccinated one (Figure 7). Clinical signs were observed on the day of vaccination and the upcoming two days. If a sign appeared, it was monitored daily until it disappeared. The assessed clinical sings can be divided as general and local. The general clinical signs were the following: depression, body condition, rough fur, incurvation, orbital tightening, others; while the local ones were inflammation, nodule, ulcer, scab, alopecia, self-mutilation, others. Only mild local inflammations were observed in some animals in both groups, PHH-1V81 and parent vaccine PHH-1V, mainly the day after vaccinations in primary-vaccination studies, and the day after the booster administration. Those mild inflammations disappeared within 1-2 days. A moderate local inflammation was observed in a few animals after the administration of both, PHH-1V and PHH-1V81 vaccine (4 animals in PHH-1V group and 1 animal in PHH-1V81 group), which disappeared in one day.

Overall, PHH-1V81 was not found less safe than Bimervax parent vaccine in animal model.

Figure 7: Body weights of each group from study EIDHH-2023-023-PHH1V81



Data is presented as a box plot: the median mark of each experimental group, the inferior and superior limit of the box representing the first and the third quartile, respectively; and whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range from the box; all other observed data points outside the boundary of the whiskers are plotted as outliers.

Taken together MAH concluded that, as expected, the parental Bimervax vaccine PHH-1V is more immunogenic against B.1.351 (beta), while the new adapted vaccine PHH-1V81 is more immunogenic against Omicron XBB.1.5 and XBB.1.16.

2.5.2.2. Secondary pharmacodynamic studies

The MAH did not perform secondary non clinical pharmacodynamic studies.

2.5.2.3. Safety pharmacology programme

Stand-alone safety pharmacology studies were not conducted. Refer to 2.5.2.1. for clinical signs and body weights in the primary pharmacodynamic studies.

2.5.2.4. Pharmacodynamic drug interactions

Specific nonclinical studies to assess pharmacodynamic interactions for PHH-1V81 were not performed.

2.5.3. Pharmacokinetics

No additional pharmacokinetic (PK) studies were conducted to support this application.

2.5.4. Toxicology

Toxicology studies have not been performed for the adapted PHH-1V81 vaccine.

2.5.5. Ecotoxicity/environmental risk assessment

PHH-1V81 is a ready-to-use adjuvanted recombinant receptor binding domain (RBD) vaccine against SARS-CoV-2. The common name is "COVID-19 Vaccine (recombinant, adjuvanted)".

The active substance is referred to as "SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion homodimer – Omicron XBB.1.16-XBB.1.16". The active substance is a biological substance according to Annex I Part I (Directive 2001/83/EC) where "a biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical- biological testing, together with the production process and its control".

SBQA adjuvant is an oil-in water emulsion for i.m. use containing squalene as the internal oil phase, sodium citrate-citric acid buffer as the external aqueous phase. The emulsion is stabilised with two non-ionic surfactants, polysorbate 80 and sorbitan trioleate. All components of the adjuvant are compendial and used in marketed vaccines such as influenza vaccine Fluad Tetra (EMA/200444/2020, 2020) and recognised as an established adjuvant in the EMA Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004, 1997). Squalene is a naturally occurring substance found in plants, animals, and humans and is manufactured in the liver of every human body and circulates in the bloodstream (Squalene - PubChem, 2022). Using the OECD Guideline 301F (Ready Biodegradability: Manometric Respirometry Test), squalene is classified as inherently biodegradable, but not readily biodegradable. An estimated bioconcentration factor (BCF) of 4 suggests the potential for bioconcentration in aquatic organisms is low. Microorganisms isolated from soil are able to use squalene as a carbon source.

No concerns are expected for the environment as a result of product manufacturing and administration to humans. In this case, the active substance is broken down by naturally occurring proteolytic enzymes into smaller (inactive) polypeptides or amino acids which are either further degraded by similar pathways or reabsorbed for recycling in other molecules and pathways. Squalene is also naturally occurring and is potentially metabolised within the body to other substances whereas it is naturally present in the environment being a part of many organisms. There are no other intermediates that have any expected toxicity or accumulation in the environment.

In accordance with the CHMP Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use EMEA/CHMP/SWP/4447/00 Rev. 1, 2018), due to their nature, vaccines and lipids are unlikely to result in a significant risk to the environment. Protein vaccines are normally exempted from the requirement to conduct ERA studies. Furthermore, PHH-1V81 is not a genetically modified organism (GMO) and it is not likely that the constituents will re-main in the environment. Consequently, the lack of ERA studies is considered acceptable. The overall approach was discussed for the parent vaccine in a scientific advice and CHMP agreed, in principle that this would be acceptable (EMA/SA/0000066056).

2.5.6. Discussion on non-clinical aspects

The MAH performed 5 novel non-clinical studies to demonstrate the immunogenicity and safety of the newly adapted Bimervax vaccine with PHH-1V81, the homodimeric form of RBD domain of Omicron XBB.1.16 SARS-CoV-2 variant, as vaccine antigen. Choosing Omicron XBB.1.16 as the variant from which the vaccine antigen made was in line with the recommendations at the time of submission. The chosen animal model, female BALB/c mice is appropriate and justified.

The non-clinical study design which consisted in a comparison between Bimervax vaccine (PHH-1V) and the adapted Bimervax vaccine (PHH-1V81) as primary and booster vaccination (after priming with bivalent Comirnaty vaccine) is considered acceptable.

The results of the primary pharmacodynamic studies clearly demonstrate that PHH-1V81 elicited stronger neutralization activity against Omicron XBB.1.5. and XBB.1.16 than the parent vaccine both as primary and booster vaccination. However, PHH-1V failed to cause higher neutralizing activity

against the studied Omicron variants when it was used as booster, as expected.The statistical analysis of the weight measurement is well written, and the applied test is appropriate.

Regarding the safety evaluation of PHH-1V81 the assessed clinical signs are appropriate even tough could have included temperature measurement of mice. The MAH could have monitored the appearance of clinical signs for a longer period than the 2-days post vaccination. Nevertheless, the data does not raise concern and the safety profile of PHH-1V81 in mice is acceptable.

2.5.7. Conclusion on the non-clinical aspects

Overall, the primary non-clinical pharmacodynamics studies provide evidence of immune response development in mice after administration of PHH-1V81. Neutralising immune response against XBB.1.5 and XBB.1.16 Omicron sublineages was higher in the PHH-1V81 group compared to the parent Bimervax vaccine group. No safety issues have been identified in the non-clinical studies conducted with the PHH-1V81 vaccine.

No toxicology studies were provided for the PHH-1V81 vaccine. During the initial MA for PHH-1V, repeat dose toxicity (including local tolerance assessment), immunotoxicity, reproductive and developmental toxicity studies were performed and assessed positively. PHH-1V81 has the same formulation, dose level, and clinical route of administration as PHH-1V parent vaccine. Therefore, the performed toxicology studies for PHH-1V are considered relevant for the adapted vaccine PHH-1V81.

There were no studies on genotoxicity, carcinogenicity and the toxicology of SQBA adjuvant, and no environmental risk assessment was carried out, which is in line with applicable guidelines (World Health Organization (WHO), 2005, 2013; ICH S6, 2011; ICH M3, 2009; EMEA/CHMP/SWP/4447/00 Rev. 1, 2018) and the Scientific Advice (EMA/SA/0000148115).

The non-clinical package for PHH-1V81 is acceptable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- **Tabular overview of clinical studies**

Table 2: Tabular overview of clinical studies

Reference / ID	Title	Phase and Design	Treatment / Route of administration / Dose	Duration / status	Country	Number of subjects	Primary endpoint(s)
HIPRA-HH-14 (EU CT number: 2023-508458-25-00 ; NCT06181292)	A Phase IIb, double-blind, randomised, active controlled, multi-centre, non-inferiority trial, to assess immunogenicity and safety of a booster vaccination with the adapted COVID-19 vaccine HIPRA (PHH-1V81) against SARS-CoV-2, in adults fully vaccinated against COVID-19	Phase IIb/III: Double-blind, randomised, active controlled, multi-centre, non-inferiority clinical trial to assess immunogenicity and safety of PHH-1V81 compared to Comirnaty Omicron XBB.1.5 Individuals had received the primary series with a EU-approved mRNA vaccine and at least one booster dose with a EU-approved mRNA vaccine at least 6 months before the booster dose with PHH-1V81 or Comirnaty Omicron XBB.1.5. Previous COVID-19 infections were allowed provided that at least 6 months had elapsed between the infection and the booster dose with PHH-1V81 or Comirnaty Omicron XBB.1.5. Participants had a negative Rapid Antigen Test for COVID-19 at Day 0 prior to vaccination.	PHH-1V81: one booster dose (40 µg) at least 6 months after the previous vaccination with an EU-approved mRNA vaccine. In case of a previous COVID-19 infection, at least 6 months had to elapse between the COVID-19 infection and the booster dose with PHH-1V81 vaccine. Control vaccine: one 30 µg booster dose with Comirnaty Omicron XBB.1.5 at least 6 months after the previous vaccination with an EU-approved mRNA vaccine. In case of a previous COVID-19 infection, at least 6 months had to elapse between the COVID-19 infection and the booster dose with Comirnaty Omicron XBB.1.5. Intramuscular	Approximately 6 months of follow-up after booster vaccination of Day 0 First participant enrolled: 15 November 2023	10 sites in Spain with competitive enrolment	*Planned*: approximately 612 individuals (≥18 years; 10% ≥60 years old). 913 participants enrolled. Of those, 800 had been vaccinated (safety population) according to the eCRF at the cut-off date (12/12/2023). For the Interim data Statistical Analysis Report and Addendum provided, the approximately 612 participants reaching Day 14 and for which immunogenicity data was available, were considered for the mITT population (599 individuals: 406 in the PHH-1V81 arm and 193 in the Comirnaty Omicron XBB.1.5 arm) 800 safety population (536 PHH-1V81; 264 Comirnaty Omicron XBB.1.5). On 2nd January 2024, in addition, another extraction of data from the eCRF was carried out to obtain updated safety information including data up to 878 subjects (587 in the PHH-1V81 arm and 291 in the Comirnaty Omicron XBB.1.5 arm). This additional information has also been included in the	*Efficacy*: • Neutralisation titre against Omicron XBB.1.16 variant measured as inhibitory concentration 50 (IC_{50}) by pseudovirion-based neutralisation assay (PBNA) and reported as reciprocal concentration for each individual sample and geometric mean titre (GMT) for treatment group comparison at Baseline and at Day 14. *Safety*: • Number, percentage, and characteristics of solicited local and systemic reactions through Day 7 after vaccination. • Number, percentage, and characteristics of unsolicited local and systemic adverse events (AEs) through Day 28 after vaccination. • Number and percentage of serious adverse events (SAEs) through the end of the study. • Number and percentage of adverse events of special interest (AESI) through the end of the study. • Number and percentage of medically attended adverse events (MAAE) through Day 28 and related MAAEs through the end of the study. • Grade 3 and 4 changes from baseline in safety laboratory parameters through the end of the study.

Reference / ID	Title	Phase and Design	Treatment / Route of administration / Dose	Duration / status	Country	Number of subjects	Primary endpoint(s)
						corresponding sections of the dossier. Randomisation: 2:1	

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

No pharmacokinetics studies have been conducted for PHH-1V81. This is because pharmacokinetics studies are generally not needed for vaccines, consistent with current WHO and EMA Guidelines on clinical evaluation of vaccines.

2.6.2.2. Pharmacodynamics

The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005). As immunogenicity data of this vaccine are used to support the authorisation of this vaccine, immunogenicity data are included under the clinical efficacy section.

In this section the mechanism of action and the respective assays applied to determine the immunogenicity data are discussed.

Mechanism of action

The PHH-1V81 is a SARS-CoV-2 RBD homologous dimer fusion protein derived from Omicron XBB.1.16 strain as vaccine antigen, and the SBQA, an oil-in-water adjuvant consisting of 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 per 0.5 mL dose. With respect to the Bimervax antigen, the PHH-1V81 antigen has the same number of amino acids in the peptide sequence (438 amino acids, corresponding to amino acids 319 to 537 of the spike protein) and maintains the dual domain dimeric structure of the original Bimervax antigen. The approach of the MAH using an homodimer of XBB.1.16 as the adapted vaccine was considered reasonable and supported in the Scientific Advice Report (EMA/SA/0000148115).

The formulation, dose level (40 µ) and the clinical route of administration (i.m. injection) for PHH-1V81 is the same as the parent vaccine Bimervax.

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, PHH-1V81 induces antigen-specific T-cell immune response, which may contribute to protection to COVID-19.

Primary and Secondary pharmacology

The pharmacodynamic activity of vaccines is defined by their immunogenicity profile. Human immunogenicity of PHH-1V81 was studied in the safety and-immunogenicity study HIPRA-HH-14 and is discussed in detail in the Clinical Efficacy and Clinical Safety parts of this assessment report.

Applied assays

Two methods were used in the application to measure neutralizing antibodies (nABs) in the sera of the subjects: a pseudovirion-based neutralisation assay (PBNA) against Omicron XBB.1.5 ad XBB.1.16 and a virus neutralisation assay (VNA) against Omicron XBB.1.5 ad XBB.1.16.

- For the **PBNA** assay, HIV-based pseudoviruses were designed that lack expression of the env and rev genes and were amended with the SARS-CoV-2 specific spike protein and a luciferase

gene. The pseudoviruses are added to HEK293T/hACE2 cells that overexpress ACE-2 on their surface. The results in this assay are obtained as RLU (relative luminescence units), whereby the RLU readout is indirectly proportional to the content of nABs in the tested sera. In the current procedure, validation studies for PBNA assay specific to Omicron sublineages XBB.1.5 and XBB.1.16 were provided. The results of the PBNA method validation studies comply with the prespecified acceptance ranges/limits. These limits are in line with the limits applied during the PBNA validation studies for Omicron BA.4 and BA.5 sub lineages. Therefore, the PBNA validation studies are acceptable.

- In the **VNA** assay, SARS-CoV-2 viruses are added to a cell culture (ACE-2 expressing Vero-E6 cells) and infectivity of the cells in the presence of patient's sera is used to determine the neutralising properties of the latter via fluorimetric readout (CellTiter-Glo luminescent cell viability assay (Promega) evaluating the number of viable cells in culture based on quantitation of the available ATP). The VNA was developed during the development of Bimervax parent vaccine, and the assay and its validation was positively assessed during the MA procedure of the parent vaccine.

Correlation between PBNA and VNA

In the initial MA of Bimervax, a correlation study between PBNA and VNA was requested. Results of this correlation study supported the Applicant's position that the measurements obtained by PBNA and VNA had adequate agreement.

In the current procedure X/14/G, correlation studies between VNA against SARS-CoV-2 Omicron XBB.1.5 and XBB.1.16 subvariant and PBNA against SARS-CoV-2 Omicron XBB.1.5 and XBB.1.16 subvariants were provided. In the PBNA-VNA correlation study against Omicron XBB.1.5, PBNA and VNA data from participants in the HIPRA-HH-2 Phase IIb clinical trial were used for the assessment of agreement between the two methods, whereas in the VNA-PBNA correlation study against Omicron XBB.1.16, data from participants in the HIPRA-HH-14 clinical trial were used for the assessment of agreement between the two analytical methods.

According to the Bland-Altman plot analysis for the correlation of PBNA and VNA against XBB.1.5, there is no evidence of bias between both methods, as the regression line does not deviate from the 0 intercept in shift or slope. This is further supported by the statistical assessment of the 95% confidence intervals around the intercept and slope estimates. To further corroborate the observed agreement, a between-groups comparison approach was followed comparing the titres using both PBNA and VNA data.

According to the Bland-Altman plot analysis for the correlation of PBNA and VNA against XBB.1.16, the GMT results received with the PBNA are constantly slightly higher compared to the VNA results.

2.6.3. Discussion on clinical pharmacology

As this application is based on immunobridging, it is of utmost importance that the immune response in terms of neutralizing antibodies is appropriately measured, assays have to be validated and the use of an assay for primary analysis need to be adequately justified.

For this purpose, besides PBNA and VNA validation studies, correlation studies between VNA against SARS-CoV-2 Omicron XBB.1.5 and XBB.1.16 subvariant and PBNA against SARS-CoV-2 Omicron XBB.1.5 and XBB.1.16 subvariants were provided.

For the evaluation of agreement of the two analytical methods, a Bland-Altman plot analysis has been performed. To complement the Bland-Altman plot analysis, the geometric mean titre (GMT) ratio also

has been estimated for VNA XBB.1.5 and PBNA XBB.1.5 and VNA XBB.1.16 and PBNA XBB.1.16 measurements in order to assess if the extent of the difference between vaccines is similarly observed by the two methods.

Bland-Altman plots and comparative analyses of GMTs and GMT ratios showed good correlation between PBNA and VNA assays for sublineage Omicron XBB.1.5, as the slope and intercept estimates were close to 0 and the 95% CIs of them did not show significant deviation from 0. These 95% CI results are indicative for the lack of proportional and constant biases between the VNA and PBNA methods. In addition, the 95% limits of agreement lie within the maximum limits of acceptance of the Bland-Altman plot indicating an agreement between both methods. Note that GMTs from PBNA assay were a slightly lower than GMTs obtained by VNA assay for the XBB.1.5 sublineage.

As for neutralising assays against Omicron XBB.1.16, the GMT results received with the PBNA are constantly slightly higher compared to the VNA results.

While the slope estimate showed the lack of proportional bias (slope is not significantly different from 0), the assessment of constant bias (shift from the 0 intercept) indicated a potential positive constant bias that is not significant. Nevertheless, the MAH position that a constant bias would not be a concern regardless of statistical significance can be accepted, since a constant bias between the VNA and PBNA assay results will not affect the relative titre comparison between vaccines or timepoints.

In addition, the Bland-Altman plot for PBNA and VNA against Omicron XBB.1.16 indicates that there is agreement between both methods, as the 95% limits of agreement lie within the maximum limits of acceptance. Further, the assay correspondence appears comparable between samples obtained from subjects vaccinated with different products (PHH-1V81 and Comirnaty XBB.1.5).

It is worth noting also that the GMT ratios obtained from PBNA and VNA assays against XBB.1.16 were found similar.

In PBNA-VNA correlation study against SARS-CoV-2 Omicron XBB.1.5, PBNA and VNA data from participants in the HIPRA-HH-2 Phase IIb clinical trial were used for the assessment of agreement between the two methods. However, In PBNA-VNA correlation study against SARS-CoV-2 Omicron XBB.1.16, PBNA and VNA data from participants in the HIPRA-HH-14 clinical trial were used. The MAH justified the above choice of samples from Study HH-2 or PBNA-VNA correlation measures against XBB.1.5 sublineage and also provided the time period when sampling for the PBNA-VNA correlation study was performed in Study HH-2 and the variant status of Omicron XBB.1.5 during the time period of this sampling.

2.6.4. Conclusions on clinical pharmacology

The PBNAs (and the VNA) do not provide absolute determinations of the nAB content in patient's sera. Consequently, throughout the clinical studies, only relative nAB titres were and can be measured with the PBNAs against XBB.1.5 and XBB.1.16. The obtained results can therefore not be directly compared to other data sources. The efficacy evaluation of PHH-1V81 solely needs to rely on a relative comparison between nAB levels between different treatment arms. Taking into consideration the above, the PBNA assays provide reliable measures on neutralising immune response in HIPRA clinical studies which are in correlation with the VNA results as well.

2.6.5. Clinical efficacy

The clinical development plan (CDP) for PHH-1V81 consists of one Phase IIb/III clinical study (HIPRA-HH-14) assessing the safety and immunogenicity of a booster vaccination with the adapted recombinant protein RBD fusion homodimer candidate (PHH-1V81) against SARS-CoV-2, in adults vaccinated against COVID-19. This clinical study was designed following and immunobridging approach to assess the non-inferiority of PHH-1V81 versus the approved adapted vaccine Comirnaty Omicron XBB.1.5 as a booster. Immunobridging approach is in alignment with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

2.6.5.1. Main study(ies)

HIPRA- HH-14

Methods

HIPRA-HH-14 is a Phase IIb/III, double-blind, randomised, active controlled, multi-centre, non-inferiority trial in adults 18 years of age and older. The primary objective was to determine and compare the changes of the immunogenicity measured by pseudovirus-based neutralisation assay (PBNA) against the Omicron XBB.1.16 variant at baseline and Day 14 after vaccine administration. The analysis included a comparison of participants who received the adapted HIPRA's COVID-19 vaccine (PHH-1V81) *versus* a booster dose of Pfizer–BioNTech (Comirnaty Omicron XBB.1.5), in both cases after complete vaccination at least 182 days before the administration of the booster dose.

- **Study Participants**

Study HIPRA-HH-14 was conducted at 10 sites located in Spain. Participants were generally healthy adults who had received a primary vaccination scheme of an mRNA vaccine (2 doses) and at least one booster dose with an EU approved mRNA vaccine (non Omicron XBB) at least 6 months before study start. A negative Rapid Antigen Test for COVID-19 was required at Day 0 prior to vaccination. Immune suppressed conditions were exclusion criteria, however, subjects with underlying chronic disease could be included in the study, provided that their underlying condition is stable. Other inclusion and exclusion criteria are standard criteria in clinical trials.

- **Treatments**

All participants received a booster dose of PHH-1V81 or Comirnaty Omicron XBB.1.5 at Day 0. Both COVID-19 vaccines were administered intramuscularly.

PHH-1V81: one booster dose (40 µg) was administered at least 6 months after the previous vaccination with an EU-approved mRNA vaccine. In case of a previous COVID-19 infection, at least 6 months had to elapse between the COVID-19 infection and the booster dose with PHH-1V81 vaccine.

Control vaccine: one 30 µg booster dose with Comirnaty Omicron XBB.1.5 was administered at least 6 months after the previous vaccination with an EU-approved mRNA vaccine. In case of a previous COVID-19 infection, at least 6 months had to elapse between the COVID-19 infection and the booster dose with Comirnaty Omicron XBB.1.5.

- **Objectives**

Primary objective

- To assess the safety and tolerability of a PHH-1V81 booster in adults who previously received primary vaccination with an EU-approved mRNA vaccine, and at least one booster dose of an EU-approved mRNA vaccine.

- To determine and compare the changes in immunogenicity measured by pseudovirus neutralisation assay (PBNA) against Omicron XBB.1.16 variant at Baseline and Day 14 in the PHH-1V81 vaccine arm versus the Comirnaty Omicron XBB.1.5 arm.

Secondary objectives

- To determine and compare the changes in immunogenicity measured by PBNA against Wuhan, Omicron BA.1 and Omicron XBB.1.5 at Baseline and at Days 14, 91 and 182, and Omicron XBB.1.16 at Days 91 and 182, after vaccination in the PHH-1V81 vaccine arm vs. the Comirnaty Omicron XBB.1.5 arm.
- To evaluate and compare the immunogenicity measured by means of total antibody against Receptor Binding Domain of the Spike protein of SARS-CoV-2, measured by an electrochemiluminescence immunoassay (ECLIA) at Baseline and at Days 14, 91 and 182 in the PHH-1V81 vaccine arm vs the Comirnaty Omicron XBB.1.5 arm.

