30 March 2023
EMA/175278/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bimervax

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

Procedure No. EMEA/H/C/006058/0000

Note

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

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List of abbreviations

AAE Antibody affinity extraction

ABTS 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)

ACA Anti-clumping agent

ACE2 Angiotensin Converting Enzyme 2

ADE Antibody-dependent enhancement

AE Adverse event

AEMPS Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices)

AESI Adverse events of special interest

AQL Acceptance Quality Level

AS Active substance

BC Blocking control

CCIT Container closure integrity test

CDP Clinical development plan

CE-SDS Capillary Electrophoresis Sodium Dodecyl Sulfate

CE-SDS-DG-R CE-SDS under reduced conditions and after deglycosylated

CHO Chinese hamster ovary

CI Confidence interval

cIEF Capillary isoelectric focusing

CMC Chemistry, manufacturing and controls

CMO Contract manufacturing organisation

COVID-19 Coronavirus disease 2019

CPP Critical process parameters

CRA Clinical Research Associate

CRO Clinical Research Organisation

CQA Critical quality attributes

DBL Data base lock

DLT Dose limiting toxicity

DP Drug product

DS Drug substance

DSMB Data and Safety Monitoring Board

ECB	Extended Cell Bank
ECDC	European Centre for Disease Control
EEA	European Economic Area
ELISA	Enzyme linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
EMA	European Medicines Agency
EP	Enrolled
ES	Spain
EU	European Union
EU	Endotoxin unit
EVA	Ethylene-vinyl acetate
FDA	Food and Drug Administration
FIH	First-in-human
FP	Finished product
GCP	Good clinical practice
GLP	Good Laboratory Practice
GMFR	Geometric mean fold rise
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
GMT	Geometric mean titre
HCP	Host cell protein
HPLC	High performance liquid chromatography
HRP	Horseradish-peroxidase
IC50	Half-maximal inhibitory concentration
ICE	Intercurrent events
ICH	International Conference on Harmonisation
ICS	Intracellular cytokine staining
ICU	Intensive care unit
ID50	Half-infective dose
IFN	Interferon
IgG	Immunoglobulin G
IGP	Immunogenicity
i.m.	Intramuscular

IMP Investigational medicinal product

INN International non-proprietary name

IPCs In-process controls

IRT Interactive Response Technology

IT Italy

ITT Intent-to-treat

LAL Limulus amoebocyte lysate

LC-MS/MS Liquid Chromatography-tandem Mass Spectrometry

LLOQ Lower limit of quantitation

LS Least square

MAA Marketing authorisation application

MAAE Medically attended adverse events

mAb Monoclonal antibody

MAPLA Monophosphoryl lipid A

mga Milligrams of activity

mITT Modified intent-to-treat

MMRM Mixed model repeated measures

mRNA Messenger RNA

MW Molecular weight

NAbs Neutralising antibodies

N/A Not applicable

NCA National competent authority

NHP Non-human primates

Non-KPP Non-key process parameters

NOR Normal operating range

NR Non-reduced

NtA Notice to Applicants

OD Optical density

OOS Out of specification

PAR Proven acceptable range

PBMC Peripheral blood mononuclear cell

PBNA Pseudovirus-based neutralisation assay

PBS Phosphate-buffered saline

PCR Polymerase chain reaction

PD Pharmacodynamic

Ph. Eur. European Pharmacopoeia

PHH-1V COVID-19 Vaccine HIPRA

PI Principal investigator

PP Per protocol

PP Process parameters

PRS Primary Reference Standard

PT Portugal

QC Quality control

QP Qualified Person

QTPP Quality Target Product Profile

R Reduced

RBD Receptor binding domain

RBM Receptor binding motif

RID Refractive index detector

RP Relative potency

RVLPs Retrovirus-like particles

S Spike protein

SAE Serious adverse events

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2

SD Standard deviation

SDS-PAGE Sodium dodecyl sulfate-polyacrylamide gel electrophoresis

SEC-HPLC Size-exclusion-high performance liquid chromatography

SmPC Summary of product characteristics

SOP Standard operating procedure

SP Safety

SPR Surface plasmon resonance

TFF Tangential flow filtration

TNF Tumour necrosis factor

TSA Thermal Shift Assay

TSE Transmissible spongiform encephalopathy

USP United States Pharmacopeia

VAERD	Vaccine-associated enhanced respiratory disease
VNA	Virus neutralisation assay
VoC	Variants of concern
WCB	working cell bank
WHO	World Health Organization
WRS	Working Reference Standard

1. Background information on the procedure

1.1. Submission of the dossier

The applicant HIPRA HUMAN HEALTH SLU submitted on 21 March 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for COVID-19 Vaccine (recombinant, adjuvanted), through the centralised procedure falling within the Article 3(1) and point <1> <3> <4> of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 December 2021.

The applicant applied for the following indication:

'BIMERVAX is indicated as a booster for active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA COVID-19 vaccine (see sections 4.2 and 5.1).

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 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 P/0465/2022 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 applicant 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.

1.4.2. New active substance status

The applicant requested the active substance SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

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	SAWP co-ordinators
5 November 2021	EMA/SA/0000066056	Rosalía Ruano Camps, Walter Janssens, Ingrid Schellens
16 February 2022	EMA/SA/0000080295	Mair Powell, Ewa Balkowiec Iskra
18 February 2022	EMA/SA/0000078033	Ingrid Schellens

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

- *Structure of the eCTD Module 3; quality development to support Phase 3 studies and MAA*
- *Overall approach to bioanalytical method validation to support phase 3 trial and MAA*
- *Characterisation and nonclinical package for the adjuvant to support MAA*
- *Approach to presenting the environmental risk assessment for MAA*
- *Non-clinical development strategy: design of the developmental and reproductive toxicity (DART) studies to support MAA; timing of DART studies with respect to phase 3 and inclusion of pregnant women in phase 3 studies; immunogenicity analysis waiver in DART studies*
- *Immunobridging strategy; design of the respective studies; comparator; selection of endpoints; non inferiority margin; population; safety database; RMP*

Scientific advice compliance

Study HH-2: Design and conduct of the study were compliant to the scientific advice (EMA/SA/0000066056)

Study HH-5: Design and conduct were partially compliant to the scientific advice EMA/SA/0000066056 and the Follow-up advice EMA/SA/0000080295

- Study HH-5 was designed as an uncontrolled study and the Comirnaty arm of Study HH-2 was planned to be used as a non-randomised control to the Study HH-5 population, all of those boostered with Bimervax. According to EMA, this approach raised some methodological concerns.
- EMA proposal on inclusion of patients primed with adenovirus vaccines or patients with heterologous priming was adopted by the Applicant in Study HH-5
- EMA proposed around a 3000-subject safety population (Safety data set) as a minimum. The applicant just reached this minimal requirement.

1.6. COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application: The ETF endorsed the Scientific Advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure. Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP. For the exact steps taken at ETF, please refer to section 1.7.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Robert Porszasz Co-Rapporteur: Daniela Philadelphy

The CHMP confirmed eligibility to the centralised procedure on	16 December 2021
ETF recommendation on a request for appointment of Rapporteurs for a potential rolling review procedure on	22 March 2022
Applicant submitted quality, non-clinical, clinical and RMP documentation as part of a rolling review to support the marketing authorisation application on	28 March 2022
The procedure (Rolling Review 1) started on	29 March 2022
The PRAC Rapporteur's first Assessment Report and List of Question was circulated to all PRAC and CHMP members on	26 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 May 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	04 May 2022
BWP discussion took place on	10 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	10 May 2022
ETF discussion on Rolling Review 1 took place on	12 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 May 2022
Applicant submitted quality, non-clinical, clinical and RMP documentation as part of a rolling review to support the marketing authorisation application on	02 June 2022
The procedure (Rolling Review 2) started on	03 June 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 June 2022
PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	01 July 2022
The CHMP Rapporteur and Co-rapporteur Assessment Report was circulated to all CHMP members on	06 July 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 July 2022
BWP discussion took place on	11 July 2022
ETF discussion on rolling review 2 took place on	14 July 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report to CHMP and PRAC members on	15 July 2022

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	21 July 2022
Applicant submitted quality, clinical and RMP documentation as part of a rolling review to support the marketing authorisation application on	28 October 2022
The procedure (Rolling Review 3) started on	31 October 2022
The CHMP assessment report was circulated to all CHMP and PRAC members on	22 December 2022
ETF discussion on rolling review 3 took place on	13 January 2023
PRAC Rapporteur's Assessment Report was circulated to all PRAC and CHMP members on	16 January 2023
The CHMP Rapporteur Joint assessment report was circulated to all CHMP and PRAC members on	17 January 2023
BWP discussion took place on	18 January 2023
PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	20 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	23 January 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Updated Rapporteurs Joint Assessment Report to CHMP and PRAC members on	23 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 January 2023
Applicant submitted quality, clinical and RMP documentation as part of a rolling review to support the marketing authorisation application on	14 February 2023
The procedure (Rolling Review 4) started on	15 February 2023
The CHMP Rapporteur assessment report was circulated to all CHMP and PRAC members on	03 March 2023
PRAC Rapporteur's Assessment Report was circulated to all PRAC and CHMP members on	06 March 2023
PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	09 March 2023
BWP ad-hoc	10 March 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
ETF discussion took place on	21 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Updated Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	23 March 2023
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	30 March 2023

Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	30 March 2023

COVID-19 Vaccine (recombinant, adjuvanted) was evaluated as part of 'OPEN', an initiative started in December 2020 with the aim of increasing international collaboration in the EU review of COVID-19 vaccines and therapeutics. More information can be found on the EMA website.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

2.1.2. Epidemiology and risk factors

As of 21 March 2023, there have been over 761 million confirmed cases of SARS-CoV-2 infection globally with approximately 6.8 million deaths resulting from infection and subsequent coronavirus disease (COVID-19) as registered by WHO (https://covid19.who.int/). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

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 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.

It is believed that SARS-CoV-2 has zoonotic origins, and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

As for all viruses, the SARS-CoV-2 virus will constantly change through mutation and, indeed, many variants of the SARS-CoV-2 virus with different sets of mutations have been observed worldwide. While most emerging SARS-CoV-2 variants will not have a significant impact on the spread of the virus, some mutations or combinations of mutations may provide the virus with a selective advantage, such as increased transmissibility or the ability to evade the host immune response. These variants could increase the risk posed by SARS-CoV-2 to human health and are considered variants of concern (VoC).