Exploratory objectives

- To assess the number of adults with SARS-CoV-2 infections ≥14 days in both vaccine arms.
- To assess the number of COVID-19 severe infections ≥14 days in both vaccine arms.
- To evaluate T-cell mediated responses against the SARS-CoV-2 S glycoprotein at Baseline and at Day 14 for descriptive analysis in a subset of participants from both vaccine arms.

- **Outcomes/endpoints**

Primary efficacy endpoint

- Neutralisation titre against Omicron XBB.1.16 variant measured as inhibitory concentration 50 (IC_{50}) by pseudovirion-based neutralisation assay (PBNA) and reported as reciprocal concentration for each individual sample and geometric mean titre (GMT) for treatment group comparison at Baseline and at Day 14.

Key secondary efficacy endpoints

- Neutralisation titre against Wuhan, Omicron BA.1 and Omicron XBB.1.5 variants measured as inhibitory concentration 50 (IC_{50}) by PBNA and reported as reciprocal concentration for each individual sample and GMT for treatment group comparison at Baseline and at Days 14, 91 and 182.
- Neutralisation titre against Omicron XBB.1.16 variant measured as inhibitory concentration 50 (IC_{50}) by PBNA and reported as reciprocal concentration for each individual sample and GMT for treatment group comparison at Days 91 and 182.
- Geometric mean fold rise (GMFR) in neutralising antibodies titres against Wuhan, Omicron BA.1, Omicron XBB.1.5 and Omicron XBB.1.16 variants for descriptive analysis, from Baseline to Day 14 in both vaccine arms.
- Binding antibodies titre measured for each individual sample and GMT for treatment group comparison at Baseline and Days 14, 91 and 182.

- **Sample size**

The sample size for HIPRA-HH-14 was calculated considering a comparator vaccine targeting the XBB variants. Consequently, the sample size was determined to have enough power to demonstrate non-inferiority of PHH-1V81 compared to the comparator vaccine in terms of elicited neutralising antibody titres against Omicron XBB variants. As success criterion, the lower bound of the 95% confidence

interval around the GMT ratio PHH-1V81: Comirnaty Omicron XBB.1.5 was set to 0.67. For consistency with previous HIPRA-HH studies, the success criterion was expressed for the GMT ratio Comirnaty Omicron XBB.1.5: PHH-1V81 as the upper bound of the two-sided 95% confidence interval around the GMT ratio should lie below 1.50.

Considering this, and with a PHH-1V81 to Comirnaty Omicron XBB.1.5 2:1 randomisation ratio, group sample sizes of 366 and 183, respectively, would achieve 90% power to detect non-inferiority using a one-sided 2.5% significance level, two-sample t-test using a SDlog10 = 0.60 for both treatments and assuming an expected GMT ratio of 1. Presuming a 10% withdrawal rate, this yielded a total of 612 subjects to be randomised in this study, 408 in the PHH-1V81 arm and 204 in the Comirnaty Omicron XBB.1.5 arm.

A sample size of 408 subjects in the PHH-1V81 group ensures a high probability of detecting at least 1 adverse event with a 'true' event rate as low as 0.5%.

- **Randomisation and Blinding (masking)**

Study participants who have received a primary scheme with an EU-approved mRNA vaccine (two doses) and at least one booster dose of an EU-approved mRNA vaccine against COVID-19 were randomly assigned to the following two treatment arms in a PHH-1V81: Comirnaty Omicron XBB.1.5 2:1 ratio.

Participants were stratified before randomisation by age group (approximately 10% of adults ≥60 years old in each treatment group), and by number of doses previously received (3 or ≥ 4 doses). Participants were allocated to treatment using an Interactive Response Technology (IRT). Randomisation was stratified by age group: 18 to 59 years and equal or over 60 years with approximately 10% of enrolled among the over 60 group and by number of previous COVID-19 vaccines received.

Participants were assigned a unique Participant ID and were identified only by the Participant ID number to protect confidentiality. The site will keep its own subject identification log to match the Participant ID number with the subject's personal data, in accordance with applicable regulatory data protection requirements. The randomisation scheme was generated by an independent statistician not otherwise associated with the study.

- **Statistical methods**

Analysis populations

Enrolled population (EP): All participants who signed the informed consent form (ICF).

Intention-to-treat (ITT): All participants of the EP who are randomised, regardless of the participant's treatment status in the study. Subjects will be grouped as randomised.

Modified Intention-to-Treat (mITT): All participants in the ITT who meet the inclusion/exclusion criteria and receive a dose of study drug, whose Baseline and Day 14 data are available and did not test positive for COVID-19 within 14 days of receiving study drug. Subjects will be grouped as randomised. This population will be used as primary population for immunogenicity analyses.

Per-protocol population (PP): All subjects in the mITT who have no important protocol deviations, as determined, and documented by the Sponsor prior to data base lock (DBL) and unblinding.

Safety population (SP): All randomised participants who receive the study drug. This population will be used for all analyses of safety. Subjects will be analysed according to the treatment they actually received. This population is the primary population for the analysis of safety endpoints.

Hypothesis testing

The primary efficacy analyses tested the following hypothesis:

- Null hypothesis, H0: The ratio of the GMTs (Licensed product: Investigational product) against XBB.1.16 exceeds the non-inferiority margin (NIm); equivalently the difference in log(GMT) exceeds log(NIm).
- Alternative hypothesis, H1: The ratio of GMTs (Licensed product: Investigational product) is below NIm; equivalently the difference in log(GMT) is less than log(NIm).

Statistical analysis of efficacy endpoints:

Descriptive analyses are performed by time-point overall and by treatment arm for each SARS-CoV-2 variant. Categorical variables are presented by means of number of cases and frequencies (%). Continuous variables are presented by number of non-missing observations, mean (or geometric mean), standard deviation (or geometric standard deviation), median and interquartile range, minimum and maximum. Missing data will not be imputed.

Statistical methods

- For the efficacy endpoints related to immunogenicity, geometric mean titres (GMT) and geometric mean fold rises (GMFR) are estimated with their 95% confidence intervals (CI) by means of Mixed Models for Repeated Measures (MMRM) or Mixed Models (MM), respectively, using log10-transformed data. The number and percentage of subjects with fold rise from Baseline to Day 14 of ≥4-fold for neutralising antibodies and ≥2-fold for total binding antibodies are presented with the corresponding exact 95% Clopper-Pearson Confidence Intervals.
- For T-cell data, ELISpot stimuli are summarised by the number and percentage of positive responses in each vaccine arm by timepoint. A subject is considered as a responder if he/she has at least one positive response to any stimulus. The number and percentage of responders by timepoint and vaccine arm are presented with the corresponding 95% exact Clopper-Pearson CI.

All confidence intervals are generated two-sided at 95% confidence level unless otherwise specified.

For immunogenicity variables, values below the lower of limit of quantification (LLOQ) are imputed to the LLOQ. On the other hand, PBNA values >20480 are reanalysed to provide a value within the analytical range. Missing data are not imputed.

The immunogenicity analyses for this Phase IIb/III study is performed using the mITT (primary analysis) and PP (secondary analysis).

Estimands

Applicant considered the GMT ratio Comirnaty Omicron XBB.1.5: PHH-1V81 as primary estimand. No intercurrent events have been defined and no action has been taken for potential intercurrent events.

Components of the primary estimand were as follows:

- Population: mITT population
- Treatment condition: Assignment to COVID-19 vaccine PHH-1V81 i.m., regardless of discontinuation, compared to assignment to COVID-19 vaccine Comirnaty XBB.1.5 i.m., regardless of discontinuation.

- Endpoint: Neutralisation titres measured as IC50 by PBNA against Omicron XBB.1.16. at Day 14

Subgroup analyses

For the neutralising antibody (nAb) levels against XBB.1.16 and XBB.1.5 in both vaccine arms, two supplementary subgroup analyses are performed to gain insight into subpopulations of individuals within the primary study population (mITT). The following subgroups are analysed:

- Age group ≥ 60 years-old.
- Prior infection groups (with prior infection or without prior infection)
- Individuals receiving 3 mRNA doses before the booster administration or ≥4 mRNA doses before the booster administration.

Interim analyses

Upon completion of the Day 14 assessments for approximately 612 enrolled participants, an interim analysis has been performed to analyse the immunogenicity response and to assess the safety of PHH-1V81 through 14 days after dosing in comparison to the Comirnaty Omicron XBB.1.5 active control. Safety data was taken into account for all enrolled participants until the cut-off date (12 December 2023).

The Interim data are presented in two Reports: Interim Data Statistical Analysis Report Version 2.0 of 3rd January 2024, and Addendum to the Interim Data Statistical Analysis Report Version 1.0 of 2nd January 2024. Upon request, applicant provided safety data up to 6 months follow up (cut off: of 13th June 2024), which is the cut off agreed to assess the safety data in this procedure.

Results

- **Participant flow**

Patient disposition is presented in Table 3. The patient disposition data are based on the interim analysis with cut-off date 12 December 2023

Table 3: Subject Enrolment and Disposition (HIPRA-HH-14) (cut-off date: 12 December 2023)

	Statistics	PHH-1V81	Comirnaty Omicron XBB.1.5	Overall
Enrolled Population	n			913
Intention-to-treat Population	n	603	302	905
Safety Population	n (%)	536 (100.0)	264 (100.0)	800 (100.0)
Modified Intention-to-treat Population	n (%)	406 (75.7)	193 (73.1)	599 (74.9)
Subjects who prematurely discontinued study	n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: n = the number of subjects meeting the criterion. (%) = n/number of subjects in the SP*100.
The Enrolled Population (EP) is defined as all subjects who signed the Informed Consent Form.
The Intention-to-treat Population (ITT) is defined as all subjects of the EP who are randomly assigned to treatment, regardless of the subject's treatment status in the study.
The Safety Population (SP) set is defined as all randomised subjects who received the study drug.
The Modified ITT Population is defined as all participants in the ITT who met the inclusion/exclusion criteria and received a dose of study drug, whose Baseline and Day 14 were available and did not test positive for COVID-19 within 14 days of receiving study drug. Cut-off date: 12 December 2023.

Please note that for the safety analysis, HIPRA provided 6 months-safety data within the procedure (cut-off date: 13th June 2024). The final number of vaccinated subjects in the clinical trial HIPRA-HH-14 is 903 (602 in the PHH-1V81 arm and 301 in the Comirnaty Omicron XBB.1.5 arm) and will conform the final safety population in the Final Analysis.

- **Recruitment**

First subject has been enrolled in the study on 15 Nov 2023. Last participant has been enrolled on 29 Nov 2023. The study is still ongoing.

- **Conduct of the study**

The clinical study enrolled subjects in 10 sites in Spain.

The final number of recruited participants was larger than the number of participants required per protocol (612 participants). A total of 905 subjects were randomised to treatment (Intention-to-treat population) as follows:

- PHH-1V81 vaccine arm: 603 individuals
- Comirnaty Omicron XBB.1.5. vaccine arm: 302 individuals

In this regard, for the interim data analysis, the first approximately 612 participants reaching Day 14 post-vaccination and for which immunogenicity data at Baseline and Day 14 were available, were considered for analysis. This eventually yielded a total of 599 participants to be included in the modified intention-to-treat population (mITT), which is the population employed in all immunogenicity assessments and the targeted population as per clinical study protocol. However, data from all subjects will be taken into account for the final clinical study report. The final clinical study report will be submitted via appropriate regulatory procedure.

On the other hand, no restrictions were set on the number of subjects in the safety population, as for the assessment of safety endpoints all available data must be thoroughly evaluated and reported. The Safety Population (SP) was defined as all randomised participants who received the study vaccine. This population was used to be analysed according to the treatment they actually received. For the safety analysis, HIPRA provided 6 months-safety data within the procedure (cut-off date: 13th June 2024). The final number of vaccinated subjects in the clinical trial HIPRA-HH-14 is 903 (602 in the PHH-1V81 arm and 301 in the Comirnaty Omicron XBB.1.5 arm), whose will conform the final safety population in the Final Analysis.

GCP considerations

The full list of protocol deviations in study HIPRA-HH-14 by the data base lock of 13 December 2023 was provided. No critical deviation was identified.

- **Baseline data**

The demographic characteristics of the safety population (cut-off: 13 June 2024) is summarised in the *Table 4* below.

Table 4: Demographics and Baseline Characteristics for Study HIPRA-HH-14 (cut-off 13th June 2024)

	Statistics	PHH-1V81 (N=602)	Comirnaty Omicron XBB.1.5 (N=301)	Overall (N=903)
Age (years)	n	602	301	903
	Mean	44.48	45.45	44.8
	SD	15.24	15.10	15.19
	Minimum	18	18	18
	Median	45.0	45.0	45.0
	Interquartile Range	22.0	19.0	21.0
	Maximum	88	86	88
Age Group n (%)	< 60 years old	523 (86.9)	260 (86.4)	783 (86.7)
	≥ 60 years old	79 (13.1)	41 (13.6)	120 (13.3)
Number of previous vaccine doses n (%)	3	402 (66.8)	199 (66.1)	601 (66.6)
	4	199 (33.1)	102 (33.9)	301 (33.3)
	5	1 (0.2)	0 (0.0)	1 (0.1)
Sex n (%)	Male	232 (38.5)	126 (41.9)	358 (39.6)
	Female	370 (61.5)	175 (58.1)	545 (60.4)
Race n (%)	White	566 (94.0)	286 (95.0)	852 (94.4)
	Not Reported	34 (5.6)	15 (5.0)	49 (5.4)
	Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0.0)	1 (0.1)
	Unknown	1 (0.2)	0 (0.0)	1 (0.2)
Ethnicity n (%)	Hispanic or Latino	135 (22.4)	74 (24.6)	209 (23.1)
	Not Hispanic or Latino	467 (77.6)	227 (75.4)	694 (76.9)
▼Systolic Blood Pressure (mmHg) at Screening	n	602	301	903
	Mean	126.0	125.9	126.0
	SD	15.02	13.61	14.56
	Minimum	91	86	86
	Median	126.0	125.0	126.0
	Interquartile Range	21.0	19.0	20.0
	Maximum	200	178	200
▲Diastolic Blood Pressure (mmHg) at Screening	n	602	301	903
	Mean	77.9	78.5	78.1
	SD	9.76	9.51	9.68
	Minimum	41	51	41
	Median	78.0	79.0	79.0
	Interquartile Range	13.0	14.0	13.0
	Maximum	109	108	109
Pulse Rate (beats per minute) at Screening	n	602	301	903
	Mean	72.0	72.0	72.0
	SD	11.10	11.87	11.36

	Statistics	PHH-1V81 (N=602)	Comirnaty Omicron XBB.1.5 (N=301)	Overall (N=903)
	Minimum	45	43	43
	Median	71.0	71.0	71.0
	Interquartile Range	15.0	16.0	15.0
	Maximum	103	133	133
Oxygen Saturation (%) at Screening	n	602	301	903
	Mean	98.2	98.2	98.2
	SD	1.09	1.15	1.11
	Minimum	94	92	92
	Median	98.0	98.0	98.0
	Interquartile Range	1.0	1.0	1.0
	Maximum	100	100	100
Body Temperature (ºC) at Screening	n	602	301	903
	Mean	36.2	36.2	36.2
	SD	0.54	0.58	0.55
	Minimum	34.2	32.4	32.4
	Median	36.3	36.2	36.3
	Interquartile Range	0.6	0.6	0.6
	Maximum	37.5	37.3	37.5

Abbreviations: N = the number of subjects in the population; n = the number of subjects meeting the criterion; (%) = n/N*100; SD = standard deviation.

- **Outcomes and estimation**

Primary efficacy endpoint: Neutralisation titre against Omicron XBB.1.16 variant measured as inhibitory concentration 50 (IC50) by pseudovirion-based neutralisation assay (PBNA) and reported as reciprocal concentration for each individual sample and geometric mean titre (GMT) for treatment group comparison at Baseline and at Day 14.

Table 5: Summary of IC50 against Omicron XBB.1.16 (Modified Intention-to-treat Population).

Visit	Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)	Overall (N=599)
Baseline	n	406	193	599
	Geometric mean	152.8026	161.8777	155.6696
	Geometric SD	3.2025	3.0330	3.1459
	Minimum	1.3010	1.3010	1.3010
	Q1	1.79652	1.84882	1.81359
	Median	2.21394	2.24873	2.23962
	Q3	2.50289	2.51298	2.50756
	Maximum	3.6684	3.5848	3.6684

Visit	Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)	Overall (N=599)
Day 14	n	406	193	599
	Geometric mean	1952.3137	1519.7485	1800.9472
	Geometric SD	3.8130	3.0152	3.5680
	Minimum	1.7089	2.2158	1.7089
	Q1	2.90780	2.88681	2.90506
	Median	3.25347	3.08826	3.19522
	Q3	3.72569	3.48510	3.63477
	Maximum	4.8346	4.8290	4.8346

Abbreviations: IC_{50} = Inhibitory Concentration 50, N = the number of subjects in the population, mITT = modified intention-to-treat population; SD = standard deviation; Q1 and Q3 refer to the first and third quartiles, respectively.
Baseline is defined as the most recent measurement prior or equal to the administration of study drug date.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.
Summary statistics have been calculated and reported (except for the geometric mean and the geometric SD) on the log_{10} scale.

Table 6: Analysis of IC50 against Omicron XBB.1.16 (Modified Intention-to-treat Population).

Visit	Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
Baseline	Number of subjects with data n (%)	406 (100.0)	193 (100.0)
	Adjusted treatment mean (LS Mean)	2.18	2.21
	Standard error	0.026	0.037
	95% CI	2.129 - 2.237	2.135 - 2.282
	GMT for adjusted treatment mean	152.46	161.57
	95% CI	134.715 - 172.541	136.404 - 191.374
	GMT for Treatment Ratio (Comirnaty Omicron XBB.1.5 vs PHH-1V81)		1.06
	95% CI for adjusted ratio		0.87 - 1.29
	p-value for ratio = 1		0.5696
Day 14	Number of subjects with data n (%)	406 (100.0)	193 (100.0)
	Adjusted treatment mean (LS Mean)	3.29	3.18
	Standard error	0.028	0.040
	95% CI	3.233 - 3.346	3.101 - 3.258

Visit	Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
	GMT for adjusted treatment mean	1946.38	1512.21
	95% CI	1708.443 - 2217.462	1261.715 - 1812.440
	GMT for Treatment Ratio (Comirnaty Omicron XBB.1.5 vs PHH-1V81)		0.78
	95% CI for adjusted ratio		0.63 - 0.96
	p-value for ratio = 1		0.0213

Abbreviations: CI = confidence interval; GMT = Geometric Mean Titre; IC50 = Inhibitory Concentration 50; LS mean = least squares mean; N = the number of subjects in the population; mITT = modified intention-to-treat; (%) = n/N*100; MMRM = mixed model repeated measures.
Baseline is defined as the most recent measurement prior or equal to the administration of the study drug date.
A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group (PHH-1V81 and Comirnaty Omicron XBB.1.5), age group (18-60, ≥60), visit (Baseline and Day 14), the number of previous vaccine doses group (3, ≥4), and the treatment-by-visit interaction term as fixed effects. Site and subject nested to site were included as random effects. An unstructured covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used to estimate the degrees of freedom. Least Square Means from the fitted model on the log10 scale.
The GMT for treatment means and the GMT for the treatment ratio are estimated using LS Means from the fitted model on the log10 scale and back-transformed.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.

Secondary efficacy endpoints

Geometric mean fold rise (GMFR) in neutralising antibodies titres against Wuhan, Omicron BA.1, Omicron XBB.1.5 and Omicron XBB.1.16 variants for descriptive analysis, from Baseline to Day 14 in both vaccine arms.

In this interim analysis, only data against Omicron XBB.1.16 at baseline and day 14 are available.

Table 7: Summary of Fold Rise in Neutralising Antibodies Titres against Omicron XBB.1.16 at Day 14 (Modified Intention-to-treat Population).

Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)	Overall (N=599)
n	406	193	599
Mean	49.18418	30.43493	43.14310
SD	182.0460	73.39815	155.7286
Geometric mean	12.77671	9.38825	11.56903
Geometric SD	4.7666	4.0665	4.5629
Minimum	0.1880	0.4545	0.1880
Q1	4.46039	3.56533	4.05760
Median	11.34719	8.37690	9.72272
Q3	33.85242	20.65729	29.66260
Maximum	3252.658	524.7539	3252.658

Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)	Overall (N=599)

Abbreviations: mITT = modified intention-to-treat population, N = the number of subjects in the population, SD = standard deviation; Q1 and Q3 refer to the first and third quartiles, respectively. Baseline is defined as the most recent measurement prior to the first administration of study drug. Fold rise is calculated as post-baseline titre/baseline titre. Raw data provided as < 20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data

Table 8: Analysis of GMFR in Neutralising Antibodies Titres against Omicron XBB.1.16 at Day 14 (Modified Intention-to-treat Population).

Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
Number of subjects with data n (%)	406 (100.0)	193 (100.0)
Adjusted treatment mean (LS Mean)	1.11	0.97
Standard error	0.033	0.047
95% CI	1.042 - 1.170	0.881 - 1.067
GMFR for adjusted treatment mean	12.76	9.42
95% CI	11.012 - 14.778	7.609 - 11.659
GMFR for Treatment Ratio (Comirnaty Omicron XBB.1.5 vs PHH-1V81)		0.74
95% CI for adjusted ratio		0.57 - 0.96
p-value for ratio = 1		0.0218

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; LS mean = least square mean; N = the number of subjects in the population; mITT = modified intention-to-treat population; MM = mixed model. Fold rise is calculated as post-baseline titre/baseline titre. A MM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group (PHH-1V81 and Comirnaty Omicron XBB.1.5), age group (18-60, ≥60) and the number of previous vaccine doses group (3, ≥4) as fixed effects. Site was included as a random effect. A compound symmetry covariance matrix was used in the model and the Kenward-Roger approximation was employed to estimate the degrees of freedom. The adjusted treatment means are estimated using Least Square (LS) Means from the fitted model on the log10 scale. The GMFR adjusted means and the GMFR for the treatment ratio are estimated using LS Means from the fitted model on the log10 scale and back-transformed.

Neutralisation titre against Wuhan, Omicron BA.1 and Omicron XBB.1.5 variants measured as inhibitory concentration 50 (IC_{50}) by PBNA and reported as reciprocal concentration for each individual sample and GMT for treatment group comparison at Baseline and at Days 14, 91 and 182.

In this interim analysis, only data against Omicron XBB.1.5 at baseline and day 14 are available.

Table 9: Summary of IC_{50} against Omicron XBB.1.5 at Baseline and Day 14 (mITT Population).

Visit	Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)	Overall (N=599)
		Observed value	Observed value	Observed value
Baseline	n	406	193	599
	Geometric mean	151.86	168.06	156.90
	Geometric SD	3.03	3.00	3.02
	Minimum	1.30	1.30	1.30
	Q1	1.81	1.83	1.82
	Median	2.24	2.27	2.25
	Q3	2.47	2.57	2.51
	Maximum	3.56	3.42	3.56
Day 14	n	406	193	599
	Geometric mean	1887.94	1487.61	1748.40
	Geometric SD	3.71	2.85	3.44
	Minimum	1.54	1.94	1.54
	Q1	2.89	2.91	2.90
	Median	3.23	3.09	3.19
	Q3	3.71	3.46	3.61
	Maximum	4.67	4.61	4.67

Abbreviations: IC50 = Inhibitory Concentration 50, N = the number of subjects in the population, mITT = modified intention-to-treat population; SD = standard deviation; Q1 and Q3 refer to the first and third quartiles, respectively. Baseline is defined as the most recent measurement prior or equal to the administration of study drug date. Raw data provided as as < 20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data

Table 10: Analysis of IC_{50} against Omicron XBB.1.5 at Baseline and Day 14 (mITT Population).