2.1.4. Clinical presentation, diagnosis

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

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The severity of COVID-19 disease varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical disease may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

Studies among hospitalised patients have found that high SARS-CoV-2 viral load is associated with worse outcomes, including increased mortality rates (Magleby, 2020) (Westblade, 2020). Community-based studies in non-hospitalised patients show symptomatic patients have higher viral load across both adults and children compared to asymptomatic individuals (Chung, 2021).

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed since the start of the pandemic, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy such as Veklury (remdesivir, EMEA/H/C/005622) or Paxlovid, that can be used in the outpatient setting (PF-07321332/ritonavir, EMEA/H/C/005973).

Monoclonal antibodies and notably bi-therapies to overcome potential escape by VOC with mutations on spike are perceived as of potential value. This was particularly true for immunocompromised individuals especially where vaccines might not induce adequate immune response in those patients of particular medical need. Thus, recently, four monoclonal antibodies Ronapreve (casirivimab/imdevimab, EMEA/H/C/005814), Regkirona (regdanvimab, EMEA/H/C/005854), Xevudy (sotrovimab, EMEA/H/C/005676) and Evusheld (tixagevimab /cilgavimab, EMEA/H/C/005788) have been authorised for the treatment of COVID-19 disease in individuals who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. In the case of Ronapreve, it is also authorised for prevention of COVID-19, and Evusheld also for pre-exposure prophylaxis of COVID-19.

Other products have been repurposed to be used for the treatment of COVID-19, such as Kineret (anakinra, EMEA/H/C/000363) in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR)≥6 ng/ml; and RoActemra (tocilizumab, EMEA/H/C/000955) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Additionally, there are 7 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), Vaxzevria (EMEA/H/C/005675), Jcovden (EMEA/H/C/005737), Nuvaxovid (EMEA/H/C/005808) , COVID-19 Vaccine (inactivated, adjuvanted) Valneva (EMEA/H/C/006019) and VidPrevtyn Beta (EMEA/H/C/005754). The mRNA vaccines include in their marketing authorisation adapted Omicron vaccines.

2.2. About the product

BIMERVAX (SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains) is intended as a booster for active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA COVID-19 vaccine. A single injection of 40 µg dosage of the vaccine is intended to be used. The vaccine contains a SARS-CoV-2 virus recombinant protein RBD fusion heterodimer – B.1.351 (Beta) -B.1.1.7 (alpha) strains.

The vaccine is formulated in a phosphate-buffered saline (PBS) solution adjuvanted with SQBA adjuvant. The SQBA adjuvant facilitates activation of the cells of the innate immune system, which

enhances the magnitude of the S protein RBD-specific immune response. The recombinant spike protein RBD domains of SARS-CoV-2 are recognised by immune cells as a foreign antigen and elicit neutralising antibody and cellular responses which may contribute to protection against COVID-19. Neutralizing antibodies against the RBD domain of SARS-CoV-2 prevent RBD binding to its cellular target ACE2, thus blocking membrane fusion and viral infection. Moreover, BIMERVAX vaccine induces antigen-specific CD4+ and CD8+ T cells, with a Th1 response.

A booster dose of BIMERVAX should be given intramuscularly at least 6 months after completion of the primary series with a mRNA vaccine.

Throughout this document, the product is referred to as Bimervax or PHH-1V.

2.3. Quality aspects

2.3.1. Introduction

Bimervax (PHH-1V, COVID-19 Vaccine (recombinant, adjuvanted)) finished product (FP) is a sterile, preservative-free 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 receptor binding domain (RBD) fusion heterodimer comprised of B.1.351-B.1.1.7 strains, adjuvanted with SQBA.
Other ingredients are disodium phosphate dodecahydrate, potassium dihydrogen phosphate, sodium chloride, potassium chloride and water for injections; SQBA adjuvant containing squalene, polysorbate 80, sorbitan trioleate, sodium citrate, citric acid monohydrate and water for injections.

The finished product is supplied in one pack size of ten multidose vials, each vial containing ten doses of 0.5 mL.

2.3.2. Active Substance

2.3.2.1. General information

The active substance (antigen) of the PHH-1V vaccine is SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion heterodimer comprising B.1.351-B.1.1.7 strains. The spike protein has 1273 amino acids, and the RBD domain corresponds to the consensus sequence from amino acid 319 to 541. Specifically, from position 437 to 508 there is the receptor binding motif, which is the region of the RBD that interacts directly with the ACE2 receptor.

Except for the nature of the bond and the number of amino acids at the C-terminal, the PHH-1 and PHH-1V immunogen proteins have a high degree of equivalence at the conformational and structural level.

This recombinant subunit antigen is a fusion (single polypeptide) dimeric RBD antigen that contains two monomers, a first monomer comprising the amino acid sequence of positions 319 to 537 of SARS-CoV- 2 Spike protein RBD monomer derived from the B.1.351 variant (South African SARS-CoV-2), and it is followed by the amino acid sequence of positions 319 to 537 of SARS-CoV-2 Spike protein RBD monomer derived from the B.1.1.7 variant (United Kingdom SARS-CoV-2) as the second monomer. The reference sequence is Uniprot P0DTC2 (D614G strain -Hu-1).