Visit	Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
Baseline	Number of subjects with data n (%)	406 (100.0)	193 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.18	2.23
	Standard error	0.026	0.037
	95% CI	2.130, 2.233	2.152, 2.298
	GMT for adjusted treatment mean [2]	151.93	167.89
	95% CI	134.888, 171.13	142.039, 198.437
	GMT for Treatment Ratio (Comirnaty Omicron XBB.1.5 vs PHH-1V81) [2]		
	Ratio		1.11
	95% CI for adjusted ratio		0.90, 1.35

Visit	Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
	p-value for ratio = 1		0.3303
Day 14	Number of subjects with data n (%)	406 (100.0)	193 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.28	3.17
	Standard error	0.026	0.037
	95% CI	3.225, 3.328	3.099, 3.245
	GMT for adjusted treatment mean [2]	1888.89	1486.03
	95% CI	1676.987, 2127.572	1257.247, 1756.448
	GMT for Treatment Ratio (Comirnaty Omicron XBB.1.5 vs PHH-1V81) [2]		
	Ratio		0.79
	95% CI for adjusted ratio		0.64, 0.96
	p-value for ratio = 1		0.0195

Abbreviations: CI = Confidence Interval; GMT = Geometric Mean Titre; IC50 = Inhibitory Concentration 50; LS mean = least squares mean; N = the number of subjects in the population; mITT = modified intention-to-treat; (%) = n/N*100; MMRM = mixed model repeated measures. Baseline is defined as the most recent measurement prior or equal to the administration of the study drug date. [1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group (PHH-1V81 and Comirnaty Omicron XBB.1.5), age group (18-60 and ≥60), visit (Baseline and Day 14), the number of previous vaccine doses group (3 and ≥4), and the treatment-by-visit interaction term as fixed effects. Site and subject nested to site were included as random effects. An unstructured covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used to estimate the degrees of freedom. Least Square Means from the fitted model on the log10 scale. [2] The GMT for treatment means and the GMT for the treatment ratio were estimated using LS Means from the fitted model on the log10 scale and back-transformed. Raw data provided as < 20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.

Geometric mean fold rise (GMFR) in neutralising antibodies titres against Wuhan, Omicron BA.1, Omicron XBB.1.5 and Omicron XBB.1.16 variants for descriptive analysis, from Baseline to Day 14 in both vaccine arms.

In this interim analysis only data against Omicron XBB.1.5 at baseline and day 14 are available.

Table 11: Summary of Fold Rise in Neutralising Antibodies Titres for Omicron XBB.1.5 at Day 14 (mITT Population).

Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)	Overall (N=599)
	Observed value	Observed value	Observed value
n	406	193	599
Geometric mean	12.43	8.85	11.14
Geometric SD	4.41	3.96	4.30
Minimum	-0.81	-0.52	-0.81
Q1	0.64	0.55	0.59
Median	1.04	0.86	0.98
Q3	1.52	1.30	1.46
Maximum	3.37	2.82	3.37

Abbreviations: mITT = modified intention-to-treat population, N = the number of subjects in the population, SD = standard deviation; Q1 and Q3 refer to the first and third quartiles, respectively. Baseline is defined as the most recent measurement prior to the first administration of study drug. Fold rise is calculated as post-baseline titre/baseline titre. Raw data provided as< 20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data

Table 12: Analysis of GMFR in Neutralising Antibody Titres for Omicron XBB.1.5 at Day 14 (mITT Population).

Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
Number of subjects with data n (%)	406 (100.0)	193 (100.0)
Fold rise adjusted treatment mean (LS Mean) [1] [2]	1.09	0.95
Standard error	0.032	0.045
95% CI	1.026, 1.162	0.857, 1.039
GMFR for adjusted treatment mean [3]	12.42	8.88
95% CI	10.622, 14.513	7.200, 10.942
GMFR for Treatment Ratio (Comirnaty Omicron XBB.1.5 vs PHH-1V81) [3]		
GMFR ratio		0.71
95% CI for ratio		0.56, 0.92
p-value for ratio = 1		0.0082

Abbreviations: CI = Confidence Interval; GMFR = Geometric Mean Fold Rise; LS mean = least squares mean; N = the number of subjects in the population; mITT = modified intention-to-treat population; MM = mixed model. Baseline is defined as the most recent measurement prior to the first administration of study drug. Fold rise is calculated as post-baseline titre/baseline titre. [1] A MM was fitted to the assess the endpoint on the log10 scale. The model included treatment group (PHH-1V81 and Comirnaty Omicron XBB.1.5), age group (18-60 and ≥60) and the number of previous vaccine doses group (3 and ≥4) as fixed effects. Site was included as a random effect. An unstructured covariance matrix was used in the model and the Kenward-Roger approximation was employed to estimate the degrees of freedom. [2] The adjusted treatment means are estimated using Least Square (LS) Means from the fitted model on the log10 scale. [3] The GMFR adjusted means and the GMFR for the treatment ratio are

estimated using LS Means from the fitted model on the log10 scale and back-transformed. Raw data provided as < 20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data

Percentage of subjects with a fold rise ≥4 in neutralising antibody titres against Omicron XBB.1.16 from Baseline to Day 14

Table 13: Analysis of Fold Change in Neutralising Antibodies Titres against Omicron XBB.1.16 at Day 14 (Modified Intention-to-treat Population).

Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
Number of subjects included in the analysis n (%)	406 (100.0)	193 (100.0)
Number of subjects with fold rise ≥4 n (%)	315 (77.6)	137 (71.0)
95% CI	0.732 - 0.816	0.640 - 0.773

Abbreviations: CI = confidence interval; N = the number of subjects in the population; mITT = modified intention-to-treat population.
Fold rise is calculated as post-baseline titre/baseline titre.
Exact CI for the proportion of subjects with fold rise ≥4 have been calculated using the Clopper-Pearson method.

Percentage of subjects with a fold rise ≥4 in neutralising antibody titres against Omicron XBB.1.5 from Baseline to Day 14

Table 14: Analysis of Fold Change in Neutralising Antibody Titres against Omicron XBB.1.5 at Day 14 (mITT Population).

Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
Number of subjects with data n (%)	406 (100.0)	193 (100.0)
Number of subjects with fold rise ≥4 n (%) [1]	310 (76.4)	136 (70.5)
95% CI [2]	71.91 – 80.41	63.49 – 76.80

Percentage of subjects experiencing an increase of ≥2-fold in total binding antibody titres against SARS-CoV-2 measured by ECLIA from Baseline to Day 14 for descriptive analysis in both vaccine arms

Table 15: Analysis of Fold Change in Binding Antibodies Titres at Day 14 (Modified Intention-to-treat Population).

Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
Number of subjects included in the analysis n (%)	406 (100.0)	193 (100.0)
Number of subjects with fold rise ≥2 n (%)	346 (85.2)	150 (77.7)
95% CI	0.814 - 0.885	0.712 - 0.834

Binding antibodies titre measured for each individual sample and GMT for treatment group comparison at Baseline and Days 14, 91 and 182.

In this interim analysis only data at baseline and day 14 are available.

Table 16: Summary of Binding Antibody Titres (Modified Intention-to-treat Population).

Visit	Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)	Overall (N=599)
Baseline	n	406	193	599
	Geometric mean	10907.65	11483.28	11089.89
	Geometric SD	2.2595	2.3584	2.2906
	Minimum	2.6304	2.8351	2.6304
	Q1	3.82679	3.78831	3.80209
	Median	4.07030	4.09788	4.07496
	Q3	4.25775	4.33345	4.27547
	Maximum	4.9737	4.8869	4.9737
Day 14	n	406	193	599
	Geometric mean	53520.79	39467.44	48517.71
	Geometric SD	2.3705	1.9576	2.2668
	Minimum	3.5100	3.7270	3.5100
	Q1	4.47502	4.40954	4.45330
	Median	4.71770	4.59002	4.67719
	Q3	4.97477	4.82380	4.90201
	Maximum	5.3522	5.3221	5.3522

Abbreviations: IC_{50} = Inhibitory Concentration 50, N = the number of subjects in the population, mITT = modified intention-to-treat population; SD = standard deviation; Q1 and Q3 refer to the first and third quartiles, respectively.
Baseline is defined as the most recent measurement prior or equal to the administration of study drug date.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.
Summary statistics have been calculated and reported (except for the geometric mean and the geometric SD) on the log_{10} scale.

Table 17: Analysis of Binding Antibody Titres (Modified Intention-to-treat Population).

Visit	Statistics	PHH-1V81 (N=406)	Comirnaty Omicron XBB.1.5 (N=193)
Baseline	Number of subjects with data n (%)	406 (100.0)	193 (100.0)
	Adjusted treatment mean (LS Mean)	4.04	4.06
	Standard error	0.018	0.026
	95% CI	4.002 - 4.072	4.010 - 4.111
	GMT for adjusted treatment mean	10896.07	11493.04
	95% CI	10057.71 - 11804.30	10232.32 - 12909.09
	GMT for Treatment Ratio (Comirnaty Omicron XBB.1.5 vs PHH-1V81)		1.05
	95% CI for adjusted ratio		0.92 - 1.21
	p-value for ratio = 1		0.4583
Day 14	Number of subjects with data n (%)	406 (100.0)	193 (100.0)
	Adjusted treatment mean (LS Mean)	4.73	4.60
	Standard error	0.018	0.025
	95% CI	4.694 - 4.762	4.547 - 4.647
	GMT for adjusted treatment mean	53457.70	39508.81
	95% CI	49378.78 - 57873.56	35215.51 - 44325.53
	GMT for Treatment Ratio (Comirnaty Omicron XBB.1.5 vs PHH-1V81)		0.74
	95% CI for adjusted ratio		0.64 - 0.85
	p-value for ratio = 1		<0.0001

Abbreviations: CI = confidence interval; GMT = Geometric Mean Titre; LS mean = least squares mean; N = the number of subjects in the population; mITT = modified intent-to-treat; (%) = n/N*100; MMRM = mixed model repeated measures.
Baseline is defined as the most recent measurement prior or equal to the administration of the study drug date.
A MMRM model was fitted to the assess the endpoint on the $\log_{10}$ scale. The model included treatment group (PHH-1V81 and Comirnaty Omicron XBB.1.5), age group (18-60, ≥60), visit (Baseline and Day 14), the number of previous vaccine doses group (3, ≥4), and the treatment-by-visit interaction term as fixed effects. Subject was included as random effect. An unstructured covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used to estimate the degrees of freedom. Least Square Means from the fitted model on the $\log_{10}$ scale.
The GMT for treatment means and the GMT for the treatment ratio are estimated using LS Means from the fitted model on the $\log_{10}$ scale and back-transformed.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.

Exploratory efficacy endpoints

To assess the number of adults with SARS-CoV-2 infections ≥14 days in both vaccine arms.To assess the number of COVID-19 severe infections ≥14 days in both vaccine arms.

No subjects experienced severe COVID-19 infections, were hospitalised due to COVID-19, or were admitted to the Intensive Care Unit (ICU) due to COVID-19 up to the database lock on 12 December 2023. There have been no deaths associated with COVID-19 through the period studied. Overall, only 1 subject had a non-severe COVID-19 infection throughout the study duration which occurred within 14 days following vaccination with PHH-1V81.

To evaluate T-cell mediated responses against the SARS-CoV-2 S glycoprotein at Baseline and at Day 14 for descriptive analysis in a subset of participants from both vaccine arms.

This exploratory objective aimed to assess the T-cellular immune response against the ancestral SARS-CoV-2Wuhan strain and Omicron variants after PHH-1V81 booster. With this purpose, the SARS-CoV-2-specific T-cell response was analysed by IFN-γ ELISpot at Baseline (pre-booster) and 14 days (Day 14) after Comirnaty Omicron XBB.1.5 or PHH-1V81 booster in a subset of 18 years old and older subjects previously immunised with primary series of an EU-mRNA approved vaccine an at least one booster dose with an EU-mRNA approved vaccine.

To evaluate the T-cell response for this Interim Data Report, 3 peptides pools overlapping the SARS-CoV-2 RBD of the Wuhan, Omicron BA.1 and Omicron XBB.1.16 variants, were used in the *in vitro* re-stimulation of peripheral blood mononuclear cells (PBMC).

The peptides used in the simulations were as follows:

- RBD Wuhan: 84 peptides overlapping the RBD region of the SARS-CoV-2 Wuhan variant;
- RBD Omicron BA.1: 84 peptides overlapping the RBD region of the SARS-CoV-2 Omicron BA.1 variant
- RBD Omicron XBB.1.16: 84 peptides overlapping the RBD region of the SARS-CoV-2 Omicron XBB.1.16 variant

At the qualitative level, a participant was considered a responder to *in vitro* stimulation at a certain timepoint if the following criteria were satisfied:

- For ELISpot, if at least 1 positive T-cell against IFN-γ was identified as a response to any of the SARS-CoV-2 peptide pools.

The cellular immune response was analysed by IFN-γ ELISpot assay after the *in vitro* restimulation of PBMC with SARS-CoV-2 peptides. PBMC from 21 subjects from the PHH-1V81 arm and 8 subjects from the Comirnaty Omicron XBB.1.5 vaccine arm were assayed for T-cell responses. Only data from valid assays was included in the data analysis.

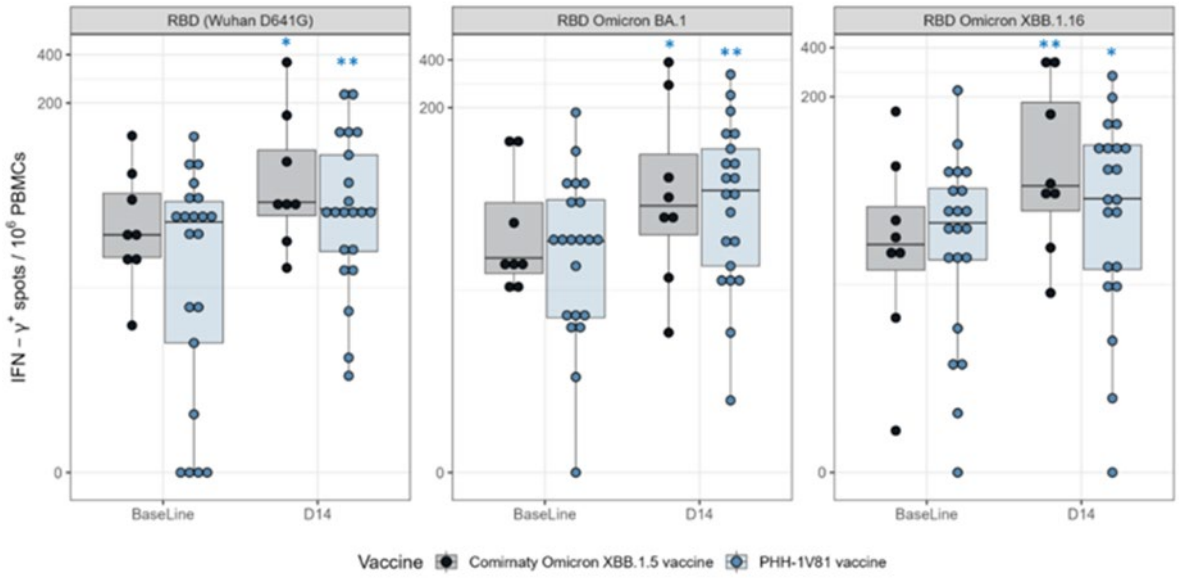
At Baseline, before the administration of the booster dose, 95.2% of the subjects in the PHH-1V81 group showed a positive IFN-γ T-cell response by ELISpot after *in vitro* re-stimulation with at least one peptide pool at this timepoint. This percentage of responder subjects was increased to 100% on Day14 after the booster dose with the PHH-1V81 vaccine. In the Comirnaty Omicron XBB.1.5 the percentage of responder subjects was 100% at both Baseline and Day 14 timepoints.

The booster dose with PHH-1V81 significantly increased the frequencies of RBD Wuhan, RBD Omicron BA.1 and RBD XBB.1.16-specific IFN- γ -producing T-cells on Day 14 in comparison with the pre-booster (Baseline) frequencies (

Figure 8). Similarly, the booster with Comirnaty Omicron XBB.1.5 induced a significant T-cell response against all the tested RBD peptide pools on Day 14. No significant differences were observed between both vaccines either at Baseline or at Day 14 post-booster.

In the quantitative analysis of data, the ELISpot results have demonstrated that the heterologous booster with the PHH-1V81 vaccine induces a cellular immune response, increasing the frequency of RBD-specific IFN-γ^+ T-cells on Day 14. After PHH-1V81 boosting, the RBD-responding IFN-γ-producing T-cells showed specificity not only against the homologous Omicron XBB.1.16 vaccine variant, but also cross-reactivity against the Omicron BA.1 and the ancestral Wuhan strain.

*Figure 8: Frequencies of IFN-γ responses determined by ELISpot assay in PBMC from groups immunised with PHH-1V81 and Comirnaty Omicron XBB.1.5***.**



PBMC were isolated before the boost immunization (Baseline) and 2 weeks (D14) after boost with PHH-1V81 and Comirnaty Omicron XBB.1.5 vaccines, stimulated with RBD Wuhan D614G, RBD Omicron BA.1 and Omicron XBB.1.16 peptides pools, and analysed by IFN-γ-specific ELISpot assay. Within-group contrasts have been displayed in the plots, comparing the extent of IFN-γ^+ response between timepoints in each treatment arm. Statistically significant differences between Baseline and Day 14 are shown in blue colour as * for p< 0.05; ** for p< 0.01.

Ancillary analyses

Subgroup analyses

For the neutralising antibody (nAb) levels against XBB.1.16 and XBB.1.5 in both vaccine arms, two supplementary subgroup analyses are performed to gain insight into subpopulations of individuals within the primary study population (mITT). The following subgroups are analysed:

- Age group ≥ 60 years-old.
- Prior infection groups (with prior infection or without prior infection)

Individuals receiving 3 mRNA doses before the booster administration or ≥4 mRNA doses before the booster administration. This section includes the descriptive analysis and GMT analysis of IC50 neutralising antibody titres against Omicron XBB.1.5 and Omicron XBB.1.16 at Baseline and Day 14 for the following Subgroups:

- Subjects with prior COVID-19 infection
- Subjects without prior COVID-19 infection
- Subjects with 3 prior doses of a COVID-19 vaccine
- Subjects with ≥4 prior doses of a COVID-19 vaccine

Note that neutralising immune response data for the Subjects ≥60 years-old subgroup is included in the section 2.6.5.2.

Neutralising antibody levels against Omicron XBB.1.16 at Baseline and Day 14 in individuals with and without prior reported COVID-19 infection

Table 18: Analysis of IC_{50} against Omicron XBB.1.16 at Baseline and Day 14 for subjects with prior reported COVID-19 infection (mITT Population).

Visit	Statistics	PHH-1V81 (N=206)	Comirnaty Omicron XBB.1.5 (N=99)
Baseline	Number of subjects with data n (%)	206 (100.0)	99 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.17	2.21
	Standard error	0.037	0.052
	95% CI	2.090, 2.240	2.104, 2.310
	GMT for adjusted treatment mean [2]	146.24	161.17
	95% CI	123.055, 173.789	127.183, 204.243
Day 14	Number of subjects with data n (%)	206 (100.0)	99 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.27	3.17
	Standard error	0.037	0.052
	95% CI	3.197, 3.347	3.071, 3.277
	GMT for adjusted treatment mean [2]	1871.73	1493.63
	95% CI	1575.005, 2224.367	1178.646, 1892.783

Abbreviations: CI = Confidence Interval; GMT = Geometric Mean Titre; IC50 = Inhibitory Concentration 50; LS mean = least squares mean; N = the number of subjects in the population; mITT = modified intention-to-treat; (%) = n/N*100; MMRM = mixed model repeated measures. Baseline is defined as the most recent measurement prior or equal to the administration of the study drug date. [1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group (PHH-1V81 and Comirnaty Omicron XBB.1.5), age group

(18-60 and ≥60), visit (Baseline and Day 14), the number of previous vaccine doses group (3 and ≥4), and the treatment-by-visit interaction term as fixed effects. Site and subject nested to site were included as random effects. An unstructured covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used to estimate the degrees of freedom. Least Square Means from the fitted model on the log10 scale. [2] The GMT for treatment means were estimated using LS Means from the fitted model on the log10 scale and back-transformed. Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.

Table 19: Analysis of IC_{50} against Omicron XBB.1.16 at Baseline and Day 14 for subjects without prior reported COVID-19 infection (mITT Population).

Visit	Statistics	PHH-1V81 (N=200)	Comirnaty Omicron XBB.1.5 (N=94)
Baseline	Number of subjects with data n (%)	200 (100.0)	94 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.20	2.22
	Standard error	0.041	0.058
	95% CI	2.117, 2.285	2.101, 2.330
	GMT for adjusted treatment mean [2]	158.90	164.18
	95% CI	130.950, 192.817	126.066, 213.828
Day 14	Number of subjects with data n (%)	200 (100.0)	94 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.31	3.19
	Standard error	0.041	0.058
	95% CI	3.223, 3.391	3.079, 3.309
	GMT for adjusted treatment mean [2]	2026.55	1562.60
	95% CI	1670.080, 2459.103	1199.813, 2035.071

Abbreviations: CI = Confidence Interval; GMT = Geometric Mean Titre; IC50 = Inhibitory Concentration 50; LS mean = least squares mean; N = the number of subjects in the population; mITT = modified intention-to-treat; (%) = n/N*100; MMRM = mixed model repeated measures. Baseline is defined as the most recent measurement prior or equal to the administration of the study drug date. [1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group (PHH-1V81 and Comirnaty Omicron XBB.1.5), age group (18-60 and ≥60), visit (Baseline and Day 14), the number of previous vaccine doses group (3 and ≥4), and the treatment-by-visit interaction term as fixed effects. Site and subject nested to site were included as random effects. An unstructured covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used to estimate the degrees of freedom. Least Square Means from the fitted model on the log10 scale. [2] The GMT for treatment means were estimated using LS Means from the fitted model on the log10 scale and back-transformed. Raw data provided as < 20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.

Neutralising antibody levels against Omicron XBB.1.5 at Baseline and Day 14 in individuals with and without prior reported COVID-19 infection

Table 20: Analysis of IC_{50} against Omicron XBB.1.5 at Baseline and Day 14 for subjects with prior reported COVID-19 infection (mITT Population).

Visit	Statistics	PHH-1V81 (N=206)	Comirnaty Omicron XBB.1.5 (N=99)
Baseline	Number of subjects with data n (%)	206 (100.0)	99 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.17	2.22
	Standard error	0.036	0.050
	95% CI	2.099, 2.244	2.121, 2.320
	GMT for adjusted treatment mean [2]	148.38	166.05
	95% CI	125.498, 175.427	131.994, 208.905
Day 14	Number of subjects with data n (%)	206 (100.0)	99 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.27	3.16
	Standard error	0.036	0.050
	95% CI	3.201, 3.347	3.057, 3.257
	GMT for adjusted treatment mean [2]	1880.24	1434.93
	95% CI	1590.311, 2223.014	1140.598, 1805.207

Table 21: Analysis of IC50 against Omicron XBB.1.5 at Baseline and Day 14 for subjects without prior reported COVID-19 infection (mITT Population).