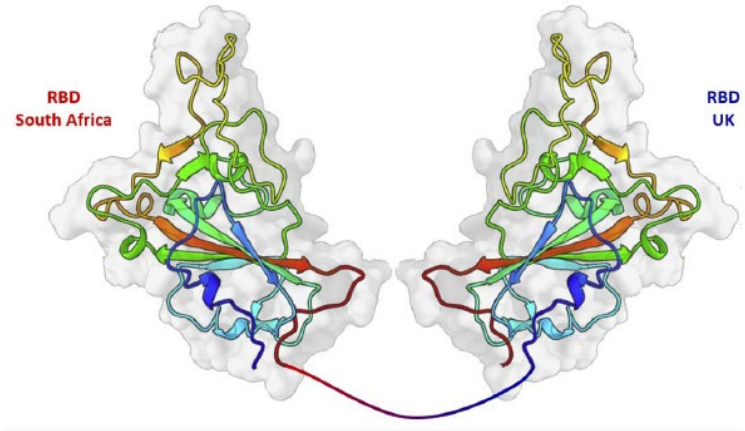


Figure 1. Structure of the B.1.351 (South Africa) - B.1.1.7 (UK) dimer receptor binding domain (RBD) immunogen of PHH-1V

The molecular weight of the RBD is around 57kDa and variable N-glycan structures are observed. Surface plasmon resonance (SPR) was used for the determination of the affinity between Human ACE2 protein and the protein from Process 4. The affinity binding constant between Human ACE2 protein and the protein is 0.110 nM.

The immunogenicity of RBD has been demonstrated by its ability to elicit neutralising antibodies (NAbs) against the virus without evident antibody-dependent enhancement (ADE) or vaccine-associated enhanced respiratory disease (VAERD) effects.

At the beginning of the development of this vaccine, the candidate antigen was a recombinant protein whose sequence was that of a homodimer of the D614G receptor binding domain (RBD) (referred to as PHH-1). However, due to the rapid emergence and spread of new variants around the world, HIPRA decided to adapt to the new pandemic situation by developing a new antigen candidate (based on the same CHO cell platform technology as the vaccine) aimed at conferring protection against these new variants.

2.3.2.2. Manufacture, characterisation, and process controls

Manufacturers and contract laboratories

The active substance (AS) is manufactured, tested and released at Laboratorios Hipra, S.A. Amer (Girona), Spain, in accordance with the good manufacturing practice (GMP). 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

The PHH-1V active substance is expressed in Chinese hamster ovary (CHO) cells and the manufacturing process is divided into upstream and downstream process.

The upstream process consists of several expansion steps in cell culture from the Working Cell bank (WCB) to the final culture in a bioreactor. Samples are taken to carry out in-process controls (IPCs). In accordance with ICH Q5A (R1), unprocessed bulk should be subjected on a routine basis to detection of extraneous agents, mycoplasma, minute virus of mice and retrovirus. Therefore, *in vitro* screening tests, using several cell lines should be used. The pre-harvest cell culture was not routinely tested for

mycoplasma and adventitious virus. Consequently, this issue was initially raised as part of a Major Objection on viral safety.

The initial approach proposed by the applicant was not endorsed as all batches should be fully tested. This safety requirement was finally accepted by the applicant, the testing introduced, and the Major Objection was considered resolved.

The downstream process for purification of the active substance includes a clarification step followed sequentially by concentration and diafiltration steps, chromatography, viral inactivation, precipitation, chromatography, concentration and diafiltration, viral clearance by nanofiltration and final sterile filtration. The active substance batches are filled into sterile bags and stored at the recommended temperature. No reprocessing during the manufacturing process of the active substance was described.

The flow charts and a narrative description of the manufacturing process were provided. Nonetheless, the initial description of the active substance manufacturing process was incomplete and insufficient. The active substance manufacturing process was described based on a very preliminary ("research-grade") version where many IPCs were proposed without acceptance criteria. The proposed control strategy also did not focus on critical quality attributes (CQAs) and was considered largely insufficient. IPCs were mixed up with critical material attributes, critical and non-critical process parameters (PP) and operating ranges. Most specified acceptance ranges were very broad and were not justified. The qualified operating ranges were not indicated. It was also unclear why individual parameters even though seen as critical had extremely broad acceptance ranges.

Critical product quality attributes were not controlled at all throughout the whole manufacturing process. Many critical process parameters (CPP) or holding times were not considered. Thus, a Major Objection on the control strategy (as further discussed also in the section control of critical steps and intermediates) was raised. The applicant was requested to completely revise its AS and FP control strategy based on the Quality Target Product Profile (QTPP) and identify AS and FP CQAs, and to justify how CPPs and IPCs and their ranges had been established. A clear and unambiguous description of the process control strategy was requested for further assessment.

With the responses all critical and key process parameters (CPP and KPP, respectively) and selected non-key process parameters (non-KPP) of the active substance upstream and downstream processes were discussed and justified. For the process parameters, ranges and criticality were also provided.

The initial acceptance criteria were further tightened taking into account clinical data and data from all commercial AS batches available. Considering all data provided for the active substance, these new proposed limits are regarded as suitable in order to guarantee the quality attributes.

Some additional specifications were proposed for unprocessed bulks with acceptable acceptance limits and the compliance of the batches manufactured was demonstrated.

The updated control strategy designed for PHH-1V active substance manufacture takes into account the QTPP and the defined CQAs in order to assure that the final active substance meets the desired quality and the Major Objection on control strategy was considered resolved.

Control of materials

Raw materials, reagents and solvents:

Raw materials used for the cell culture and purification process are listed together with their quality standard (in-house, Ph. Eur., USP/NF) and their intended use. Non-compendial materials are identified but in-house specifications were initially not provided but were further presented with the responses to the list of questions. For all critical raw materials such as cell culture media, chromatographic resins

and filters, and the filters casettes for concentration and diafiltration, acceptance criteria have been adequately provided.

Source, History and Generation of the cell Substrate:

A stable cell line of genetically engineered CHO cells was established under non-GMP conditions. The master cell bank (MCB) and working cell bank (WCB) were established and qualified under GMP conditions. The MCB and WCB were tested and found free of adventitious virus, mycoplasma and are sterile. The genetic stability of the CHO cell line MCB, WCB and Extended Cell Bank (ECB) has been demonstrated and the proposed specifications for future WCBs are endorsed.

The applicant claimed that the results obtained on the MCB and ECB (in the culture and study conditions performed) are comparable to each other. No infectious retrovirus activity was found in the MCB and ECB.

Control of critical steps and intermediates

IPCs for manufacturing Process 4 (commercial process) regarding the upstream and downstream processes were described. However, the characterisation of the active substance had not been finalised initially therefore, it was unclear how the Quality Target Product Profile and/or critical quality attributes could be set, how process qualification was performed and how CPPs and critical and non-critical in-process controls were set. Apparently, no process data were used to define critical and non-critical parameters, operating ranges, and product impurities. Differences were observed when characterising the RBD fusion heterodimer obtained by the different manufacturing processes. In addition, most of the parameter ranges were extremely wide.

The control of critical steps and intermediates section presented was unclear and ambiguous. Limits for critical product quality attributes that should be controlled throughout the whole manufacturing process, were still to be determined. Similarly, some aspects of the provided risk assessment were not supported such as the proposed low risk assigned to extraneous agents. Only a brief and vague summary was provided concerning the justification for the proposed process parameters' ranges and their criticality. However, for both PPs and IPCs, it was not clear if the limits were acceptance criteria, normal operating range (NOR) or proven acceptable range (PAR). Therefore, it was unclear when a batch would be rejected. It was also unclear why individual parameters were defined as critical, when their acceptance ranges were extremely broad. Taken together, serious deficiencies related to the manufacturing control strategy of the active substance were initially identified (Major Objection).

With the responses, the control strategy of the active substance manufacturing process was substantially improved. PP and IPCs for commercial process for the upstream and downstream processes were further discussed and described taking into account the data on the QTPP and/or CQAs.

Control of intermediates

There are no intermediates defined for the active substance manufacturing process. Holding times were established.

Process validation and/or evaluation

Three consecutive commercial scale batches were manufactured with the proposed commercial process (Process 4). The initial validation was performed in accordance with Annex 13 from GMP guideline related to Investigational Medicinal Products. Therefore, a new validation in compliance with the requirements of 'Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission' (EMA/CHMP/BWP/187338/2014) was

carried out. The validation was performed with 3 consecutive batches. It should be noted that these validations were performed with batches manufactured when some of the updated control strategy proposals currently implemented were not included or assessed in those validations. As a result of the recently improved control strategy with the addition of several IPCs and PPs, a complementary validation of the whole active substance manufacturing process is currently on-going. The validation protocol scheme of this new exercise was provided. The applicant's proposal to submit additional and complementary data in order to update the current manufacturing process validation with the recently added controls of the manufacturing process is endorsed. The validation protocol should be updated in accordance with the revised control strategy and the updated validation results should be submitted within 4 months after the marketing authorisation (**Recommendation 5**).

Resin and filter reusability:

Resin lifetime verifications at industrial scale have been provided.

Process development

Different manufacturing process versions have been in place during development. Manufacturing of clinical active substance material started with process 2 which was a small-scale manufacturing process. Active substance material from process 2 was used to supply the phase I/IIa, first in human clinical trials to select the antigen dose. Process 2 was upscaled to process 3 to support the phase IIb pivotal efficacy trial. Further development activities led then to process 4 which was used to supply the extended phase IIb pivotal efficacy trial as well as the phase III extended safety and immunogenicity trial. Process 4 is also the intended commercial manufacturing process. Whereas a total of thirty-seven batches are currently available for the intended commercial process 4 only a limited number of active substance batches have been manufactured with the previous process versions. Five active substance batches were produced according to process 2, and only one batch was produced with process 3.