Visit	Statistics	PHH-1V81 (N=200)	Comirnaty Omicron XBB.1.5 (N=94)
Baseline	Number of subjects with data n (%)	200 (100.0)	94 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.19	2.23
	Standard error	0.042	0.057
	95% CI	2.101, 2.275	2.120, 2.349
	GMT for adjusted treatment mean [2]	154.17	171.63
	95% CI	126.323, 188.153	131.884, 223.35
Day 14	Number of subjects with data n (%)	200 (100.0)	94 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.27	3.19
	Standard error	0.042	0.057
	95% CI	3.188, 3.361	3.078, 3.307
	GMT for adjusted treatment mean [2]	1879.39	1558.09
	95% CI	1539.938, 2293.676	1197.283, 2027.632

Neutralising Antibody levels Against Omicron XBB.1.16 Subvariant for subjects with 3 and ≥4 prior doses of a COVID-19 vaccine

Table 22: Analysis of IC_{50} against Omicron XBB.1.16 at Baseline and Day 14 for subjects with 3 prior doses of a COVID-19 vaccine (mITT Population).

Visit	Statistics	PHH-1V81 (N=272)	Comirnaty Omicron XBB.1.5 (N=129)
Baseline	Number of subjects with data n (%)	272 (100.0)	129 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.17	2.23
	Standard error	0.033	0.047
	95% CI	2.100, 2.233	2.134, 2.321
	GMT for adjusted treatment mean [2]	146.77	168.96
	95% CI	125.988, 170.982	136.292, 209.468
Day 14	Number of subjects with data n (%)	272 (100.0)	129 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.33	3.18
	Standard error	0.033	0.047
	95% CI	3.259, 3.392	3.084, 3.271
	GMT for adjusted treatment mean [2]	2115.66	1504.10
	95% CI	1816.085, 2464.661	1213.261, 1864.667

Table 23: Analysis of IC_{50} against Omicron XBB.1.16 at Baseline and Day 14 for subjects with ≥4 prior doses of a COVID-19 vaccine (mITT Population).

Visit	Statistics	PHH-1V81 (N=134)	Comirnaty Omicron XBB.1.5 (N=64)
Baseline	Number of subjects with data n (%)	134 (100.0)	64 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.21	2.16
	Standard error	0.051	0.069
	95% CI	2.105, 2.318	2.023, 2.300
	GMT for adjusted treatment mean [2]	162.77	145.07
	95% CI	127.315, 208.111	105.421, 199.635
Day 14	Number of subjects with data n (%)	134 (100.0)	64 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.21	3.18
	Standard error	0.051	0.069
	95% CI	3.105, 3.318	3.042, 3.319
	GMT for adjusted treatment mean [2]	1628.06	1516.10
	95% CI	1273.392, 2081.500	1101.722, 2086.328

Neutralising antibody levels against XBB.1.5 in individuals with 3 or ≥4 previous mRNA doses

Table 24: Analysis of IC_{50} against Omicron XBB.1.5 at Baseline and Day 14 for subjects with 3 prior doses of a COVID-19 vaccine (mITT Population).

Visit	Statistics	PHH-1V81 (N=272)	Comirnaty Omicron XBB.1.5 (N=129)
Baseline	Number of subjects with data n (%)	272 (100.0)	129 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.16	2.23
	Standard error	0.032	0.046
	95% CI	2.095, 2.222	2.145, 2.325
	GMT for adjusted treatment mean [2]	143.93	171.71
	95% CI	124.309, 166.652	139.567, 211.261
Day 14	Number of subjects with data n (%)	272 (100.0)	129 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.32	3.18
	Standard error	0.032	0.046
	95% CI	3.255, 3.382	3.093, 3.273
	GMT for adjusted treatment mean [2]	2081.44	1524.36
	95% CI	1797.669, 2409.995	1238.992, 1875.451

Table 25: Analysis of IC_{50} against Omicron XBB.1.5 at Baseline and Day 14 for subjects with ≥4 prior doses of a COVID-19 vaccine (mITT Population).

Visit	Statistics	PHH-1V81 (N=134)	Comirnaty Omicron XBB.1.5 (N=64)
Baseline	Number of subjects with data n (%)	134 (100.0)	64 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.22	2.20
	Standard error	0.051	0.068
	95% CI	2.112, 2.327	2.060, 2.334
	GMT for adjusted treatment mean [2]	165.80	157.51
	95% CI	129.493, 212.284	114.918, 215.886
Day 14	Number of subjects with data n (%)	134 (100.0)	64 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.18	3.14
	Standard error	0.051	0.068
	95% CI	3.074, 3.288	3.005, 3.279
	GMT for adjusted treatment mean [2]	1516.64	1385.97
	95% CI	1184.533, 1941.87	1011.195, 1899.641

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections)

Table 26: Summary of Efficacy for trial HIPRA HH-14

Title: A Phase IIb/III, Double-Blind, Randomised, Active-Controlled, Multi-Center, Non-Inferiority Clinical Trial, to assess the safety and immunogenicity of a booster vaccination with an adapted recombinant protein RBD fusion homodimer candidate (PHH-1V81) against SARS-CoV-2, in adults vaccinated against COVID-19.			
Study identifier	HIPRA-HH-14 EU CT: 2023-508458-25-00 NCT06181292		
Design	Phase IIb/III, Double-Blind, Randomised, Active-Controlled, Multi-Center		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months (182 days) not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	PHH-1V81		PHH-1V81 vaccine. One booster dose of 0.5 ml (40 µg), intramuscular administration, 603
	Comirnaty Omicron XBB.1.5		Comirnaty Omicron XBB.1.5. One booster dose of 0.3 ml (30 µg), intramuscular administration, 302
Endpoints and definitions	Primary endpoint	GMT against Omicron XBB.1.16	Neutralisation titre against Omicron XBB.1.16 variant measured as inhibitory concentration 50 (IC_{50}) by pseudovirion-based neutralisation assay (PBNA) and reported as reciprocal concentration for each individual sample and geometric mean titre (GMT) for treatment group comparison at Baseline and at Day 14.
	Secondary endpoint	GMT against other variants	Neutralisation titre against Wuhan, Omicron BA.1 and Omicron XBB.1.5 variants measured as IC_{50} by PBNA and reported as reciprocal concentration for each individual sample and GMT for treatment group comparison at Baseline and at Days 14, 91 and 182.

		GMFR	Geometric mean fold rise (GMFR) in neutralising antibodies titres against Wuhan, Omicron BA.1, Omicron XBB.1.5 and Omicron XBB.1.16 variants for descriptive analysis, from Baseline to Day 14 in both vaccine arms.
		GMT in binding antibodies	Binding antibodies titre measured for each individual sample and GMT for treatment group comparison at Baseline and Days 14, 91 and 182.
Database lock	12 December 2023 (Interim analysis)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	modified Intent to treat (mITT): All participants in the Intention-to-treat (ITT) who met the inclusion/exclusion criteria and received a dose of study drug, whose Baseline and Day 14 data were available and did not test positive for COVID-19 within 14 days of receiving study drug. Subjects were grouped as randomised. This population has been used as primary population for immunogenicity analysis. Time points planned: Baseline, Day 14, Day 91 and Day 182. Time points analysed (Interim Analysis): Baseline, Day 14. 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 (mITT population).		
Descriptive statistics and estimate variability	Treatment group	**PHH-1V81**	**Comirnaty Omicron XBB.1.5**
	Number of subject	406	193
	Baseline		

GMT against Omicron XBB.1.16 (for adjusted treatment mean)	152.46	161.57
95% CI	134.72 – 172.54	136.40 – 191.37
GMT against other variants (for adjusted treatment mean)	151.93 (Omicron XBB.1.5)	167.89 (Omicron XBB.1.5)
95% CI	134.89, 171.13 (Omicron XBB.1.5)	142.04, 198.44 (Omicron XBB.1.5)
GMT in binding antibodies (for adjusted treatment mean)	10896.07	11493.04
95% CI	10057.71 - 11804.30	10232.32 - 12909.09
Day 14		
GMT against Omicron XBB.1.16 (for adjusted treatment mean)	1946.38	1512.21
95% CI	1708.44 - 2217.46	1261.72 - 1812.44
GMT against various variants (for adjusted treatment mean)	1888.89 (Omicron XBB.1.5)	1486.03 (Omicron XBB.1.5)

	95% CI	1676.99, 2127.57 (Omicron XBB.1.5)	1257.25, 1756.45 (Omicron XBB.1.5)
	GMFR (for adjusted treatment mean)	12.76 (Omicron XBB.1.16)	9.42 (Omicron XBB.1.16)
	95% CI	11.01 - 14.78 (Omicron XBB.1.16)	7.61 - 11.66 (Omicron XBB.1.16)
	GMFR (for adjusted treatment mean)	12.42 (Omicron XBB.1.5)	8.88 (Omicron XBB.1.5)
	95% CI	10.62, 14.51 (Omicron XBB.1.5)	7.20, 10.94 (Omicron XBB.1.5)
	GMT in binding antibodies (for adjusted treatment mean)	53457.70	39508.81
	95% CI	49378.78 - 57873.56	35215.51 - 44325.53
Effect estimate per comparison	Primary endpoint: GMT against Omicron XBB.1.16	**Baseline**	
		Comparison groups	Comirnaty Omicron XBB.1.5 (vs) PHH-1V81
		GMT for Treatment Ratio	1.06
		95% CI for adjusted ratio	0.87 - 1.29
		p-value for ratio = 1	0.5696
		Day 14	

		Comparison groups	Comirnaty Omicron XBB.1.5 (vs) PHH-1V81
		GMT for Treatment Ratio	0.78
		95% CI for adjusted ratio	0.63 - 0.96
		p-value for ratio = 1	0.0213
	Secondary endpoint: GMT against other variants	**Baseline**	
		Comparison groups (Omicron XBB.1.5)	Comirnaty Omicron XBB.1.5 (vs) PHH-1V81
		GMT for Treatment Ratio (Omicron XBB.1.5)	1.11
		95% CI for adjusted ratio (Omicron XBB.1.5)	0.90 - 1.35
		p-value for ratio = 1 (Omicron XBB.1.5)	0.3303
		Day 14	
		Comparison groups	Comirnaty Omicron XBB.1.5 (vs) PHH-1V81
		GMT for Treatment Ratio (Omicron XBB.1.5)	0.79
		95% CI for adjusted ratio	0.64, 0.96

		(Omicron XBB.1.5)	
		p-value for ratio = 1 (Omicron XBB.1.5)	0.0195
	Secondary endpoint: GMFR	**Day 14**	
		Comparison groups	Comirnaty Omicron XBB.1.5 (vs) PHH-1V81
		GMFR for Treatment Ratio (Omicron XBB.1.16)	0.74
		95% CI for adjusted ratio (Omicron XBB.1.16)	0.57 - 0.96
		p-value for ratio = 1 (Omicron XBB.1.16)	0.0218
		GMFR for Treatment Ratio (Omicron XBB.1.5)	0.71
		95% CI for adjusted ratio (Omicron XBB.1.5)	0.56 - 0.92
		p-value for ratio = 1 (Omicron XBB.1.5)	0.0082
		Baseline	

Secondary endpoint: GMT in binding antibodies	Comparison groups	Comirnaty Omicron XBB.1.5 (vs) PHH-1V81
	GMT for Treatment Ratio	1.05
	95% CI for adjusted ratio	0.92 - 1.21
	p-value for ratio = 1	0.4583
	Day 14	
	Comparison groups	Comirnaty Omicron XBB.1.5 (vs) PHH-1V81
	GMT for Treatment Ratio	0.74
	95% CI for adjusted ratio	0.64 - 0.85
	p-value for ratio = 1	<0.0001

Notes	GMT ratio is the result of the GMT values Comirnaty Omicron XBB.1.5/PHH-1V81. Non-inferiority of PHH-1V81 to Comirnaty Omicron XBB.1.5 is concluded if the upper limit of the 2 sided 95% CI of the GMT ratio is < 1.5. Superiority of PHH-1V81 to Comirnaty Omicron XBB.1.5 is concluded if the upper limit of the 2-sided 95% CI of the GMT ratio is < 1.0. Superiority of PHH-1V81 was met for all variants tested (Omicron XBB.1.16 and Omicron XBB.1.5) at Day 14. Please note that some of the timepoints specified in the secondary endpoints for the study HIPRA-HH-14 were not analysed (immunogenicity data available up to Day 14). In addition, some of the analysis assessing the response against other variants (Wuhan, Omicron BA.1) were not included. These data will be provided once the clinical study report is available.

2.6.5.2. Clinical studies in special populations

In the mITT population (cut-off 13 December 2024), there were a total of 75 subjects 60 years of age and older, 52 in the PHH-1V81 group and 23 in the Comirnaty group. Immunogenicity results in this age group are provided below.

Neutralising antibody levels against Omicron XBB.1.16 at Baseline and Day 14 in individuals ≥60 years old

Table 27: Analysis of IC_{50} against Omicron XBB.1.16 at Baseline and Day 14 for subjects ≥60 years-old (mITT Population).

Visit	Statistics	PHH-1V81 (N=52)	Comirnaty Omicron XBB.1.5 (N=23)
Baseline	Number of subjects with data n (%)	52 (100.0)	23 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.11	2.24
	Standard error	0.104	0.138
	95% CI	1.888, 2.326	1.964, 2.521
	GMT for adjusted treatment mean [2]	127.94	174.81
	95% CI	77.242, 211.915	91.986, 332.193
Day 14	Number of subjects with data n (%)	52 (100.0)	23 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.30	3.26
	Standard error	0.104	0.138
	95% CI	3.077, 3.516	2.982, 3.539
	GMT for adjusted treatment mean [2]	1979.20	1822.30
	95% CI	1194.912, 3278.251	958.925, 3463.008

Abbreviations: CI = Confidence Interval; GMT = Geometric Mean Titre; IC_{50} = Inhibitory Concentration 50; LS mean = least squares mean; N = the number of subjects in the population; mITT = modified intention-to-treat; (%) = n/N*100; MMRM = mixed model repeated measures.
Baseline is defined as the most recent measurement prior or equal to the administration of the study drug date.
[1] A MMRM model was fitted to the assess the endpoint on the log_{10} scale. The model included treatment group (PHH-1V81 and Comirnaty Omicron XBB.1.5), visit (Baseline and Day 14), the number of previous vaccine doses group (3 and ≥4), and the treatment-by-visit interaction term as fixed effects. Site and subject nested to site were included as random effects. An unstructured covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used to estimate the degrees of freedom. Least Square Means from the fitted model on the log_{10} scale.
[2] The GMT for treatment means were estimated using LS Means from the fitted model on the log_{10} scale and back-transformed.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.

Neutralising antibody levels against Omicron XBB.1.5 at Baseline and Day 14 in individuals ≥60 years old

Table 28: Analysis of IC_{50} against Omicron XBB.1.5 at Baseline and Day 14 for subjects ≥60 years-old (mITT Population).

Visit	Statistics	PHH-1V81 (N=52)	Comirnaty Omicron XBB.1.5 (N=23)
Baseline	Number of subjects with data n (%)	52 (100.0)	23 (100.0)
	Adjusted treatment mean (LS Mean) [1]	2.14	2.24
	Standard error	0.098	0.128
	95% CI	1.928, 2.343	1.982, 2.497
	GMT for adjusted treatment mean [2]	136.61	173.46
	95% CI	84.809, 220.047	95.888, 313.804
Day 14	Number of subjects with data n (%)	52 (100.0)	23 (100.0)
	Adjusted treatment mean (LS Mean) [1]	3.26	3.23
	Standard error	0.098	0.128
	95% CI	3.053, 3.467	2.971, 3.486
	GMT for adjusted treatment mean [2]	1817.99	1692.08
	95% CI	1128.633, 2928.388	935.35, 3061.038

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development is based on an immunobridging approach to extrapolate efficacy from the approved adapted mRNA vaccine Comirnaty XBB.1.5 to the vaccine candidate PHH-1V81. This approach is considered acceptable and was agreed to in an EMA-SA procedure (EMA/SA/0000148115) and is aligned with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

This line extension submission is based on the interim report of clinical study HIPRA-HH-14 (DBL: 13 December 2023, date of the report: 3 Jan 2024) and its addendum (Date of the report: Jan 2 2024)

HIPRA-HH-14 is a Phase IIb/III, double-blind, randomised, active-controlled, multi-center, non-inferiority clinical trial, to assess the safety and immunogenicity of a booster vaccination with the adapted vaccine PHH-1V81 in adults vaccinated against COVID-19. The study was conducted at 10 sites located in Spain. It was conducted in accordance with the Declaration of Helsinki and with GCP guidelines. The choice for Comirnaty XBB.1.5 as active comparator is considered adequate as this vaccine is authorised for booster vaccination and efficacy has been established.

Booster vaccination with either PHH-1V81 or Comirnaty Omicron XBB.1.5 was administered at least 182 days after at least one previous booster dose of an EU-approved mRNA vaccine. Participants were stratified per protocol by number of doses previously received (3 or ≥ 4 doses) and by age group (approximately 10% of adults ≥60 years old in each treatment group).

The primary objectives were to assess safety and tolerability of PHH-1V81 and the immunogenicity against Omicron XBB.1.16 variant at baseline and day 14 in the PHH-1V81 arm compared to Comirnarty Omicron XBB.1.5

Overall, the chosen objectives and endpoints are appropriate to investigate immune responses for a booster application and were also accepted in the Scientific Advice. The Statistical methods, blinding and randomisation methods are overall acceptable.

Study power and sample size calculation are adequate. Immunobridging approach with non-inferiority testing of PHH-1V81 compared to Comirnaty XBB.1.5 and NI margin of 0.67 of GMT ratio of Comirnaty XBB.1.5: PHH-1V81 is compliant with the SA. Null hypothesis and alternative hypothesis are appropriate for an immunobridging approach and both are similar to those performed of Study HIPRA-HH-2.

Primary estimand is similar to those defined in the SAP of Study HH-2 and is considered acceptable.

Secondary estimands and secondary endpoints defined for Study HH-14 can be considered adequate.

The sampling time points (Day 14, Day 98, and Day 182, (final visit)) are considered adequate to observe the immune response and its maintenance. In the interim report assessed in this procedure, only immunogenicity data available for Day 14. Day 98 and Day 182 will be presented in the final Clinical Study Report in a separate regulatory procedure.

Overall, the study design of Study HH-14 appears acceptable.

Inclusion and exclusion criteria

Inclusion and exclusion criteria are considered appropriate.

Participants with some underlying conditions (e.g. hepatic or renal impairment, hypertension) that were stable conditions or not considered clinically significant by the investigator were enrolled in this study, in alignment with inclusion and exclusion criteria.

It can be concluded that the subjects enrolled in the study met the inclusion/exclusion criteria.

Subject disposition

The final number of vaccinated subjects in the clinical trial is 903 (602 in the PHH-1V81 arm and 301 in the Comirnaty Omicron XBB.1.5 arm), whose will be considered as the final safety population in the Final Analysis (cut-off date 13 June 2024).

For the immunogenicity interim analysis, only the first 612 subjects reaching Day 14 post vaccination were taken into consideration, and from them, 599 subjects had immunogenicity data at baseline and Day 14. These 599 subjects (366 in the PHH-1V81 arm and 183 in the Comirnaty XBB.1.5 arm) were included in the mITT population. The MAH will provide clinical efficacy data for the whole vaccinated subject population in the final CSR that will be submitted in a separate regulatory procedure.

GCP issues

Applicant stated that Study HIPRA-HH-14 was conducted in compliance with GCP and Helsinki Declaration.

Up to 13 December 2023, no critical protocol deviation has been observed.

Efficacy data and additional analyses

Clinical assays

Two methods were used in the application to measure nABs in the sera of the subjects: a pseudovirion-based neutralisation assay (PBNA) against Omicron XBB.1.5 ad XBB.1.16 and a virus neutralisation assay (VNA) against Omicron XBB.1.5 ad XBB.1.16.

As this application is based on immunobridging, a proven surrogacy of PBNA for VNA for all different variants tested is a prerequisite for using PBNA as primary immunogenicity assay. Validation of the PBNA assay against Omicron sublineages XBB.1.5 and XBB.1.16 as well as comparative studies of VNA and PBNA assays against the above Omicron sublineages are discussed in details in section 2.6.2. Clinical Pharmacology and are considered acceptable.

Efficacy endpoints

At Day 14, primary efficacy endpoint was met, since GMT ratio against Omicron XBB.1.16 showed superiority of PHH-1V81 over Comirnaty XBB.1.5.

As it was already discussed in the assessment of variation procedures II/04 and II/13, and also according to the CHMP Guideline *Points to consider on switching between superiority and non-inferiority* if the 95% confidence interval for the treatment effect not only lies entirely above -Δ but also above zero then there is evidence of superiority in terms of statistical significance at the 5% level ($p<0.05$). However, the guideline refers for the case when the *difference* in an efficacy variable observed in the study product's group and in the comparator group is studied (i.e. result of a given efficacy variable in the study product's group minus the result in the comparator group). In this case a negative NI margin makes sense, since lower efficacy in the study product group compared to the comparator group will result in a negative difference in the efficacy variable. If zero is included in the 95% CI of the treatment difference, this is indicative for NI (if the lower limit of the 95% CI lies above the (negative) non-inferiority margin) and also precludes superiority. However, in Study HIPRA-HH-14 and also in previous Bimervax clinical studies, data is provided in GMT ratios (instead of differences). Therefore, in this case, 1. positive NI margin is appropriate, 2. inclusion of 1 (instead of zero) in the 95% CI of GMT ratio is indicative for non-inferiority (when the upper limit of 95% CI is below the (positive) NI margin) and precludes superiority. The case, when the upper limit of the 95% CI of GMT ratio is below 1 with significance level of 5% ($p<0.05$) however, is indicative for superiority.

According to the guideline, in such a case it is acceptable to calculate the p-value associated with a test of superiority and to evaluate whether this is sufficiently small to reject convincingly the hypothesis of no difference.

Apart from the treatment difference and confidence interval data indicative for superiority instead of non-inferiority, switching the objective of a trial from non-inferiority to superiority is considered feasible provided that:

- The trial has been properly designed and carried out in accordance with the strict requirements of a non-inferiority trial, including the establishment of predefined NI margin (in case of NI one sided NI margin is enough – this was 0.67' for Study HH-14 when GMT ratio of Comirnaty XBB.1.5: PHH-1V81 was counted with as it was discussed earlier, this NI margin is equivalent to an NI margin of 1.5 when GMT ratio of PHH-1V81:Coimrnaty XBB.1.5 is counted with in Study HH-2 Part B.
- Actual p-values for superiority are presented to allow independent assessment of the strength of the evidence (p value is <0.021 for the primary efficacy endpoint of Study HIPRA-HH-14)
- Analysis according to the intention-to-treat principle is given greatest emphasis. (This condition was also fulfilled in Study HIPRA-HH-14)

To sum up, switch from non-inferiority to superiority can be considered adequate for primary efficacy endpoint of Study HIPRA-HH-14 and the above mentioned considerations apply for the noninferiority analysis of all other GMT data observed in Study HH-14 and also for its eventual switch to superiority.

As for secondary efficacy endpoints, analysis of GMFR in Neutralising Antibodies Titres against Omicron XBB.1.16 and XBB.1.5 at Day 14 shows superiority of PHH-1V81 over Comirnaty XBB.1.5.

At Day 14, GMT ratio against for binding antibody also demonstrated superiority of PHH-1V81 over Comirnaty XBB.1.5

The percentage of subjects with a fold rise ≥4 in neutralising antibody titres against Omicron XBB.1.16 and XBB.1.5 from Baseline to Day 14 as well as the percentage of subjects with a fold rise ≥2 in binding antibody titres were higher in the PHH-1V81 treatment arm compared to the Comirnaty Omicron XBB.1.5 treatment arm.

Cellular immunity assays were carried out only on a small subset of subjects, and therefore, this data should be interpreted with caution. Therefore, the only conclusion that can be drawn is that the cellular immune responses in the PHH-1V81 group and the Comirnaty XBB.1.5 group of Study HH-14 were comparable.

Subgroup analyses were performed by age (below and ≥60 yoa), by the previous vaccination status (3 or 4/more prior COVID-19 vaccines) and by prior reported COVID-19 infection (with or without infection). Albeit only descriptive statistical analyses were performed for the subgroups, the results of these analyses are aligned with the results of main analyses.

Indication and posology

The proposed indication is as follows:

PHH-1V81 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. (SmPC 4.1)

The proposed posology for individuals 16 years and older is as follows:

A single intramuscular dose (0.5 mL) of PHH-1V81 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, PHH-1V81 should be administered at least 6 months after the most recent dose of a COVID-19 vaccine.

The sought indication is the same as the approved one for Comirnaty XBB.1.5 and Nuvaxovid XBB.1.5 and is in line with the ECDC-EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants.

Taking into account that

- the adult population of the EU cannot be considered as immunologically naïve concerning SARS-CoV2 anymore and
- the parent Bimervax vaccine cannot be considered relevant anymore and will most likely not be used for vaccination in the EU given the recommendations to use the most updated vaccine. Therefore the indication of the adapted Bimervax vaccine should not be affected by the indication of the parent vaccine

the proposed indication is accepted.

2.6.7. Conclusions on the clinical efficacy

The available clinical efficacy results of immunobridging HIPRA-HH-14 study show a comparable or even superior immune response of COVID-19 vaccine PHH-1V81 against Omicron sublineages XBB.1.5 and XBB.1.16 when compared to Comirnaty XBB.1.5 at day 14 post-vaccination. Despite the spread of new variants and waning of Omicron XBB variants, the efficacy data of Study HH-14 has remarkable relevance, since this line extension is the first strain update for Bimervax and a positive outcome is a

prerequisite for further strain updates. Therefore, data are still relevant for the purpose of this line extension even though the more relevant strain update for use at the current moment is the JN.1 variant.

It is noted that even if the choice of Omicron XBB.1.16 variant for the antigen (RBD dimer) development was compliant with the WHO and EMA-ECDC recommendations of Q2 2023 at the time of the development of PHH-1V81, recently the virus variant JN.1 is recommended as the target variant for development of adapted COVID vaccines for vaccination in the autumn-winter season of 2024/25.

2.6.8. Clinical safety

Safety data from study HIPRA-HH-14 is available up to 6-month post- vaccination with a data cut off of 13th June 2024.

Collection of safety data in study HIPRA-HH-14

Participants were provided with a participant paper diary on Day 0 to record solicited local and systemic reactions after vaccination through Day 7. Unsolicited local and systemic adverse events are recorded through Day 28 after vaccination. AEs, SAEs, AESIs and MAAEs, will be recorded through the end of study. After Day 28 post-vaccination, only related MAAEs will be recorded.

Participants were to return to the site at Days 14, 91 and 182 for a follow-up. On Day 28 participants were contacted by phone to record additional AEs up to Day 28. Participants will be followed for approximately 6 months after the study treatment.

2.6.8.1. Patient exposure

A total of 903 subjects have received at least one study vaccine dose, from which 602 received the PHH-1V81 vaccine and 301 received Comirnaty Omicron XBB.1.5.

Table 29: Overall extent of exposure in the PHH-1V81 clinical development plan

Product and Dose level	Number of doses	HIPRA-HH-14 Phase IIb/III[1]
PHH-1V81 40 µg	One (booster)	602
Comirnaty Omicron XBB.1.5 30 µg mRNA	One (booster)	301

[1]Study is ongoing. Number of safety populations are available. Cut-off date: 6-month data.

2.6.8.2. Adverse events

Solicited Local Adverse Events

A summary of solicited local adverse events is provided in Table 37. The percentage of subjects who had at least one solicited local event was 69.10% for PHH-1V81 and 76.08% for Comirnaty Omicron XBB.1.5. The most frequently reported solicited local AEs in the PHH-1V81 group were injection site pain/tenderness/discomfort (68.11 of subjects in PHH-1V81 vs 74.42% of subjects in Comirnaty Omicron XBB.1.5) and injection site induration/swelling (15.78 % PHH-1V81 vs 22.92% Comirnaty Omicron XBB.1.5).

Table 30: Summary of Solicited Local Events from Day 0 through Day 7 (Safety Population, HIPRA-HH-14)

	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N= 301)		Overall (N= 903)	
Events	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
Total number of Solicited Local Events	**878**	**416 (69.10)**	**523**	**229 (76.08)**	**1401**	**645 (71.43)**
Injection site pain/ tenderness/ discomfort	702	410 (68.11)	396	224 (74.42)	1098	634 (70.21)
Injection site erythema/ redness	74	67 (11.13)	54	48 (15.95)	128	115 (12.74)
Injection site induration/ swelling	102	95 (15.78)	73	69 (22.92)	175	164 (18.16)

Abbreviations: N = the number of subjects in the population; n = the number of subjects meeting the criterion; (%) = n/N*100.
If a subject experienced more than one event, the subject is counted once for each type of event.

Table 28 describes the summary of solicited local events by day. The higher frequency of solicited local events were reported on day 1 post-vaccination (60,3 % of subjects in PHH-1V81 vs 71.10 % in Comirnaty Omicron XBB.1.5) and most of them lasted for 3 days. Overall, in all timepoints from Day 0 to Day 7, the percentages of subjects reporting solicited local events were higher in the Comirnaty Omicron XBB.1.5 vaccine arm compared to PHH-1V81 vaccine arm.

Table 31: Summary of Solicited Local Events separately by days between Day 0 and Day 7, by PT (Safety Population, HIPRA-HH-14)

		PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
Day post-vaccination	**PT**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
12h	Total number of events	584	323 (53.65)	262	152 (50.50)	846	475 (52.6)
	Injection site erythema/redness	35	34 (5.65)	14	14 (4.65)	49	48 (5.32)
	Injection site induration/swelling	54	54 (8.97)	23	23 (7.64)	77	77 (8.53)
	Injection site pain/tenderness/discomfort	495	317 (52.66)	225	148 (49.17)	720	465 (51.50)
Day 1	Total number of events	701	363 (60.3)	452	214 (71.10)	1153	577 (63.9)
	Injection site erythema/redness	61	59 (9.80)	44	44 (14.62)	105	103 (11.41)
	Injection site induration/swelling	86	83 (13.79)	65	65 (21.59)	151	148 (16.39)
	Injection site pain/tenderness/discomfort	554	352 (58.47)	343	208 (69.10)	897	560 (62.02)
Day 2	Total number of events	339	172 (28.57)	273	128 (42.52)	612	300 (33.22)
	Injection site erythema/redness	47	42 (6.98)	42	41 (13.62)	89	83 (9.19)
	Injection site induration/swelling	54	49 (8.14)	38	36 (11.96)	92	85 (9.41)
	Injection site pain/tenderness/discomfort	238	158 (26.25)	193	121 (40.20)	431	279 (30.90)
Day 3	Total number of events	168	78 (12.96)	126	58 (19.27)	294	136 (15.06)
	Injection site erythema/redness	33	29 (4.82)	27	26 (8.64)	60	55 (6.09)
	Injection site induration/swelling	34	30 (4.98)	23	21 (6.98)	57	51 (5.65)
	Injection site pain/tenderness/discomfort	101	68 (11.30)	76	50 (16.61)	177	118 (13.07)
Day 4	Total number of events	80	39 (6.48)	46	22 (7.31)	126	61 (6.76)
	Injection site erythema/redness	18	17 (2.82)	11	11 (3.65)	29	28 (3.10)
	Injection site induration/swelling	17	15 (2.49)	11	11 (3.65)	28	26 (2.88)
	Injection site pain/tenderness/discomfort	45	32 (5.32)	24	17 (5.65)	69	49 (5.43)
Day 5	Total number of events	35	26 (4.32)	22	11 (3.65)	57	37 (4.10)
	Injection site erythema/redness	9	9 (1.50)	6	6 (1.99)	15	15 (1.66)

		PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
Day post-vaccination	**PT**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
	Injection site induration/swelling	7	7 (1.16)	4	4 (1.33)	11	11 (1.22)
	Injection site pain/tenderness/discomfort	19	16 (2.66)	12	7 (2.33)	31	23 (2.55)
Day 6	Total number of events	22	19 (3.16)	13	7 (2.33)	35	26 (2.88)
	Injection site erythema/redness	6	6 (1.00)	2	2 (0.66)	8	8 (0.89)
	Injection site induration/swelling	1	1 (0.17)	3	3 (1.00)	4	4 (0.44)
	Injection site pain/tenderness/discomfort	15	12 (1.99)	8	6 (1.99)	23	18 (1.99)
Day 7	Total number of events	18	15 (2.49)	11	5 (1.66)	29	20 (2.21)
	Injection site erythema/redness	5	5 (0.83)	2	2 (0.66)	7	7 (0.78)
	Injection site induration/swelling	0	0 (0)	3	3 (1.00)	3	3 (0.33)
	Injection site pain/tenderness/discomfort	13	10 (1.66)	6	4 (1.33)	19	14 (1.55)

Solicited Systemic Adverse Events

A summary of solicited systemic adverse events is provided in Table 29. The percentage of subjects who had at least one systemic solicited event was 36.54% for PHH-1V81 and 46.18% for Comirnaty Omicron XBB.1.5. The most frequently reported solicited systemic AEs in the PHH-1V81 group were headache (23.42% of subjects in PHH-1V81 vs 24.58% of subjects in Comirnaty Omicron XBB.1.5), fatigue (19.6 % PHH-1V81 vs 25.58% Comirnaty Omicron XBB.1.5) and myalgia (13.62% PHH-1V81 vs 17.61% Comirnaty Omicron XBB.1.5).

Table 32: Summary of Solicited Systemic Events from Day 0 through Day 7 (Safety Population, HIPRA-HH-14)

	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
Events	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
Total number of Solicited Systemic Events	**586**	**220 (36.54)**	**383**	**139 (46.18)**	**969**	**359 (39.75)**
Axillary Pain	17	17 (2.82)	25	23 (7.64)	42	40 (4.43)
Diarrhoea	31	27 (4.49)	13	13 (4.32)	44	40 (4.43)

	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
Events	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
Total number of Solicited Systemic Events	**586**	**220 (36.54)**	**383**	**139 (46.18)**	**969**	**359 (39.75)**
Fatigue	139	118 (19.60)	84	77 (25.58)	223	195 (21.59)
Fever	7	5 (0.83)	3	3 (1.00)	10	8 (0.89)
Headache	168	141 (23.42)	90	74 (24.58)	258	215 (23.81)
Lymphadenopathy	18	18 (2.99)	15	13 (4.32)	33	31 (3.43)
Malaise/Discomfort	91	77 (12.79)	75	66 (21.92)	166	143 (15.83)
Myalgia	94	82 (13.62)	59	53 (17.61)	153	135 (14.95)
Nausea/Vomiting	21	21 (3.49)	19	17 (5.65)	40	38 (4.21)

Abbreviations: N = the number of subjects in the population; n = the number of subjects meeting the criterion; (%) = n/N*100.
If a subject experienced more than one event, the subject is counted once for each type of event.

Among the gastrointestinal disorders, nausea and/or vomiting were reported more frequently in the Comirnaty Omicron XBB.1.5 vaccine arm (5.65%) compared to PHH-1V81 (3.49%), and diarrhoea was reported very similarly in both vaccine arms with 4.49% and 4.32% in the PHH-1V81 and Comirnaty Omicron XBB.1.5 vaccine arms, respectively. Fever was reported in less than 1% of the participants in each group.

Table 30 describes the summary of solicited systemic events by day. The higher frequency of solicited systemic events were reported on Day 1 post-vaccination (23.59 % of subjects in PHH-1V81 vs 35.22% in Comirnaty Omicron XBB.1.5) and most of them lasted for 3 days. Overall, in all timepoints from Day 0 to Day 7, the percentages of subjects reporting solicited systemic events were higher in the Comirnaty Omicron XBB.1.5 vaccine arm compared to PHH-1V81 vaccine arm.

Table 33: Summary of Solicited Systemic Events separately by days between Day 0 and Day 7, by PT (Safety Population, HIPRA-HH-14)

		PHH-1V81 (N=602)		**Comirnaty Omicron XBB.1.5 (N=301)**		**Overall (N=903)**	
Day post-vaccination	**PT**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
12h	Total number of events	213	116 (19.27)	131	64 (21.26)	344	180 (19.93)
	Axillary pain	6	6 (1.00)	9	9 (2.99)	15	15 (1.66)
	Diarrhoea	6	6 (1.00)	0	0 (0)	6	6 (0.66)
	Fatigue	50	49 (8.14)	31	31 (10.30)	81	80 (8.86)
	Fever	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
	Headache	66	66 (10.96)	32	32 (10.63)	98	98 (10.85)
	Lymphadenopathy	5	5 (0.83)	3	3 (1.00)	8	8 (0.89)
	Myalgia	39	39 (6.48)	17	17 (5.65)	56	56 (6.20)
	Nausea/vomiting	6	6 (1.00)	9	9 (2.99)	15	15 (1.66)
	Malaise/discomfort	34	34 (5.65)	29	29 (9.63)	63	63 (6.98)
Day 1	Total number of events	308	142 (23.59)	250	106 (35.22)	558	248 (27.46)
	Axillary pain	10	10 (1.66)	16	16 (5.32)	26	26 (2.88)
	Diarrhoea	14	14 (2.33)	4	4 (1.33)	18	18 (1.99)
	Fatigue	73	71 (11.79)	59	59 (19.60)	132	130 (14.40)

		PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
Day post-vaccination	**PT**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
	Fever	5	4 (0.66)	3	3 (1.00)	8	7 (0.78)
	Headache	79	78 (12.96)	56	55 (18.27)	135	133 (14.73)
	Lymphadenopathy	11	11 (1.83)	10	10 (3.32)	21	21 (2.33)
	Myalgia	59	58 (9.63)	41	41 (13.62)	100	99 (10.96)
	Nausea/vomiting	9	9 (1.50)	11	11 (3.65)	20	20 (2.21)
	Malaise/discomfort	48	48 (7.97)	50	49 (16.28)	98	97 (10.74)
Day 2	Total number of events	174	92 (15.28)	127	61 (20.27)	301	153 (16.94)
	Axillary pain	7	7 (1.16)	17	17 (5.65)	24	24 (2.66)
	Diarrhoea	9	9 (1.50)	4	4 (1.33)	13	13 (1.44)
	Fatigue	41	41 (6.81)	27	27 (8.97)	68	68 (7.53)
	Fever	1	1 (0.17)	0	0 (0)	1	1 (0.11)
	Headache	44	44 (7.31)	25	24 (7.97)	69	68 (7.53)
	Lymphadenopathy	10	10 (1.66)	10	10 (3.32)	20	20 (2.21)
	Myalgia	32	31 (5.15)	19	19 (6.31)	51	50 (5.54)
	Nausea/vomiting	6	6 (1.00)	5	5 (1.66)	11	11 (1.22)
	Malaise/discomfort	24	24 (3.99)	20	20 (6.64)	44	44 (4.87)
Day 3	Total number of events	104	57 (9.47)	67	38 (12.62)	171	95 (10.52)
	Axillary pain	4	4 (0.66)	9	9 (2.99)	13	13 (1.44)
	Diarrhoea	8	8 (1.33)	5	5 (1.66)	13	13 (1.44)
	Fatigue	26	26 (4.32)	10	10 (3.32)	36	36 (3.99)
	Fever	0	0 (0)	0	0 (0)	0	0 (0)
	Headache	24	24 (3.99)	16	16 (5.32)	40	40 (4.43)

		PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
Day post-vaccination	**PT**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
	Lymphadenopathy	7	7 (1.16)	7	7 (2.33)	14	14 (1.55)
	Myalgia	14	14 (2.33)	12	12 (3.99)	26	26 (2.88)
	Nausea/vomiting	5	5 (0.83)	2	2 (0.66)	7	7 (0.78)
	Malaise/discomfort	16	16 (2.66)	6	6 (1.99)	22	22 (2.44)
Day 4	Total number of events	60	33 (5.48)	46	26 (8.64)	106	59 (6.53)
	Axillary pain	1	1 (0.17)	6	6 (1.99)	7	7 (0.78)
	Diarrhoea	7	7 (1.16)	5	5 (1.66)	12	12 (1.33)
	Fatigue	14	13 (2.16)	7	7 (2.33)	21	20 (2.21)
	Fever	1	1 (0.17)	0	0 (0)	1	1 (0.11)
	Headache	16	16 (2.66)	9	9 (2.99)	25	25 (2.77)
	Lymphadenopathy	3	3 (0.50)	5	5 (1.66)	8	8 (0.89)
	Myalgia	5	5 (0.83)	7	7 (2.33)	12	12 (1.33)
	Nausea/vomiting	3	3 (0.50)	3	3 (1.00)	6	6 (0.66)
	Malaise/discomfort	10	9 (1.50)	4	4 (1.33)	14	13 (1.44)
Day 5	Total number of events	56	29 (4.82)	31	21 (6.98)	87	50 (5.54)
	Axillary pain	1	1 (0.17)	4	4 (1.33)	5	5 (0.55)
	Diarrhoea	4	4 (0.66)	4	4 (1.33)	8	8 (0.89)
	Fatigue	12	11 (1.83)	6	6 (1.99)	18	17 (1.88)
	Fever	1	1 (0.17)	0	0 (0)	1	1 (0.11)
	Headache	17	17 (2.82)	4	4 (1.33)	21	21 (2.33)
	Lymphadenopathy	2	2 (0.33)	4	4 (1.33)	6	6 (0.66)
	Myalgia	7	7 (1.16)	6	6 (1.99)	13	13 (1.44)

		PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
Day post-vaccination	**PT**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
	Nausea/vomiting	1	1 (0.17)	2	2 (0.66)	3	3 (0.33)
	Malaise/discomfort	11	10 (1.66)	1	1 (0.33)	12	11 (1.22)
Day 6	Total number of events	52	26 (4.32)	20	14 (4.65)	72	40 (4.43)
	Axillary pain	0	0 (0)	2	2 (0.66)	2	2 (0.22)
	Diarrhoea	5	5 (0.83)	2	2 (0.66)	7	7 (0.78)
	Fatigue	9	8 (1.33)	3	3 (1.00)	12	11 (1.22)
	Fever	0	0 (0)	0	0 (0)	0	0 (0)
	Headache	16	16 (2.66)	3	3 (1.00)	19	19 (2.1)
	Lymphadenopathy	2	2 (0.33)	4	4 (1.33)	6	6 (0.66)
	Myalgia	7	7 (1.16)	3	3 (1.00)	10	10 (1.11)
	Nausea/vomiting	3	3 (0.50)	1	1 (0.33)	4	4 (0.44)
	Malaise/discomfort	10	9 (1.50)	2	2 (0.66)	12	11 (1.22)
Day 7	Total number of events	44	23 (3.82)	24	15 (4.98)	68	38 (4.21)
	Axillary pain	0	0 (0)	1	1 (0.33)	1	1 (0.11)
	Diarrhoea	4	4 (0.66)	3	3 (1.00)	7	7 (0.78)
	Fatigue	11	10 (1.66)	3	3 (1.00)	14	13 (1.44)
	Fever	0	0 (0)	0	0 (0)	0	0 (0)
	Headache	11	11 (1.83)	6	6 (1.99)	17	17 (1.88)
	Lymphadenopathy	2	2 (0.33)	4	4 (1.33)	6	6 (0.66)
	Myalgia	6	6 (1)	2	2 (0.66)	8	8 (0.89)
	Nausea/vomiting	2	2 (0.33)	2	2 (0.66)	4	4 (0.44)
	Malaise/discomfort	8	7 (1.16)	3	3 (1.00)	11	10 (1.11)

Abbreviations: N = the number of subjects in the population; n = the number of subjects meeting the criterion; (%) = n/N*100; PT = preferred term.

If a subject experienced more than one event, the subject is counted once for each type of event.

Unsolicited adverse events

Up to 6 months cut-off, a total of 191 unsolicited AEs were reported in 150 (16.61%) subjects: 131 AEs in 103 (17.11%) subjects in the PHH-1V81 vaccine arm, and 60 AEs in 47 (15.61%) subjects in the Comirnaty XBB.1.5 vaccine arm).

The most frequently reported System Organ Class was Infections and infestations with 58 AEs reported in 57 (6.31 %) subjects followed by Musculoskeletal and connective tissue disorders SOC with 17 AE in 17 subjects (1.88%).

By preferred term (PT), the most frequently reported adverse event was nasopharyngitis (28 AEs in 28 subjects (3.10 %))

There is a numerical imbalance in the reporting frequencies of nasopharyngitis (in 3.82% of subjects in PHH-1V81 vs 1.66% in Comirnaty Omicron XBB.1.5) and for similar PTs (URTI, respiratory tract infections, Laryngitis ad Rhinitis) in the Infections and infestations SOC. Note that numerical imbalance between treatment groups can be seen in the Respiratory, thoracic and mediastinal disorders SOC, and the majority of the AEs in this SOC are indicative for upper respiratory tract infection or nasopharyngitis (Aphonia, Rhinorrhoea, Oropharyngeal pain, Cough, Dysphonia, Nasal congestion and Throat irritation AEs). Additional information on the imbalance in Nasopharyngitis AE and related pathologies is available in *other adverse events of interest* section.