A multidisciplinary Major Objection was raised on the inadequate evaluation of comparability between batches from different versions of the manufacturing process. Among the main concerns was that the analytical portfolio used to assess the impact of the manufacturing process changes on CQAs was considered insufficient and inadequate. Furthermore, significant differences in CQAs between the active substance material from the different process versions were observed but were not further discussed or justified. High variability was observed between different manufacturing processes. The applicant should have justified the acceptance criteria *a priori* and demonstrated that the applied methods were qualified for the intended purpose. Samples should have been analysed head-to-head and a sufficiently representative number of batches should have been used. At the end the methodological portfolio was considerably improved to obtain insight into product- and process-related impurities, size-variants, degradation products.

These shortcomings left critical questions as to whether the safety and efficacy profile of the clinical batches was representative of the commercial material. Unfortunately, active substance material manufactured by process 2 and 3 was no longer available, therefore a full new head-to-head analytical comparison using an improved analytical portfolio and including a sufficient and representative number of batches could not be performed. To address these limitations on comparability, the applicant presented a holistic approach. As full confirmation of comparability through analytical studies at quality level alone was no longer possible, a non-clinical comparability exercise including a specific bridging study as well as a comparison of data from different clinical trials using batches manufactured from different manufacturing processes was further performed and presented.

The comparability evaluation at quality level was primarily conducted at the active substance level however it included as well, a comparability discussion of the SBQA adjuvant and the final PHH-1V

vaccine derived from different process versions. Process 2 was a small-scale process which was upscaled to the final scale for the upstream processing whereas no changes were introduced for the downstream processing when proceeding from process 2 to process 3. Process 3 was further optimised to the final process 4, which included the implementation of certain process parameters in the upstream processing and an upscaling of the downstream processing. Except for the removal of a step, the rest of the downstream process steps are identical between process 3 and 4 following the same order and with adjustment only of the process parameters and volumes for bigger equipment. A discussion on the implemented changes in the active substance manufacturing process was further provided. Another aspect of the active substance comparability evaluation, i.e. a comparison of the in-process control results, where feasible, was also presented and discussed. A comparison of characterisation data was also provided. A total of five batches from process 2, one batch from process 3 and five batches from process 4 have been further characterised. A comparison of the release batch data of all available batches of active substance manufactured following process 2, 3 and 4 was performed and presented. As discussed above, the active substance material manufactured by process 2 and 3 was no longer available, and therefore complementary analysis of process 2 and 3 batches versus process 4 batches with the improved/extended method panel was no longer possible.

A retrospective evaluation of comparability based on statistically derived comparability criteria was performed. The raw data were provided and for the majority of the investigated quality attributes, scatter plots were included which made the assessment of comparability possible. For several quality attributes the visual assessment of the scatter plots did not indicate any significant differences. Some differences were noted in the quality profile when clinical active substance material was compared with the commercial material (oligo-saccharide structures, deamination, oxidation and charge isoforms). The discussion of comparability at the quality level focused on the biological relevance of the observed differences and their potential impact on safety and efficacy. No negative impact on the efficacy and safety profile of the PHH-1V vaccine is expected from these differences. This conclusion was also supported by the non-clinical and clinical comparison. In summary, taken together the arguments and justifications brought forward by the applicant were considered sufficient to solve this Major Objection on comparability.

Characterisation

The characterisation of the RBD fusion heterodimer involved a battery of physicochemical and biological tests using sensitive and orthogonal state-of-the-art qualified analytical methods in order to elucidate the primary, secondary and higher-order structure, glycosylation, purity and impurities, quantity and biological activity in accordance with ICH Q6B 'Guideline on specifications: test procedures and acceptance criteria for biotechnological/biological products'. Furthermore, according to the applicant, the quality attributes of the purified antigen have been tested to confirm the identity and integrity of the antigen in accordance with Ph. Eur. 0784 (Products of recombinant DNA technology). The analytical methods used for the characterisation of active substance were listed and included:

1) for the structural characterisation and confirmation of primary structure: (a) determination of the intact protein and (b) subunit MW; (c) Identity;

2) for the structural characterisation and confirmation of carbohydrate structure: (a) N-glycan profile and (b) total Glycosylation;

3) for the structural characterisation and stability of the secondary and higher-order structure: (a) determination of secondary and higher-order structure of the protein; and (b) determination of stability parameters of the protein;

4) for physicochemical properties: (a) Product-related substances; (b) Product-related impurities and purity of dimeric RBD protein; and (c) Total protein content;

5) Quantity: antigen quantification;

6) Biological activity: (a) determination of the affinity between hACE2 protein and the protein by SPR and (b) by ELISA

As requested, the applicant has determined the de-amidated and oxidized forms in the three process validation batches as well as in 10 commercial batches manufactured with the intended commercial process 4. These data indicate quite constant levels of de-amidated and oxidized forms within acceptable ranges and thus support the conclusion that routine control for these quality attributes is not required.

Overall, the active substance was extensively characterised with orthogonal physicochemical and biological methods and covered the relevant products attributes.