Table 34: Unsolicited AEs (related and unrelated) by MedDRA SOC and PT (Safety Population, HIPRA-HH-14, from Day 0 through Day 28)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
Total number of unsolicited AEs	131	103 (17.11)	60	47 (15.61)	191	150 (16.61)
Infections and infestations	**40**	**39 (6.48)**	**18**	**18 (5.98)**	**58**	**57 (6.31)**
Nasopharyngitis	23	23 (3.82)	5	5 (1.66)	28	28 (3.10)
Upper respiratory tract infection	5	5 (0.83)	1	1 (0.33)	6	6 (0.66)
COVID-19	3	3 (0.50)	1	1 (0.33)	4	4 (0.44)
Influenza	1	1 (0.17)	2	2 (0.66)	3	3 (0.33)
Gastroenteritis	0	0 (0)	3	3 (1.00)	3	3 (0.33)
Lower respiratory tract infection	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Respiratory tract infection	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Bronchitis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Conjunctivitis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Conjunctivitis bacterial	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Laryngitis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Otitis externa	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Pneumonia	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Pyelonephritis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Rhinitis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Sinusitis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Urinary tract infection	1	1 (0.17)	0	0 (0)	1	1 (0.11)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Musculoskeletal and connective tissue disorders	**13**	**13 (2.16)**	**4**	**4 (1.33)**	**17**	**17 (1.88)**
Back pain	3	3 (0.50)	1	1 (0.33)	4	4 (0.44)
Myalgia	3	3 (0.50)	1	1 (0.33)	4	4 (0.44)
Muscle contracture	3	3 (0.50)	0	0 (0)	3	3 (0.33)
Chondromalacia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Haematoma muscle	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Intervertebral disc protrusion	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Limb discomfort	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Osteochondritis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Pain in extremity	0	0 (0)	1	1 (0.33)	1	1 (0.11)
General disorders and administration site conditions	**8**	**7 (1.16)**	**10**	**9 (2.99)**	**18**	**16 (1.77)**
Injection site pain	2	2 (0.33)	2	2 (0.66)	4	4 (0.44)
Asthenia	2	2 (0.33)	1	1 (0.33)	3	3 (0.33)
Pain	1	1 (0.17)	2	2 (0.66)	3	3 (0.33)
Fatigue	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Pyrexia	0	0 (0)	2	2 (0.66)	2	2 (0.66)
Injection site discomfort	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Hunger	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Injection site pruritus	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Secretion discharge	1	1 (0.17)	0	0 (0)	1	1 (0.11)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Gastrointestinal disorders	**9**	**9 (1.50)**	**2**	**2 (0.66)**	**11**	**11 (1.22)**
Odynophagia	5	5 (0.83)	1	1 (0.33)	6	6 (0.66)
Abdominal pain	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Abdominal pain lower	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Gastritis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Tongue ulceration	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Toothache	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Respiratory, thoracic and mediastinal disorders	**13**	**10 (1.66)**	**1**	**1 (0.33)**	**14**	**11 (1.22)**
Aphonia	3	3 (0.50)	0	0 (0)	3	3 (0.33)
Rhinorrhoea	2	2 (0.33)	1	1 (0.33)	3	3 (0.33)
Oropharyngeal pain	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Cough	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Dysphonia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Nasal congestion	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Pulmonary embolism	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Sneezing	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Throat irritation	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Nervous system disorders	**9**	**8 (1.33)**	**2**	**2 (0.66)**	**11**	**10 (1.11)**
Headache	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Migraine	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Sciatica	2	2 (0.33)	0	0 (0)	2	2 (0.22)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Status migrainosus	2	1 (0.17)	0	0 (0)	2	1 (0.11)
Migraine with aura	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Paraesthesia	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Tension headache	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Injury, poisoning and procedural complications	**3**	**3 (0.50)**	**7**	**6 (1.99)**	**10**	**9 (1.00)**
Medication error *	1	1 (0.17)	2	2 (0.66)	3	3 (0.33)
Fall	0	0 (0)	2	2 (0.66)	2	2 (0.22)
Animal bite	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Contusion	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Femur fracture	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Humerus fracture	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Ligament sprain	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Blood and lymphatic system disorders	**6**	**5 (0.83)**	**2**	**2 (0.66)**	**8**	**7 (0.78)**
Anaemia	3	2 (0.33)	1	1 (0.33)	4	3 (0.33)
Lymphopenia	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Normocytic anaemia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Thrombocytosis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Investigations	**6**	**5 (0.83)**	**2**	**2 (0.66)**	**8**	**7 (0.78)**
Alanine aminotransferase increased	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Aspiration joint	1	1 (0.17)	0	0 (0)	1	1 (0.11)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Blood creatinine increased	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Blood glucose increased	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Cardiac murmur	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Gamma-glutamyltransferase increased	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Glycosylated haemoglobin increased	0	0 (0)	1	1 (0.33)	1	1 (0.11)
International normalised ratio increased	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Reproductive system and breast disorders	**5**	**5 (0.83)**	**2**	**1 (0.33)**	**7**	**6 (0.66)**
Dysmenorrhoea	2	2 (0.33)	1	1 (0.33)	3	3 (0.33)
Balanoposthitis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Galactorrhoea	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Intermenstrual bleeding	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Vaginal haemorrhage	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Skin and subcutaneous tissue disorders	**1**	**1 (0.17)**	**3**	**3 (1.00)**	**4**	**4 (0.44)**
Rash	0	0 (0)	2	2 (0.66)	2	2 (0.22)
Dermatitis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Dermatitis atopic	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Vascular disorders	**2**	**2 (0.33)**	**2**	**2 (0.66)**	**4**	**4 (0.44)**
Hypertension	0	0 (0)	2	2 (0.66)	2	2 (0.22)
Essential hypertension	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Hypertensive crisis	1	1 (0.17)	0	0 (0)	1	1 (0.11)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Surgical and medical procedures	**2**	**2 (0.33)**	**0**	**0 (0)**	**2**	**2 (0.22)**
Cataract operation	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Tooth extraction	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Metabolism and nutrition disorders	**4**	**3 (0.5)**	**0**	**0 (0)**	**4**	**3 (0.33)**
Hypercholesterolaemia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Iron deficiency	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Vitamin B12 deficiency	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Vitamin D deficiency	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Psychiatric disorders	**3**	**3 (0.50)**	**0**	**0 (0)**	**3**	**3 (0.33)**
Anxiety	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Insomnia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Ear and labyrinth disorders	**1**	**1 (0.17)**	**1**	**1 (0.33)**	**2**	**2 (0.22)**
Vertigo	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Hepatobiliary disorders	**0**	**0 (0)**	**2**	**2 (0.66)**	**2**	**2 (0.22)**
Biliary colic	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Hypertransaminasaemia	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Renal and urinary disorders	**2**	**2 (0.33)**	**1**	**1 (0.33)**	**3**	**3 (0.33)**
Renal colic	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Renal failure	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Nephrolithiasis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Cardiac disorders	**1**	**1 (0.17)**	**0**	**0 (0)**	**1**	**1 (0.11)**
Palpitations	1	1 (0.17)	0	0 (0)	1	1 (0.11)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Endocrine disorders	**1**	**1 (0.17)**	**0**	**0 (0)**	**1**	**1 (0.11)**
Hyperthyroidism	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Eye disorders	**1**	**1 (0.17)**	**0**	**0 (0)**	**1**	**1 (0.11)**
Vitreous floaters	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Immune system disorders	**1**	**1 (0.17)**	**0**	**0 (0)**	**1**	**1 (0.11)**
Hypersensitivity	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0 (0)**	**1**	**1 (0.33)**	**1**	**1 (0.11)**
Acute myeloid leukaemia	0	0 (0)	1	1 (0.33)	1	1 (0.11)

The frequency of the related unsolicited AEs was slightly higher in the Comirnaty group (3.99%) compared to the Bimervax group (2.66%) (Table 32). Regarding the unsolicited related AEs assessed as severe (Grade 3) in intensity, only 1 AE was reported in 1 (0.17%) subject that received the PHH-1V81 vaccine. No subjects experienced life-threatening (Grade 4) unsolicited related AEs.

Table 35: Unsolicited related AEs by intensity (Safety Population, HIPRA-HH-14, from Day 0 through Day 28)

	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Total number of unsolicited related AEs	18	16 (2.66)	14	12 (3.99)	32	28 (3.10)
Grade 1	15	14 (2.33)	11	10 (3.32)	26	24 (2.66)
Grade 2	2	1 (0.17)	3	3 (1.00)	5	4 (0.44)
Grade 3	1	1 (0.17)	0	0 (0)	1	1 (0.11)

Table 33 describes the unsolicited AE occurred between Day 0 and Day 28 and reported as related to vaccination by the investigator. The most frequently reported related unsolicited AEs were from the General disorders and administration site conditions SOC, with 15 events reported in 13 (1.44%) subjects. Within this SOC, the most common event was Injection site pain (0.33% of subjects in the PHH-1V81 vaccine arm and 0.66% of subjects in the Comirnaty Omicron XBB.1.5 arm). Other frequently reported related unsolicited AEs belonged to Infections and Infestations SOC (overall 4 events reported in 4 [0.44%] subjects) and to the Musculoskeletal and connective tissue disorders SOC (overall 4 events reported in 4 [0.44%] subjects).

Table 36: Unsolicited related AEs by MedDRA SOC and PT (Safety Population, HIPRA-HH-14, from Day 0 through Day 28)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Total number of unsolicited related AEs	18	16 (2.66)	14	12 (3.99)	32	28 (3.10)
General disorders and administration site conditions	**6**	**5 (0.83)**	**9**	**8 (2.66)**	**15**	**13 (1.44)**
Injection site pain	2	2 (0.33)	2	2 (0.66)	4	4 (0.44)
Asthenia	2	2 (0.33)	1	1 (0.33)	3	3 (0.33)
Pain	1	1 (0.17)	2	2 (0.66)	3	3 (0.33)
Injection site discomfort	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Fatigue	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Pyrexia	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Hunger	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Injection site pruritus	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Infections and infestations	**2**	**2 (0.33)**	**2**	**2 (0.66)**	**4**	**4 (0.44)**
Nasopharyngitis	1	1 (0.17)	2	2 (0.66)	3	3 (0.33)
Laryngitis	1	1 (0.17)	0	0 (0)	1	1 (0.11)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Musculoskeletal and connective tissue disorders	**3**	**3 (0.50)**	**1**	**1 (0.33)**	**4**	**4 (0.44)**
Myalgia	2	2 (0.33)	1	1 (0.33)	3	3 (0.33)
Back pain	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Respiratory, thoracic and mediastinal disorders	**3**	**3 (0.50)**	**0**	**0 (0)**	**3**	**3 (0.33)**
Rhinorrhoea	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Aphonia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Nervous system disorders	**2**	2 (0.33)	**1**	1 (0.33)	**3**	**3 (0.33)**
Migraine	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Migraine with aura	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Paraesthesia	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Gastrointestinal disorders	**1**	1 (0.17)	**0**	**0 (0)**	**1**	**1 (0.11)**
Odynophagia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Investigations	**1**	1 (0.17)	**0**	**0 (0)**	**1**	**1 (0.11)**
International normalised ratio increased	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Skin and subcutaneous tissue disorders	**0**	**0 (0)**	**1**	1 (0.33)	**1**	**1 (0.11)**
Rash	0	0 (0)	1	1 (0.33)	1	1 (0.11)

Abbreviations: AE = Adverse Event; COVID-19 = Coronavirus 2019; N = the number of subjects in the population; n = the number of subjects meeting the criterion; (%) = n/N*100; PT = preferred term; SOC = system organ class.
If a subject experienced more than one unsolicited AE, the subject is counted once for each soc and once for each PT.
SOCs are ordered in decreasing frequency of the total number of subjects with unsolicited AEs reported in each SOC and PTs are ordered within a SOC in decreasing frequency of the total number of subjects with each unsolicited AE.

Note that tabulated presentation and discussion of unsolicited AEs was provided until Day 28 of Study HH-14. The tabulated presentation of AEs through the end of the study will be provided in the final Clinical Study Report of Study HIPRA-HH-14.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

Up to 6 months cut-off, a total of 14 SAEs were reported in 11 (1.22%) subjects: 8 SAEs in 7 (1.16%) subjects in the PHH-1V81 vaccine arm, and 6 SAEs in 4 (1.33%) subjects in the Comirnaty XBB.1.5 vaccine arm). None of them were assessed as related to study treatment by the Investigator or Sponsor neither with PHH-1V81 vaccine nor with Comirnaty Omicron XBB.1.5 vaccine.

The most frequently reported System Organ Class were Neoplasm benign, malignant and unspecified SOC with 3 SAEs reported in 3 (0.33%) subjects, as well as from the Nervous system disorder SOC with also 3 SAEs reported in 3 (0.33%) subjects.

Table 37: Serious Adverse Events classified by SOC and PT (Safety Population, HIPRA-HH-14, 6-month data)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Total number of SAEs	8	7 (1.16)	6	4 (1.33)	14	11 (1.22)
Cardiac disorders	**0**	**0 (0)**	**1**	**1 (0.33)**	**1**	**1 (0.11)**
Myocardial infarction	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Infections and infestations	**1**	**1 (0.17)**	**0**	**0 (0)**	**1**	**1 (0.11)**
Pneumonia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Injury, poisoning and procedural complications	**0**	**0 (0)**	**1**	**1 (0.33)**	**1**	**1 (0.11)**
Fracture	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**2 (0.33)**	**1**	**1 (0.33)**	**3**	**3 (0.33)**
Acute myeloid leukaemia	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Lung carcinoma cell type unspecified stage iv	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Tracheal neoplasm	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Nervous system disorders	**2**	**2 (0.33)**	**1**	**1 (0.33)**	**3**	**3 (0.33)**
Migraine with aura	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Status migrainosus	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Syncope	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Respiratory, thoracic and mediastinal disorders	**2**	**2 (0.33)**	**0**	**0 (0)**	**2**	**2 (0.22)**
Pulmonary embolism	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Renal and urinary disorders	**0**	**0 (0)**	**1**	**1 (0.33)**	**1**	**1 (0.11)**
Nephrolithiasis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Surgical and medical procedures	**0**	**0 (0)**	**2**	**2 (0.66)**	**2**	**2 (0.22)**
Vascular disorders	**1**	**1 (0.17)**	**0**	**0 (0)**	**1**	**1 (0.11)**
Hypertensive crisis	1	1 (0.17)	0	0 (0)	1	1 (0.11)

Abbreviations: N = the number of subjects in the population; n = the number of subjects meeting the criterion; (%) = n/N*100. PT = preferred term; SAE = Serious Adverse Event; SOC = System Organ Class.

As for numerical imbalances in the SAEs by treatment groups, two pulmonary embolism events were observed in the PHH-1V81 group at days Day 17 and Day 107 respectively, and none in Comirnaty group.

- A >80 YOA participant with an ongoing hypertrophic cardiomyopathy (HCM) experienced Lung carcinoma cell type unspecified stage IV and pulmonary embolism on day 102 after vaccination with PHH-1V81. The participant experienced two events of pulmonary embolism, at day 102

and 108 after vaccination. The subject did not receive anticoagulant therapy as element of management of the HCM condition. The underlying condition (HCM) of the patient could explain the event of pulmonary embolism. The investigator considered the event as not related to vaccination.

- A >70 YOA participant experienced a bilaterial pulmonary thromboembolism 17 days after vaccination with PHH-181. The medical history included hypercholesterolemia and hypertension as underlying conditions. At the time of reporting the outcome was recovering. The investigator considered the event as unrelated to vaccination.

In addition, two of the three malignancy conditions (Lung carcinoma cell type unspecified stage IV at Day 102 and Tracheal neoplasm) were observed in the PHH-1V81 group.

- A >80 YOA participant with an ongoing hypertrophic cardiomyopathy (HCM) experienced Lung carcinoma cell type unspecified stage IV and pulmonary embolism on day 102 after vaccination with PHH-1V81.
- A >50 YOA participant with no relevant past medical history experienced a tracheal neoplasm at day 95 after vaccination with PHH-1V81.
- A >80 YOA participant in the Comirnaty XBB.1.5 group was diagnosed with Acute myeloid leukaemia on the day of vaccination following the screening test for the study. The participant also experienced fracture, 3 days after vaccination and a fatal myocardial infarction on day 98 post vaccination.
- One case of hypertensive crisis was reported in the PHH-1V81 group. A >80 years-old participant experienced Hypertensive crisis 14 days after vaccination. The participant had arterial Hypertension as an underlying condition and with an abnormal Systolic Blood Pressure at screening.

Deaths

Up to 6 months cut-off, no SAE with fatal outcome was reported in the PHH-1V81 vaccine group. There was one SAE with fatal outcome (myocardial infarction 98 days after vaccination in a >80 years of age participant) in the Comirnaty Omicron XBB.1.5 vaccine group (refer also to SAE section).

Adverse Events of Special Interest (AESIs)

AESIs include potential immune-mediated medical conditions that were listed in the study protocol.

No Adverse Events of Special Interest (AESIs) have been reported in any of the two vaccine arms up to 6 months post-vaccination.

Medically Attended Adverse events (MAAES)

A summary of the Medically Attended Adverse Events classified by relationship and intensity is provided in Table 35.Table 39

Overall, a total of 266 MAAEs in 163 (18.05%) subjects were reported. Most of them were assessed by the investigator as unrelated to the study treatment, specifically 265 events in 162 (17.94%) subjects. Only 1 MAAE in 1 (0.17%) subject was assessed as related in the PHH-1V81 vaccine arm. It consisted of a Grade 3 migraine MAAE (PT: Migraine; SOC: Nervous system disorders) experienced by a subject with medical history of migraine. The subject had a basal Grade 1 migraine at the time of vaccination and experienced a worsening of migraine in the following days requiring medical assistance.

In the Comirnaty Omicron XBB.1.5 vaccine arm, there were 98 unrelated MAAEs in 56 (18.60%) subjects. In the PHH-1V81 vaccine arm, there were 167 unrelated MAAEs in 106 (17.61%) subjects.

Table 38: Summary of Medically Attended Adverse Events classified by relationship and intensity (Safety Population, HIPRA-HH-14, 6-month data)

	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Total number of MAAEs	168	107 (17.77)	98	56 (18.60)	266	163 (18.05)
MAAE relationship to study treatment						
Related	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Unrelated	167	106 (17.61)	98	56 (18.60)	265	162 (17.94)
MAAE intensity						
Grade 1	133	81 (13.46)	74	41 (13.62)	207	122 (13.51)
Grade 2	31	28 (4.65)	24	16 (5.32)	55	44 (4.87)
Grade 3	3	3 (0.5)	0	0 (0)	3	3 (0.33)
Grade 4	1	1 (0.17)	0	0 (0)	1	1 (0.11)

Abbreviations: MAAE = Medically Attended Adverse Event; N = the number of subjects in the population; n = the number of subjects meeting the criterion; (%) = n/N*100.

The most frequently reported System Organ Class were Infections and infestations with 90 MAAEs reported in 71 (7.86%) subjects. Out of these, 56 MAAEs were reported in 43 (7.14%) subjects administered with the PHH-1V81 vaccine and 34 MAAEs were reported in 28 (9.30%) subjects administered with the Comirnaty Omicron XBB.1.5 vaccine. The most common event within this SOC was Nasopharyngitis (1.33 % of subjects in both vaccine arms). Other frequently reported MAAEs belonged to Musculoskeletal and connective tissue disorders SOC (26 events reported in 25 [2.77%] subjects).

Some numerical imbalances in the frequencies of MAAEs in the Renal and urinary disorders SOC was observed with higher overall incidence in the PHH-1V81 group. However, this imbalance was led by the nephrolithiasis and renal colic AEs, and relationship of both to the administration of PHH-1V81 is considered to be unlikely.

A case of papillary thyroid cancer is mentioned in the table of MAAEs but it will be classified as a SAE in the final study report.

Table 39: Medically Attended Adverse Events classified by SOC and PT (Safety Population, HIPRA-HH-14, 6-month data)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Total number of MAAEs	168	107 (17.77)	98	56 (18.60)	266	163 (18.05)
Infections and infestations	**56**	**43 (7.14)**	**34**	**28 (9.30)**	**90**	**71 (7.86)**
Nasopharyngitis	8	8 (1.33)	4	4 (1.33)	12	12 (1.33)
Upper respiratory tract infection	5	5 (0.83)	2	2 (0.66)	7	7 (0.78)
Bronchitis	5	4 (0.66)	2	2 (0.66)	7	6 (0.66)
Gastroenteritis	2	2 (0.33)	4	3 (1.00)	6	5 (0.55)
Tonsillitis	3	3 (0.5)	2	2 (0.66)	5	5 (0.55)
Urinary tract infection	4	4 (0.66)	2	1 (0.33)	6	5 (0.55)
Influenza	1	1 (0.17)	3	3 (1.00)	4	4 (0.44)
Pneumonia	2	2 (0.33)	2	2 (0.66)	4	4 (0.44)
Viral infection	4	4 (0.66)	0	0 (0)	4	4 (0.44)
Conjunctivitis	2	2 (0.33)	1	1 (0.33)	3	3 (0.33)
Covid-19	2	2 (0.33)	1	1 (0.33)	3	3 (0.33)
Cystitis	1	1 (0.17)	2	2 (0.66)	3	3 (0.33)
Gastroenteritis viral	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Otitis externa	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Tooth abscess	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Acarodermatitis	2	1 (0.17)	0	0 (0)	2	1 (0.11)
Bacterial prostatitis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Bacterial vaginosis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Candida infection	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Ear infection	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Fungal foot infection	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Genital herpes zoster	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Helicobacter infection	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Herpes simplex	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Herpes zoster	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Hordeolum	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Klebsiella infection	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Lower respiratory tract infection	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Pharyngitis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Pyelonephritis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Respiratory tract infection	2	1 (0.17)	0	0 (0)	2	1 (0.11)
Tooth infection	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Vulvitis	0	0 (0)	1	1 (0.33)	1	1 (0.11)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Musculoskeletal and connective tissue disorders	**15**	**15 (2.49)**	**11**	**10 (3.32)**	**26**	**25 (2.77)**
Arthralgia	4	4 (0.66)	6	6 (1.99)	10	10 (1.11)
Back pain	2	2 (0.33)	3	3 (1.00)	5	5 (0.55)
Neck pain	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Enthesopathy	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Haematoma muscle	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Intervertebral disc protrusion	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Muscle contracture	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Muscle spasms	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Musculoskeletal chest pain	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Polyarthritis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Rotator cuff syndrome	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Spinal stenosis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Injury, poisoning and procedural complications	**10**	**10 (1.66)**	**6**	**5 (1.66)**	**16**	**15 (1.66)**
Contusion	3	3 (0.50)	1	1 (0.33)	4	4 (0.44)
Fall	1	1 (0.17)	2	2 (0.66)	3	3 (0.33)
Radius fracture	3	3 (0.50)	0	0 (0)	3	3 (0.33)
Epicondylitis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Animal bite	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Humerus fracture	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Ligament sprain	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Tendon rupture	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Toxicity to various agents	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Gastrointestinal disorders	**10**	**8 (1.33)**	**6**	**5 (1.66)**	**16**	**13 (1.44)**
Abdominal pain	4	3 (0.50)	0	0 (0)	4	3 (0.33)
Dyspepsia	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Odynophagia	0	0 (0)	2	2 (0.66)	2	2 (0.22)
Abdominal pain lower	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Abdominal pain upper	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Colitis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Haemorrhoids	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Hiatus hernia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Mouth haemorrhage	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Nausea/vomiting	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Oesophagitis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Respiratory, thoracic and mediastinal disorders	**8**	**8 (1.33)**	**4**	**3 (1.00)**	**12**	**11 (1.22)**
Nasal congestion	3	3 (0.5)	0	0 (0)	3	3 (0.33)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Catarrh	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Asthma	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Chronic obstructive pulmonary disease	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Cough	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Epistaxis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Pulmonary embolism	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Rhinorrhoea	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Sleep apnoea syndrome	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Psychiatric disorders	**7**	**7 (1.16)**	**3**	**3 (1)**	**10**	**10 (1.11)**
Anxiety	6	6 (1.00)	2	2 (0.66)	8	8 (0.89)
Anxiety disorder	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Persistent depressive disorder	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Skin and subcutaneous tissue disorders	**5**	**4 (0.66)**	**5**	**5 (1.66)**	**10**	**9 (1.00)**
Acne	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Alopecia	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Decubitus ulcer	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Dermatitis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Neurodermatitis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Rash pruritic	2	1 (0.17)	0	0 (0)	2	1 (0.11)
Seborrheic keratosis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Skin papilloma	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Urticaria	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Surgical and medical procedures	**9**	**9 (1.50)**	**0**	**0 (0)**	**9**	**9 (1.00)**
Wisdom teeth removal	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Bunion operation	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Cataract operation	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Dental implantation	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Surgery	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Tendon operation	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Tooth extraction	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Vasodilation	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Renal and urinary disorders	**7**	**7 (1.16)**	**2**	**2 (0.66)**	**9**	**9 (1.00)**
Nephrolithiasis	3	3 (0.50)	0	0 (0)	3	3 (0.33)
Renal colic	3	3 (0.50)	0	0 (0)	3	3 (0.33)
Nephropathy	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Renal failure	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Ureterolithiasis	0	0 (0)	1	1 (0.33)	1	1 (0.11)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Blood and lymphatic system disorders	**3**	**3 (0.50)**	**4**	**4 (1.33)**	**7**	**7 (0.78)**
Anaemia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Iron deficiency anaemia	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Lymphadenopathy	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Lymphopenia	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Normocytic anaemia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Thalassaemia beta	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Thrombocytosis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Reproductive system and breast disorders	**5**	**5 (0.83)**	**2**	**2 (0.66)**	**7**	**7 (0.78)**
Balanoposthitis	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Breast cyst	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Erectile dysfunction	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Galactorrhoea	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Intermenstrual bleeding	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Testicular pain	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Uterine polyp	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Nervous system disorders	**5**	**5 (0.83)**	**2**	**2 (0.66)**	**7**	**7 (0.78)**
Migraine	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Cerebral small vessel disease	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Cognitive disorder	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Essential tremor	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Headache	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Sciatica	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Investigations	**6**	**5 (0.83)**	**2**	**2 (0.66)**	**8**	**7 (0.78)**
Blood creatinine increased	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Antinuclear antibody positive	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Aortic bruit	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Aspiration joint	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Blood glucose increased	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Blood thyroid stimulating hormone decreased	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Laparoscopy	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Metabolism and nutrition disorders	**5**	**4 (0.66)**	**3**	**2 (0.66)**	**8**	**6 (0.66)**
Iron deficiency	2	2 (0.33)	1	1 (0.33)	3	3 (0.33)
Vitamin B12 deficiency	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Vitamin D deficiency	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Metabolic syndrome	0	0 (0)	1	1 (0.33)	1	1 (0.11)

SOC PT	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N=301)		Overall (N=903)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Ear and labyrinth disorders	**2**	**2 (0.33)**	**3**	**3 (1)**	**5**	**5 (0.55)**
Vertigo	2	2 (0.33)	1	1 (0.33)	3	3 (0.33)
Ear pain	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Tinnitus	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**2 (0.33)**	**3**	**3 (1)**	**5**	**5 (0.55)**
Colorectal adenoma	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Metastatic neoplasm	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Papillary thyroid cancer	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Seborrhoeic keratosis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Skin papilloma	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Vascular disorders	**2**	**2 (0.33)**	**5**	**3 (1)**	**7**	**5 (0.55)**
Hypertension	2	2 (0.33)	4	3 (1.00)	6	5 (0.55)
Hypertensive crisis	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Eye disorders	**3**	**3 (0.50)**	**0**	**0 (0)**	**3**	**3 (0.33)**
Cataract	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Conjunctivitis allergic	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Vitreous floaters	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Cardiac disorders	**3**	**3 (0.50)**	**0**	**0 (0)**	**3**	**3 (0.33)**
Palpitations	2	2 (0.33)	0	0 (0)	2	2 (0.22)
Sinus tachycardia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Hepatobiliary disorders	**1**	**1 (0.17)**	**2**	**2 (0.66)**	**3**	**3 (0.33)**
Drug-induced liver injury	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Biliary colic	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Endocrine disorders	**2**	**2 (0.33)**	**0**	**0 (0)**	**2**	**2 (0.22)**
Goitre	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Hyperthyroidism	1	1 (0.17)	0	0 (0)	1	1 (0.11)
General disorders and administration site conditions	**1**	**1 (0.17)**	**1**	**1 (0.33)**	**2**	**2 (0.22)**
Pyrexia	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Ulcer	0	0 (0)	1	1 (0.33)	1	1 (0.11)
Congenital, familial and genetic disorders	**1**	**1 (0.17)**	**0**	**0 (0)**	**1**	**1 (0.11)**
Phimosis	1	1 (0.17)	0	0 (0)	1	1 (0.11)

Abbreviations: COVID-19 = Coronavirus 2019; MAAE = Medically Attended Adverse Events; N = the number of subjects in the population; PT = preferred term; SOC = system organ class.
If a subject experienced more than one MAAE, the subject is counted once for each SOC and once for each PT.
SOCs are ordered in decreasing frequency of the total number of subjects with MAAEs reported in each SOC and PTs are ordered within a SOC in decreasing frequency of the total number of subjects with each MAAE.

Other significant events

Hypertension and thromboembolic events

Considering that hypertension and thromboembolic events are known ADR for other COVID-19 vaccines and, given the numerical imbalance on SAEs for pulmonary embolism, the MAH was requested to evaluate all hypertension and thromboembolic events reported in in study HH-14.

Up to 6 months cut-off, a total of 16 events of hypertension and thromboembolic events were reported in 12 (1.33%) subjects: 9 AEs in 7 (1.16%) subjects in the PHH-1V81 vaccine arm, and 7 AEs in 5 (1.66%) subjects in the Comirnaty XBB.1.5 vaccine arm). None of them were assessed as related to study treatment by the Investigator or Sponsor neither with PHH-1V81 vaccine nor with Comirnaty Omicron XBB.1.5 vaccine.

Table 40: Hypertension and Thromboembolic AEs observed in HIPRA-HH-14 study (Safety Population, HIPRA-HH-14, 6-month data)

SOC PT	**PHH-1V81 (N=602)**		**Comirnaty Omicron XBB.1.5 (N=301)**		**Overall (N=903)**	
	Events	**Subjects (%)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
Total number of Hypertension and Thromboembolic events	9	7 (1.16)	7	5 (1.66)	16	12 (1.33)
Blood and lymphatic system disorders	**1**	**1 (0.17)**	**1**	**1 (0.33)**	**2**	**2 (0.22)**
Thrombocytosis	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)
Respiratory, thoracic and mediastinal disorders	**3**	**2 (0.33)**	**0**	**0 (0)**	**3**	**2 (0.22)**
Pulmonary embolism	3	2 (0.33)	0	0 (0)	3	2 (0.22)
Vascular disorders	**5**	**4 (0.66)**	**6**	**4 (1.33)**	**11**	**8 (0.89)**
Essential hypertension	1	1 (0.17)	0	0 (0)	1	1 (0.11)
Hypertension	3	2 (0.33)	5	4 (1.33)	8	6 (0.66)
Hypertensive crisis	1	1 (0.17)	1	1 (0.33)	2	2 (0.22)

Abbreviations: PT = preferred term; SOC = system organ class.

Thromboembolic events

Thromboembolic AEs included two Thrombocytosis AEs one for each treatment groups, and three Pulmonary embolism SAEs reported in two subjects in the PHH-1V81 group.

Pulmonary embolism SAEs are described in the SAE section.

The event of thrombocytosis was reported as a MAAE in a >20 YOA participant who also reported iron deficiency 91 days after administration of PHH-1V81. The event resolved and was considered not related to vaccination.

Vascular disorders (hypertension)

Hypertension AES included 5 events in 4 subjects in the PHH-1V81 group (0.66%) and 6 events in the Comirnaty Omicron XBB.1.5 group (1.33%). No numerical imbalance is observed.

Nasopharyngitis

As referred in the unsolicited adverse events section, a numerical imbalance of the preferred term of nasopharyngitis has been reported in 3.82% of subjects in PHH-1V81 vs 1.66% in Comirnaty Omicron XBB.1.5 among unsolicited AEs. Furthermore, other preferred terms related to upper respiratory tract infections (e.g. upper respiratory tract infections, sinusitis, rhinitis…) have also been reported as unsolicited AE and with a higher frequency in the PHH-1V81 group compared to the comparator.

An additional analysis combining all PTs related to upper respiratory tract infections as proposed by the MAH is shown in *Table 37*.

Table 41: Preferred Terms related to respiratory tract infections AEs observed in HIPRA-HH-14 study (Safety Population, HIPRA-HH-14, 6-month data

SOC PT	Treatment				
	PHH-1V81 (N=602)		Comirnaty Omicron XBB.1.5 (N= 301)		Total (%) (N=903)
	Related (%)	Unrelated (%)	Related (%)	Unrelated (%)	
Infections and infestations	**2 (0.33)**	**35 (5.81)**	**2 (0.66)**	**9 (2.99)**	**49 (5.43)**
Nasopharyngitis	1 (0.17)	22 (3.65)	2 (0.66)	3 (1)	28 (3.10)
Respiratory tract infection	0 (0)	2 (0.33)	0 (0)	0 (0)	2 (0.22)
Rhinitis	0 (0)	1 (0.17)	0 (0)	0 (0)	1 (0.11)
Sinusitis	0 (0)	1 (0.17)	0 (0)	0 (0)	1 (0.11)
Upper respiratory tract infection	0 (0)	5 (0.83)	0 (0)	1 (0.33)	6 (0.66)
Bronchitis	0 (0)	0 (0)	0 (0)	1 (0.33)	1 (0.11)
COVID-19	0 (0)	3 (0.50)	0 (0)	1 (0.33)	4 (0.44)
Influenza	0 (0)	1 (0.17)	0 (0)	2 (0.66)	3 (0.33)
Laryngitis	1 (0.17)	0 (0)	0 (0)	0 (0)	1 (0.11)
Lower respiratory tract infection	0 (0)	1 (0.17)	0 (0)	1 (0.33)	2 (0.22)

Up to 6 months cut-off, there are 49 unsolicited adverse events (product-related and non-related) (5.43%) related to respiratory infections. Of these, 28 (3.10%) were considered related to PHH-1V81 and 2 (0.66%) to the Comirnaty Omicron XBB.1.5 arm. Out of the 49 events, 37 AEs were in the PHH-1V81 vaccine arm, and 11 AEs in the Comirnaty XBB.1.5 vaccine arm. Two AEs in each group were assessed as related to study treatment by the Investigator. Majority of the adverse events occurred with an onset from 10 days post-vaccination onwards, no temporal association to vaccination can be established.

Most events (related and non-related) (19 [67.86%]) were mild (grade 1) in intensity, while 9 (32.14%) were moderate (grade 2). 2 product related events were reported in the Comirnaty Omicron XBB.1.1.5 arm, being one of them of Grade 1 and one of them Grade 2 in intensity. One product related event of Grade 1 in intensity was reported in the PHH-1V81 arm.

2.6.8.4. Laboratory findings

Haematology and biochemistry parameters were assessed at screening, at Day 14, at Day 91 and at Day 182.

Abnormal conditions detected at screening were recorded as medical history of subjects, whereas abnormal laboratory parameters that were considered clinically significant in the medical and scientific judgement of the Principal Investigator at the other time points were recorded as AEs.

Considering the whole safety population (N = 903) and the 6 months post-vaccination data, no noteworthy changes or trends occurred in haematology or biochemistry laboratory evaluations among the subjects. No Grade 3 and 4 changes from baseline in safety laboratory parameters were reported.

2.6.8.5. Safety in special populations

The available safety data of PHH-1V81 in special populations, including hepatic impairment, renal impairment, pregnant or lactating women and immunocompromised populations is provided in Table 38.

Table 42: Number and percentage of subjects with AE by special population (Safety population, HIRPA-HH-14, 6-month data)

	Active				**Comparator**			
MedDRA Terms	**Hepatically impaired n (%) N=0**	**Renally impaired n (%) N=2**	**Pregnant n (%) N=3**	**Other n (%) N=7**	**Hepatically impaired n (%) N=0**	**Renally impaired n (%) N=1**	**Pregnant n (%) N=0**	**Other n (%) N=8**
Total AEs	0 (0)	1 (50.00)	3 (100.00)	6 (85.71)	0 (0)	1 (100.00)	0 (0)	7 (87.50%)
Serious AEs – Total	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Safety data from elderly subjects ≥65 years is in Table 39 below.

Table 43: Number and percentage of participants with AEs by age group (related and non-related AEs; safety population, HIPRA-HH-14, 6-month data)

	PHH-1V81				Comirnaty Omicron XBB.1.5			
MedDRA Terms	**Age <65 n (%) N=547**	**Age 65-74 n (%) N=18**	**Age 75-84 n (%) N=33**	**Age 85+ n (%) N=4**	**Age <65 n (%) N=269**	**Age 65-74 n (%) N=15**	**Age 75-84 n (%) N=15**	**Age 85+ n (%) N=2**
Total subjects with AEs	449 (82.08)	13 (72.22)	24 (72.73)	2 (50.00)	239 (88.85)	11 (73.33)	12 (80.00)	2 (100.00)
Serious AEs – Total	4 (0.73)	0 (0)	2 (6.06)	1 (25.00)	3 (1.12)	0 (0)	0 (0)	1 (50.00)
- Fatal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50.00)
- Hospitalization/prolong existing hospitalization	4 (0.73)	0 (0)	2 (6.06)	1 (25.00)	3 (1.12)	0 (0)	0 (0)	2 (100.00)
- Life-threatening	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50.00)
- Disability/ incapacity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
- Other (medically significant)	2 (0.37)	0 (0)	1 (3.03)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50.00)
AE leading to drop-out	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	9 (1.64)	1 (5.56)	0 (0)	0 (0)	2 (0.74)	0 (0)	0 (0)	1 (50.00)
Nervous system disorders	145 (26.51)	1 (5.56)	3 (9.09)	0 (0)	73 (27.14)	2 (13.33)	0 (0)	0 (0)
Accidents and injuries	10 (1.83)	1 (5.56)	2 (6.06)	0 (0)	6 (2.23)	1 (6.67)	1 (6.67)	1 (50.00)
Cardiac disorders	2 (0.37)	1 (5.56)	1 (3.03)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50.00)
Vascular disorders	3 (0.55)	0 (0)	0 (0)	1 (25.00)	3 (1.12)	1 (6.67)	0 (0)	0 (0)
Cerebrovascular disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations	89 (16.27)	4 (22.22)	6 (18.18)	0 (0)	50 (18.59)	3 (20.00)	6 (40.00)	1 (50.00)
Anticholinergic syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Quality of life decreased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	5 (0.91)	1 (5.56)	0 (0)	0 (0)	1 (0.37)	1 (6.67)	1 (6.67)	1 (50.00)
Other AEs appearing more frequently in older patients*								
	Active				Comparator			
MedDRA Terms	**Age <65 n (%) N=547**	**Age 65-74 n (%) N=18**	**Age 75-84 n (%) N=33**	**Age 85+ n (%) N=4**	**Age <65 n (%) N=269**	**Age 65-74 n (%) N=15**	**Age 75-84 n (%) N=15**	**Age 85+ n (%) N=2**
General disorders and administration site conditions	422 (77.15)	7 (38.89)	5 (15.15)	1 (25.00)	223 (82.90)	8 (53.33)	7 (46.67)	0 (0)
Musculoskeletal and connective tissue disorders	103 (18.83)	1 (5.56)	4 (12.12)	0 (0)	61 (22.68)	2 (13.33)	1 (6.67)	0 (0)

Abbreviations: N = the number of subjects in the population; n = the number of subjects with AEs; (%) = Subjects/N*100
* Of note, other frequently reported AEs included solicited local and systemic events, being most of them assessed as mild and moderate in intensity.

Table 44: Number and percentage of participants with related AEs by age group (Safety population, HIPRA-HH-14, 6-month data)

	Active				Comparator			
MedDRA Terms	**Age <65 n (%) N=547**	**Age 65-74 n (%) N=18**	**Age 75-84 n (%) N=33**	**Age 85+ n (%) N=4**	**Age <65 n (%) N=269**	**Age 65-74 n (%) N=15**	**Age 75-84 n (%) N=15**	**Age 85+ n (%) N=2**
Total AEs	428 (78.24)	8 (44.44)	7 (21.21)	1 (25.00)	227 (84.39)	8 (53.33)	7 (46.67)	0 (0)
Serious AEs – Total	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fatal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hospitalization/prolong existing hospitalization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Life-threatening	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Disability/incapacity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other (medically significant)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AE leading to drop-out	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	138 (25.23)	0 (0)	2 (6.06)	0 (0)	72 (26.77)	2 (13.33)	0 (0)	0 (0)
Accidents and injuries	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cerebrovascular disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations	2 (0.37)	0 (0)	0 (0)	0 (0)	2 (0.74)	0 (0)	0 (0)	0 (0)
Anticholinergic syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Quality of life decreased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other related AEs appearing more frequently in older patients*								

	Active				Comparator			
MedDRA Terms	**Age <65 n (%) N=547**	**Age 65-74 n (%) N=18**	**Age 75-84 n (%) N=33**	**Age 85+ n (%) N=4**	**Age <65 n (%) N=269**	**Age 65-74 n (%) N=15**	**Age 75-84 n (%) N=15**	**Age 85+ n (%) N=2**
General disorders and administration site conditions	420 (76.78)	7 (38.89)	5 (15.15)	1 (25.00)	222 (82.53)	8 (53.33)	7 (46.67)	0 (0)
Musculoskeletal and connective tissue disorders	85 (15.54)	0 (0)	0 (0)	0 (0)	51 (18.96)	2 (13.33)	0 (0)	0 (0)

Abbreviations: N = the number of subjects in the population; n = the number of subjects with AEs; (%) = Subjects/N*100
Related AEs include those assessed as related by the Principal Investigator as well as those AEs with missing causality assessment, which are 27 AEs that occurred in 12 subjects. The missing AE causality assessment will be requested to Investigators.
* Of note, other frequently reported AEs included solicited local and systemic events, being most of them assessed as mild and moderate in intensity.

2.6.8.6. Immunological events

Refer to AESI section.

2.6.8.7. Safety related to drug-drug interactions and other interactions

One study of co-administration of the parent Bimervax vaccine with seasonal surface antigen inactivated adjuvanted influenza vaccine is ongoing. No other drug-drug interaction studies were conducted, which is acceptable for a vaccine.

2.6.8.8. Discontinuation due to adverse events

Up to 6 months cut-off data one fatal SAE of Myocardial infarction occurred in the Comirnaty XBB.1.5 group. No other discontinuation due to adverse events was reported in any of the vaccine groups.

2.6.8.9. Post marketing experience

Limited post-marketing data of Bimervax parent vaccine are available. No safety concern has been identified in the available data.

2.6.9. Discussion on clinical safety

Safety Population was defined as all randomised participants who received the study vaccine. The safety assessment of this procedure is based on available safety data up to 6 months-post last vaccination (cut-off date: 13th June 2024)

A total of 903 subjects have received at least one dose of PHH-1V81, from which 602 received the PHH-1V81 vaccine and 301 received Comirnaty Omicron XBB.1.5.

Participants were provided with a participant paper diary on Day 0 to record solicited local and systemic reactions after vaccination through Day 7. Unsolicited adverse events are recorded through Day 28 after vaccination. AEs, SAEs, AESIs and MAAEs, will be recorded through the end of study. After Day 28 post-vaccination, only related MAAEs will be recorded. Participants were followed for approximately 6 months after the study treatment. The methods for collecting safety data are appropriate and similar to those conducted in study HIPRA-HH-2.

Solicited systemic events

The percentage of subjects who had at least one systemic solicited event was 36.54% for PHH-1V81 and 46.18% for Comirnaty Omicron XBB.1.5.

The most frequently reported solicited systemic AE was headache, with a total of 23.81% subjects, 23.42% in the PHH-1V81 vaccine arm and 24.58% in the Comirnaty Omicron XBB.1.5 vaccine arm.

Another frequently reported solicited systemic event was fatigue. Overall, 21.59% of subjects reported fatigue, 19.60% in the PHH-1V81 vaccine arm and 25.58% in the Comirnaty Omicron XBB.1.5 vaccine arm.

Myalgia was reported in 14.95% of subjects, 13.62% in the PHH-1V81 vaccine arm and 17.61% in the Comirnaty Omicron XBB.1.5 vaccine arm, followed by malaise and discomfort that was reported in 12.79% of subjects in the PHH-1V81 vaccine arm and 21.92% in the Comirnaty Omicron XBB.1.5 vaccine arm.

Among the gastrointestinal disorders, nausea and/or vomiting were reported more frequently in the Comirnaty Omicron XBB.1.5 vaccine arm (5.65%) compared to PHH-1V81 (3.49%), and diarrhoea was reported very similarly in both vaccine arms with 4.49% and 4.32% in the PHH-1V81 and Comirnaty Omicron XBB.1.5 vaccine arms, respectively.

Of note, fever was scarcely reported in both vaccine arms.

Most remarkable difference in frequencies has been found for Malaise/Discomfort PT with frequency of 12.8% in the PHH-1V81 groups and 21.9% in the Comirnaty XBB.1.5 group. Frequencies of another PTs were numerically higher for the Comirnaty XBB.1.5 group.

The time course of the solicited AEs is of high importance in the tolerability of any vaccine. Majority of solicited systemic AEs were reported on Day 0 and Day 1 post-vaccination.

During days 0-3, AE frequencies of the different solicited AEs were generally higher in the Comirnaty group. However, this difference seems to somewhat disappear with time. In case of fatigue and malaise PTs, these solicited AEs seem to be more maintained in the PHH-1V81 group compared to Comirnaty group. However, since the number of overall participants reporting AE from day 5 is low, any conclusion on the time course of solicited AEs as well as the difference in it between the PHH-1V81 and Comirnaty XBB.1.5 should be handled with caution.

Solicited local AE

The percentage of subjects who had at least one systemic local event was 69.10 % for PHH-1V81 and 76.08% for Comirnaty Omicron XBB.1.5.

The most frequently reported event was injection site pain/tenderness/discomfort, with a total of 70.21% of subjects, 68.11% in the PHH-1V81 vaccine arm and 74.42% in the Comirnaty Omicron XBB.1.5 vaccine arm.

Another frequently reported solicited local event was injection site induration or swelling. Overall, 18.16% of subjects reported injection site induration or swelling, 15.78% in the PHH-1V81 vaccine arm and 22.92% in the Comirnaty Omicron XBB.1.5 vaccine arm.

Injection site erythema or redness was reported in 12.74% of subjects, 11.13% in the PHH-1V81 vaccine arm and 15.95% in the Comirnaty Omicron XBB.1.5 vaccine arm.

All solicited local AEs occurred with higher frequencies in the Comirnaty XBB.1.5 group.