Impurities

Product-related impurities:

Product-related impurities/substances are controlled by different analytical techniques such as SEC-HPLC, SDS-PAGE and Capillary Electrophoresis Sodium Dodecyl Sulfate (CE-SDS). This approach for the characterisation of the active substance product-related impurities/substances was considered acceptable. Nonetheless, the initial resolution of SEC-HPLC, and resolution and sensitivity of SDS-PAGE for the detection of PHH-1V variants, AS degradation, degradation components of vaccine and AS/FP impurities was too low and more sensitive methods needed to be developed. The applicant was requested to improve these methods to obtain better resolution, identification and quantification of the different product related impurities (details on this Major Objection and how it was considered resolved are further discussed in the specifications section below).

Process-related impurities:

The process-related impurities are specific to the process used for the active substance manufacture and the host cell used (HCP). The following process-related impurities have been identified during the active substance manufacture: host cell proteins (HCP), which are controlled by a generic ELISA method and host DNA, which is determined by qPCR testing.

The capacity of individual purification steps to reduce process-related impurities such as HCP and DNA have been further studied. The reduction of DNA has been demonstrated. The reduction of process-related impurities, DNA antifoam and anti-clumping agent (ACA) impurities were addressed and considered acceptable. However, the HCP reduction strategy was not fully optimised. No specific step was developed to reduce HCP levels. The HCP reduction was insufficient and not validated, and the proposed HCP specification was not clinically justified by safety data (Major Objection). A multidisciplinary Major Objection was raised. Thus, the applicant was asked to implement a validated and robust HCP reduction step.

With the responses, the applicant improved the HCP control strategy by implementing an alternative generic HCP-assay with higher coverage to replace the initially proposed assay. Coverage was assessed by two orthogonal methods using a solid phase, HCP kit specific antibody affinity extraction (AAE) and image-based computer assisted evaluation of 2D-PAGE as well as LC-MS detection. The assessment of coverage by two orthogonal methods is supported. Thus, the CHO HCP ELISA Kit shows an appropriate coverage, and the proposed replacement of the initial HCP is supported.

The new assay was validated according to ICH Q2 R1 guideline for its accuracy, precision, specificity, linearity, range, limit of quantitation (LoQ) and robustness, and considered suitable for its intended application. HCP content data from 16 batches measured by the second generic assay were presented,

and HCP levels from commercial batches seem reproducible. The Major Objection was considered resolved.

The HCP content has been qualified in clinical trials. However, no information on the HCP profile was given. HCPs that can be considered high-risk include those that are immunogenic, biologically active, or enzymatically active with the potential to degrade either product molecules or excipients used in formulation, and these are often difficult-to-purify. Clinical and non-clinical material was found representative of the commercial manufacturing process. The applicant was requested to perform an in-depth characterisation of the qualitative HCP profile, including a risk assessment based on the outcome of the qualitative HCP assessment and is acceptable post approval (**Recommendation 7**).

2.3.2.3. Specification

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 initial proposed panel of tests did not reflect the complexity of the molecule. The proposed specifications for a complex, post-translationally highly modified and a relatively unstable recombinant protein were imprecise and incomplete and were requested to be updated. The applicant was asked to improve its analytical portfolio for release and shelf-life assessment including validated state of the art methods to assess CQAs at the active substance and finished product level, for identity, potency, charge-variants, glyco-variants (consistency of glycosylation regarding side occupancy, amounts and structures), size-variants, degradation products.

The resolution of SEC-HPLC and resolution and sensitivity of SDS-PAGE for the detection of PHH-1V variants, active substance degradation, degradation components of vaccine and AS/FP impurities was too low and more sensitive methods were requested to be developed. With the responses it was agreed that the SEC-HPLC method for AS and FP had been improved and duly validated. The new method is now capable of adequately distinguishing pre and post-peaks.

In relation to CE-SDS it was noted that the elution pattern in CE-SDS did not correspond to the expected theoretical molecular weight (MW). This needed to be thoroughly discussed and the proposed evaluation procedure for CE-SDS results under reducing and non-reducing conditions, for the assessment of the active substance and finished product needed to be further improved. This resulted in a Major Objection.

To address this MO and in order to achieve better reproducibility of CE-SDS, the applicant ran deglycosylated samples under reduced conditions. The data of the RBD fusion heterodimer analysed by CE-SDS under reduced and deglycosylated conditions showed reproducible electropherograms in which the full-length protein(s) is the predominant structure. Overall, the method has demonstrated to be a relevant and useful test for active substance batch release and stability monitoring. Therefore, this new method has been included in the release specification and will be routinely used for assessment of new manufactured commercial active substance batches (Process 4) and will be included in the protocol of future stability studies.

CE-SDS under reduced conditions and after deglycosylated (CE-SDS-DG-R) methods for AS and FP have been improved and duly validated and the Major Objection was considered resolved.

Nevertheless, the applicant is recommended to identify the 2 apparently both active identities in the major peak, as well as the 3 peaks related to product degradation (**Recommendation 1**). For CE-SDS-DG-R, the applicant is also recommended to revise the active substance (AS) and finished product (FP) CE-SDS-DG-R specifications after 15 commercial AS and FP batches have been manufactured (**Recommendation 2**).

In summary, concerning the purity and product-related impurities, 3 different orthogonal methods are in place (SEC-HPLC, SDS-PAGE (reduced & non-reduced), and CE-SDS (reduced and non-reduced). Significant improvements of these methods have been implemented; consequently, the method panel for control of AS and FP purity/impurity can be considered acceptable. The specification limits for purity/impurity testing were considered adequate and have been sufficiently justified taking clinical batch data into account (however, regarding CE-SDS reference is made to **Recommendations 1 and 2**).