During the first 12 hours post-vaccination, the overall frequency of solicited local AEs as well as the frequencies of the different PTs were higher in the PHH-1V81 group than in the Comirnaty XBB.1.5 group. During the first day post-vaccination, when the highest frequencies of solicited local AEs were observed this relationship turned to the opposite, as injection site pain/tenderness/discomfort was reported in 58.47% of subjects in the PHH-1V81 vaccine arm and 69.10% in the Comirnaty Omicron XBB.1.5 vaccine arm on Day 1 post-vaccination, decreasing to 26.25% and 40.20% respectively on Day 2. At Day 7 post-vaccination, 1.66% of subjects reported injection site pain in the PHH-1V81 vaccine arm and 1.33% in the Comirnaty Omicron XBB.1.5 vaccine arm. Similar weak trend of more prolonged AE occurrence in the PHH-1V81 group can be observed for the solicited local AEs, as it was mentioned for the solicited systemic AEs, however, this finding should be handled with caution due to the low patient number who experienced any solicited local AE between Day 5 and Day 7 post vaccination.

Overall, solicited systemic and local adverse event occur most frequently during the first day's post-vaccination and are short in duration.

Unsolicited adverse events

The overall frequency of unsolicited AEs reported within 28 days post vaccination was slightly higher in PHH-1V81 group (17.11%) than in the Comirnaty XBB.1.5 group (15.61%). Unsolicited AE number and frequency was led by the Infections and infestations SOC and Nasopharyngitis PT for PHH-1V81.

There was an imbalance in frequencies between the two treatment groups for nasopharyngitis AE and also for the cumulated frequencies of similar PTs (URTI, respiratory tract infections, Laryngitis ad Rhinitis) in the Infections and infestations SOC. Note that some imbalance between treatment groups can be seen in the Respiratory, thoracic and mediastinal disorders SOC as well, and the majority of the AEs in this SOC are indicative for upper respiratory tract infection or nasopharyngitis (Aphonia, Rhinorrhoea, Oropharyngeal pain, Cough, Dysphonia, Nasal congestion and Throat irritation AEs). An additional analysis considering a group of relevant PTs associated to upper respiratory tract infections showed that most of these events occurred from 10 days post-vaccination onwards. Therefore, temporal association is weak, which is consistent to the fact that most of them are considered unrelated to the study vaccine. Additionally, most events (related and non-related) (19 [67.86%]) were mild (grade 1) in intensity, while 9 (32.14%) were moderate (grade 2). 2 product related events were reported in the Comirnaty Omicron XBB.1.1.5 arm, being one of them of Grade 1 and one of them Grade 2 in intensity. 1 product related event of Grade 1 in intensity was reported in the PHH-1V81 arm. The frequency of PTs related to respiratory tract infections occurred with higher frequencies in the PHH-1V81 group. Note that there were some respiratory tract infection-related PTs in the Respiratory, thoracic and mediastinal disorders SOC indicative for respiratory tract infection (e.g. cough, rhinorrhoea etc), however these PTs were not considered in the analysis.

Considering the lack of temporal plausibility, it is concluded that there is no need to include Nasopharyngitis as an ADR to the SmPC 4.8. Note also that nasopharyngitis or any other PTs concerning upper respiratory tract infections are not included in the SmPC 4.8 of other COVID-19 vaccines.

Considering that hypertension is a known ADR for another COVID-19 vaccine, an evaluation of all hypertension reported in study HH-14 was done. No numerical imbalance was observed in the analysis (5 events in 4 subjects in the PHH-1V81 group (0.66%) and 6 events in the Comirnaty Omicron XBB.1.5 group (1.33%)).

The frequency of the related unsolicited AEs reported within 28 days post-vaccination was slightly higher in the Comirnaty group (3.99%) compared to the Bimervax group (2.66%). Very few Grade 3 unsolicited AEs were observed in both groups and one Grade 4 unsolicited AE was observed in the Comirnaty XBB.1.5 group.

The most frequently reported related unsolicited AEs were from the General disorders and administration site conditions SOC, with 15 events reported in 13 (1.44%) subjects. Within this SOC, the most common event was Injection site pain (0.33% of subjects in the PHH-1V81 vaccine arm and 0.66% of subjects in the Comirnaty Omicron XBB.1.5 arm), which is a recognised adverse reaction in the product information of Bimervax. Other frequently reported related unsolicited AEs belonged to Infections and Infestations SOC (overall 4 events reported in 4 [0.44%] subjects) and to the Musculoskeletal and connective tissue disorders SOC (overall 4 events reported in 4 [0.44%] subjects).

Serious adverse events

Overall, a total of 14 SAEs were reported in 11 (1.22%) subjects: 8 SAEs in 7 (1.16%) subjects in the PHH-1V81 vaccine arm, and 6 SAEs in 4 (1.33%) subjects in the Comirnaty XBB.1.5 vaccine arm. None of them were assessed as related to study treatment by the Investigator or Sponsor neither with PHH-1V81 vaccine nor with Comirnaty Omicron XBB.1.5 vaccine.

Among the SAEs reported as severe (Grade 3) in intensity, 8 SAEs were reported in 7 (1.16%) subjects that received the PHH-1V81 vaccine, and 3 SAEs were reported in 3 (1.00%) subjects that

received the Comirnaty Omicron XBB.1.5 vaccine. As for the SAEs assessed as life-threatening (Grade 4) and as death (Grade 5) in intensity, both were experienced by the same subject from the Comirnaty Omicron XBB.1.5 vaccine arm.

As for imbalances in the SAEs by treatment groups, two subjects experienced three pulmonary embolism events in the PHH-1V81 group and none in Comirnaty group. Two of these pulmonary embolism events occurred in a patient with underlying condition of Hypertrophic cardiomyopathy who did not report anticoagulation therapy as element of management of the HCM condition. This patient also reported a SAE of Lung carcinoma cell type unspecified stage IV which is also considered as a risk factor for pulmonary embolism. In the second case, the event occurred 17 days after vaccination and no alternative explanation can be concluded based on the data reported up to the data cut-off. The investigator considered the two events not related to vaccination.

Considering the numerical imbalance on the SAE of pulmonary embolism an evaluation of Thromboembolic events in study HH-14 was requested. Besides the three pulmonary embolism events, two Thrombocytosis AE were also found, one for each treatment groups. Overall, there is no increased risk of the occurrence of these events after vaccination with PHH-1V81 and these cannot be considered as ADR at this stage.

Nevertheless, Thromboembolic events, including pulmonary embolism are Adverse events of special interest that are being closely monitored by routine pharmacovigilance and in post-authorisation safety studies included in the RMP.

Two of the three malignancy conditions (Lung carcinoma cell type unspecified stage IV and Tracheal neoplasm) were observed in the PHH-1V81 group either. No concern is raised in these cases.

One SAE of hypertensive crisis was reported in the PHH-1V81 group and none in the Comirnaty group. The patient had arterial hypertension as an underlying condition and abnormal Systolic Blood Pressure at screening.

With regards to the outcomes of the SAEs, overall, 10 out of the 14 reported SAEs in the PHH-1V81 group were resolved at the time of this report. Only 1 subject from the PHH-1V81 vaccine arm that experienced the SAE Pulmonary embolism was recovering/resolving at the time of this report.

No SAEs of pericarditis or myocarditis (important identified risk and important potential risk in Bimervax RMP, respectively) have been reported in study HIPRA-HH14.

Deaths

Up to the cut-off date of 13th June 2024, no deaths have been reported in PHH-1V81 and one death occurred in the Comirnaty XBB.1.5 group (myocardial infarction, not related to vaccination).

Adverse Events of special interests (AESIs)

AESIs include potential immune-mediated medical conditions that were listed in the study protocol

No AESIs have been reported in any of the two treatment arms for the safety population (N = 903) in study HIPRA-HH-14 up to 6 months post-vaccination.

Medically attended events

Overall, a total of 266 MAAEs in 163 (18.05%) subjects were reported, being nearly all of them assessed as unrelated to the study treatment, specifically 265 events in 162 (17.94%) subjects. Only 1 MAAE in 1 (0.17%) subject was considered to be related in the PHH-1V81 vaccine arm. It consisted of a Grade 3 migraine MAAE (PT: Migraine; SOC: Nervous system disorders) experienced by a subject with medical history of migraine. The subject had a basal Grade 1 migraine at the time of vaccination and experienced a worsening of migraine in the following days requiring medical assistance.

In the Comirnaty Omicron XBB.1.5 vaccine arm, there were 98 unrelated MAAEs in 56 (18.60%) subjects. In the PHH-1V81 vaccine arm, there were 167 unrelated MAAEs in 106 (17.61%) subjects.

The most frequently reported types of events were from the Infections and infestations SOC with 90 MAAEs reported in 71 (7.86%) subjects. Out of these, 56 MAAEs were reported in 43 (7.14%) subjects administered with the PHH-1V81 vaccine and 34 MAAEs were reported in 28 (9.30%) subjects administered with the Comirnaty Omicron XBB.1.5 vaccine. The most common event within this SOC was Nasopharyngitis (1.33 % of subjects in both vaccine arms). Other frequently reported MAAEs belonged to Musculoskeletal and connective tissue disorders SOC (26 events reported in 25 [2.77%] subjects).

Some imbalances in the frequencies of MAAEs in the Renal and urinary disorders SOC was observed with higher overall incidence in the PHH-1V81 group. However, this imbalance was led by the nephrolithiasis and renal colic AEs, and relationship of both events to the administration of PHH-1V81 is considered to be unlikely due to the onset time from the administration of the vaccine and/or biological implausibility

Up to the cut-off of 13 June 2024, no subjects discontinued the study due to an adverse event with the exception of the fatal case reported in Comirnaty XBB.1.5 group.

Safety in special populations

Safety data was also provided by age subgroup in the elderly population and other special populations and specified ADRs for these subpopulations shows that the overall AE frequencies in all age groups are lower in the PHH-1V81 group than in the Comirnaty Omicron XBB.1.5 group.

The number of subjects in the age group 65-74, 75-84 and > 85 was very limited in both study groups. Therefore, no robust safety conclusion can be drawn.

As for the SOCs Nervous system disorders, Accidents and injuries and Cardiac disorders, AE frequencies were slightly lower in all elderly subgroups treated with PHH-1V81 compared to those treated with Comirnaty. As for Psychiatric disorders, AE frequencies are higher in the PHH-1V81 group. Based on the available limited data, administration of PHH-1V81 do not increase the risk of AE of AEs in the elderly compared to Comirnaty XBB.1.5. Similar conclusion can be drawn for the related AEs.

Baseline Comorbidities in the Study HH-14 included hepatitis, Type 1 diabetes mellitus (T1DM), Crohn’s disease, HIV infection and Lupus erythematosus. Pregnant or breastfeeding women were excluded from participation in the study, all female participants had a negative urine pregnancy test at screening. However, three pregnancy events took place after having received the study treatment.

Among the subjects with renal impairment, 1 subject in the PHH-1V81 vaccine arm experienced 1 non-serious AE (PT: Anaemia), and 1 subject in the Comirnaty Omicron XBB.1.5 arm experienced 5 non-serious AEs (two PT: Malaise, PT: Ulcer, PT: Muscle spasms and PT: Nephropathy). Regarding the subjects that became pregnant after having received PHH-1V81, all of them experienced AEs. Of note, all AEs occurred before their pregnancies and most of them were solicited AEs. Regarding the subjects with other co-morbidities, 6 (85.71%) subjects in the PHH-1V81 vaccine arm and 7 (87.50%) subjects in the Comirnaty Omicron XBB.1.5 arm experienced AEs, being most of them solicited local and systemic AEs.

To conclude, none of the subjects with co-morbidities presented SAEs and none of them lead to drop out from the study. No trend can be observed among these subjects, suggesting that a booster dose with PHH-1V81 does not differently affect special populations. However, it is worth noting that the number of subjects with a certain baseline comorbidity and the overall number of such patients is very low, therefore all safety findings observed among them should be handled with caution.

One study of co-administration of the parent Bimervax vaccine with seasonal surface antigen inactivated adjuvanted influenza vaccine is ongoing. No other drug-drug interaction studies were conducted, which is acceptable for a vaccine.

Post-marketing data

Limited post-marketing data with Bimervax parent vaccine are available. No safety concern has been identified in post-marketing up to date.

2.6.10. Conclusions on the clinical safety

Based on the available data, it can be concluded that PHH-1V81 has a favourable safety profile. No new safety concerns have been identified. No new adverse drug reactions have been identified.

2.7. Risk Management Plan

No Risk Management Plan (RMP) was submitted in this application.

Based on the review of the available safety data, no changes to the safety concerns, pharmacovigilance plan and risk minimisation measures are required. The current RMP version 1.4 remains as the approved version.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Bimervax. The bridging report submitted by the MAH has been found acceptable.

2.9.2. Quick Response (QR) code

A request to include a QR code in the package leaflet for the purpose of providing statutory information to healthcare professional and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: Summary of Product Characteristics (SmPC), package leaflet, vaccination card, blue box information as required by each Member State.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Bimervax (SARS-CoV-2, variant XBB.1.16, spike protein, receptor binding domain fusion homodimer / Selvacovatein) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

At the time of authorisation of this adapted vaccine, several products have received marketing authorisation for the treatment of COVID-19. These encompass antiviral therapy (nirmatrelvir/ ritonavir, remdesivir), anti-inflammatory therapy (dexamethasone), IL-6 inhibitor (tocilizumab), IL-1 inhibitor (anakinra) as well as monoclonal antibodies directed against the SARS-CoV-2 spike protein (casirivimab/imdevimab, regdanvimab, sotrovimab and tixagevimab / cilgavimab). These therapies have shown variable efficacy depending on the severity and duration of illness as well as against different variants of concern.

Besides Bimervax, there are currently three approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease: Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791) and Nuvaxovid (EMEA/H/C/005808). The mRNA vaccines as well as Nuvaxovid include in their marketing authorisation adapted Omicron vaccines.

3.1.3. Main clinical studies

HIPRA-HH-14 is a Phase IIb/III, double-blind, randomised, active-controlled, multi-center, non-inferiority clinical trial, to assess the safety and immunogenicity of a booster vaccination with the adapted vaccine PHH-1V81 in adults vaccinated against COVID-19.

Approximately 903 participants aged 18 or older who had received a primary scheme with an EU-approved mRNA vaccine (two doses) and at least one booster dose of an EU-approved mRNA vaccine against COVID-19, were to be randomly assigned to the following two treatment arms in a PHH-1V81: Comirnaty (Omicron XBB.1.5) 2:1 ratio.

Study HIPRA-HH-14 used neutralising immunogenicity assessment as a PD surrogate of clinical efficacy. Neutralising immune responses against Omicron sublineages XBB.1.16 and XBB.1.5 were measured by PBNA assay at different time points of the study.

The primary efficacy endpoint is measured 14 days after the booster dose. During the clinical study HIPRA-HH-2 of the parent vaccine Bimervax samples at both, 14 days and 28 days post-booster dose, were analysed and data show that Day 14 is a relevant time point for the assessment on the immune response.

3.2. Favourable effects

Primary endpoint

For the Omicron XBB.1.16 strain, the GMT ratio of Comirnaty XBB.1.5 : PHH-1V81 on Day 14 is 0.78 which met the non-inferiority and superiority criteria.

Secondary endpoints

For the Omicron XBB.1.5 strain, the GMT ratio of Comirnaty XBB.1.5 : PHH-1V81 on Day 14 is 0.79 which met the non-inferiority and superiority criteria.

Among the secondary endpoints, the fold rise in neutralising antibody titres against all strains was also tested and the GMFR ratio calculated.

For the Omicron XBB.1.16 strain, the GMFR ratio of Comirnaty XBB.1.5 : PHH-1V81 on Day 14 is 0.74 which met the non-inferiority and superiority criteria.

For the Omicron XBB.1.5 strain, the GMFR ratio of Comirnaty XBB.1.5 : PHH-1V81 on Day 14 is 0.71 which met the non-inferiority and superiority criteria.

Exploratory endpoints

The boost with PHH-1V81, after a primary immunization and boosting with EU-approved mRNA vaccine(s), elicited a Th1-CD4+ T cell response, as potent than the response induced by the boost with Comirnaty XBB.1.5,

No subjects experienced severe COVID-19 infections, were hospitalised due to COVID-19, or were admitted to the Intensive Care Unit (ICU) due to COVID-19 up to the database lock on 12 December 2023. There have been no deaths associated with COVID-19 through the period studied. Overall, only 1 subject had a non-severe COVID-19 infection throughout the study duration which occurred within 14 days following vaccination with PHH-1V81.

3.3. Uncertainties and limitations about favourable effects

The present submission is a strain update of Bimervax vaccine from Alpha/Beta strains to Omicron XBB.1.16 sub lineage.

No correlate of protection against COVID-19 exists. The immunobinding approach of PHH-1V81 to Comirnaty with known efficacy is therefore essential for the interpretation of a potential protective effect of PHH-1V81 and is aligned with Guideline on clinical evaluation of vaccines

(EMEA/CHMP/VWP/164653/05 Rev. 1). Maintenance of immune response caused by a booster dose PHH-1V81 is unknown, since only Day 14 immunogenicity against XBB.1.15 and XBB.1.16 data are available at the moment. The final CSR will be submitted in a separate regulatory procedure.

Finaly, the relevance of the available immunogenicity data at this stage is questionable with the decline of the Omicron sub lineages XBB.1.5 and 1.16 and with the spread of sublineages JN.1 and KP.2. There's no neutralisation data information on the neutralising immunity of PHH-1V81 against recently spreading variants like JN.1 and KP.2.

3.4. Unfavourable effects

The clinical development plan of PHH-1V81 consisted of 903 participants from the one ongoing Phase IIb/III study HIPRA-HH-14 who had received one dose of study vaccine. From these, 602 received the PHH-1V81 vaccine and 301 received Comirnaty Omicron XBB.1.5. Six months safety follow up data is available.

The most common vaccination site reactions were injection site pain/tenderness/discomfort. The most common systemic adverse reactions were headache, fatigue, myalgia and malaise. The frequency of solicited local adverse reports was lower than in the comparator group.

No new adverse drug reaction has been identified.

Pericarditis and myocarditis are important identified and important potential risk in the RMP of Bimervax. No cases of pericarditis and myocarditis have been reported with PHH-1V81. No cases with fatal outcome have been reported in the PHH-1V81 group.

3.5. Uncertainties and limitations about unfavourable effects

The clinical study supporting the authorisation of PHH-1V81 is currently ongoing. This application is based on 6 months post-vaccination follow up. The final clinical study report will be provided in a follow up procedure. Long term safety is considered missing information in the current RMP and is to be further characterised with additional pharmacovigilance activities.

Most of the unsolicited adverse events reported in the PHH-1V81 group were infections and infestations, mainly led by the preferred term of nasopharyngitis. The review of cases of upper respiratory tract infections did not raise any concern, as the time to onset was not plausible.

Three SAEs of pulmonary embolism were reported in the PHH-1V81 group. Two of these pulmonary embolism events occurred in a patient with underlying condition of Hypertrophic cardiomyopathy (HCM) who did not report anticoagulation therapy as element of management of the HCM condition. This patient also reported a SAE of Lung carcinoma cell type unspecified stage IV which is also considered as a risk factor for pulmonary embolism, therefore, causal association with vaccine is excluded. In the second case, the event occurred 17 days after vaccination and no alternative explanation can be concluded based on the data reported until the data cut-off, but the investigator considered it as not related to vaccination. An evaluation of Thromboembolic events reported in study HIPRA-HH-14 showed that there is no increased risk of the occurrence of these events after vaccination with PHH-1V81 and cannot be considered as ADR at this stage. Thromboembolic events, including pulmonary embolism, are adverse events of special interest that are being closely monitored by routine pharmacovigilance and in post-authorisation safety studies included in the RMP.

As per study protocol, participants were randomised by age group (approximately 10% of the subjects above 60 years old). Around 13% of the participants in both groups were older than 60 years old. However, limited numbers of participants in the older age strata are available, which precludes having

a robust safety conclusion in this population. Safety in frail subjects with underlying conditions is being characterised as part of the RMP.

Certain populations such as patients with immune supressed conditions or pregnant women were exclusion criteria in the clinical trial. However, subjects with underlying chronic disease could be included in the study, provided that their underlying condition is stable or not considered clinically significant by the investigator. Nevertheless, the number of participants with underlying chronic conditions such as hepatic impairment, renal impairment, immunocompromised, pregnant or lactating women was too limited to allow safety conclusions.

These populations (pregnancy and breastfeeding, immunocompromised patients, frail patients with comorbidities, patients with autoimmune or inflammatory disorders) are considered as missing information in the current approved RMP and are planned to be further characterised via post-authorisation safety studies.

As for all clinical trials, the limited sample size only allows to detect common and very common adverse reactions. Post-authorization safety surveillance is therefore very important in order to detect any rare or very rare side effect that might only be observed when a larger number of subjects are exposed to the vaccine.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The emergence of SARS-CoV-2 variants with multiple mutations have led MAHs to develop variant vaccine constructs. To assist in the continued management of the COVID-19 public health threat, a new updated vaccine PHH-1V81 is being introduced to the MA of Bimervax as a new variant vaccine.

While PHH-1V81 demonstrated non-inferiority or even superiority compared to Comirnaty XBB.1.5 after a 3rd or 4th or more dose of mRNA COVID-19 vaccines, immunogenicity data is only available 14 days after vaccination. There's no information of the maintenance of the immune response induced by PHH-1V81 at the moment.

Relevance of immune response data against sublineages not existing anymore (XBB.1.15 and XBB.1.16) might be questionable. There's no information on the neutralising immunity against recently spreading variants like JN.1 and KP.2.

Based on the available 6 months follow safety data, it's concluded that clinical PHH-1V81 adapted vaccine is safe and well tolerated. No new adverse drug reactions or safety concerns have been identified.

3.6.2. Balance of benefits and risks

In the context of this procedure, the selection of Omicron XBB.1.16 variant for the antigen (RBD dimer) development was compliant with the WHO and EMA-ECDC recommendations of Q2 2023 at the time of the development of PHH-1V81. In 2024, the variant JN.1 is recommended as the target variant for development of adapted COVID vaccines for vaccination in the autumn-winter season of 2024/25.

The immunobinding approach used for this application is considered acceptable and aligned with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

The available clinical efficacy results of immunobridging HIPRA-HH-14 study show a comparable or

even superior immune response of COVID-19 vaccine PHH-1V81 against Omicron sublineages XBB.1.5 and XBB.1.16 when compared to Comirnaty XBB.1.5 at day 14 post-vaccination.

Despite the spread of new variants and the waning of Omicron XBB variants, the immunogenicity data of Study HH-14 is relevant, since this line extension is the first strain update for Bimervax and a positive outcome is a prerequisite for further strain updates.

Therefore, data are indeed still relevant for the purpose of this procedure although the more relevant strain update for use at the current moment is the JN.1 variant.

The available safety data up to 6 months post-last vaccination show an acceptable safety profile, overall comparable to the parental Bimervax vaccines.

The benefit/risk balance of Bimervax XBB1.16 for the sought indication active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older is positive.

3.7. Conclusions

The overall benefit/risk balance of Bimervax XBB.1.16 is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Bimervax XBB.1.16 is favourable in the following indication(s):

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.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Bimervax subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.