The applicant used the same ELISA to assess AS and FP potency and identity. The relevance of the assay for the vaccine's mode of action and the assay's specificity were questioned and eventually confirmed by experimental data provided by the applicant (see Analytical Procedures section). Nevertheless, the applicant was recommended to assess selectivity between alpha- and beta-strain specific epitopes (see analytical procedures section) in displacement experiments (**Recommendation 6**).

Regarding potency, new tightened acceptance criteria of relative potency (RP) for the AS was finally proposed. Manufacturing consistency, stability results from active substance/finished product, data from batches used in clinical studies and the method variability were considered in the recalculation of the potency acceptance criteria. The currently proposed acceptance criteria for potency are considered acceptable.

Analytical procedures

Biological activity by Quantitative ELISA

The ELISA, as depicted by the applicant, recognizes two different structural epitopes of the vaccine: one consists of the ACE2 binding motif of the recombinant protein, and the other one of a different, not overlapping but most probably immunologically irrelevant epitope. It was unclear if both RBD-chains of the heterodimer interact differently with ACE2, and if the proposed assay is able to detect changes or alterations of epitopes on just one chain of the heterodimer. The applicant presented further experimental data which confirmed that the assay specifically detects the dimeric structure of the immunisation antigen and that it is able to discriminate between intact and degraded active substance. Results from presented immunisation studies showed a correlation between the assay and the vaccine's mode of action, and the initial concern was considered resolved. The proposed ELISA might reflect the Mechanism of Action, but it remained unclear if the assay can discriminate between strain-specific epitopes present on both RBD-chain binding motifs of the heterodimer. As a post-authorisation commitment, the applicant will also assess the specificity of the potency assay in displacement experiments using monoclonal alpha- and beta-strain specific antibodies (**Recommendation 6**).

Quantify CHO host cell proteins

A commercially available ELISA has been validated to quantify CHO host cell proteins.

Purity of RBD fusion heterodimer – SDS PAGE

SDS-PAGE is used for the determination of the purity, product-related substances/impurities and presence of glycosylation.

RBD fusion heterodimer Quantification by SEC-HPLC

The resolution and the reproducibility of the SEC-HPLC method has been improved in order to quantify the main peak as well as high and low molecular weights peaks.

Concerning the purity and product-related impurities, 3 different orthogonal methods are in place (SEC-HPLC, SDS-PAGE (reduced & non-reduced), and CE-SDS (reduced and non-reduced). Significant

improvements of these methods have been implemented and the methods have been adequately validated.

In summary, the improved analytical methods panel for control of active substance can be considered acceptable. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Reference standards

Two process 4 batches were qualified as Primary Reference Standard (PRS) and Working Reference Standard (WRS). The analytical methods used to characterise structural attributes of the reference standard have been presented. The analysis of the batches used as Reference Standards has been included. The current Reference Standard has been qualified. New Reference Standard should comply with all tests performed at the time of AS release and with tight requirements for qualification of the antigen. The information provided on reference standards is acceptable.

Batch analysis

Results of active substance batch analyses from: 4 batches produced by process 2, 1 batch produced by process 3 and 37 active substance batches manufactured with the process 4 (commercial process) were provided. The results complied with the specification that was in-force at the time of their release and confirm consistency of the manufacturing process.

2.3.2.4. Stability

A shelf-life of six months was initially claimed for the active substance when stored at 2 ºC – 8 ºC. Stability data have been provided from the ongoing long-term ICH stability studies at 5°C ± 3°C and from the completed accelerated stability studies at 25°C ± 2°C. At this time, 9-months stability data at long-term conditions and 6-months stability data at accelerated conditions are available for the first ICH stability studies. This stability study included the Process 4 batches considered representative for the intended commercial process. An extractable study has been performed in order to detect and identify extractables substances which could be released from the primary packaging system. The levels of impurities identified in the primary packaging system extracts did not exceed the proposed limits in any case during the extractable study. Thus, there are no concerns with regard to toxicity hazard from these impurities released from the primary packaging system.

Unfortunately, all stability data were still generated with the "old" portfolio of the analytical methods which was not considered suitable for monitoring the stability of this complex recombinant protein (as discussed in the sections above). Consequently, the value of this stability data which was generated with a highly insufficient method panel was questionable as a basis for the shelf-life claim and thus this data was considered as supportive only.

The results from this initial stability study showed that all tested parameters remained within the established acceptance criteria (at that time) after 6 months of storage at 5ºC ± 3ºC whereas certain outliers were observed after 9 months storage. A decrease in purity and a concomitant increase of product-related substances/impurities was observed. Similar but more pronounced trends were observed when stored at accelerated (25°C ± 2°C) conditions with out of specification values already, after storage for 1 month. These changes in purity/impurity profile were accompanied by a drop in the biological activity of the RBD fusion heterodimer, although with values still within the acceptance criteria after three months of storage at 25°C ± 2°C. These data indicate that this protein seems to be highly susceptible to product degradation and this certainly limits the long-term storage of the active substance.

More recently, a new ICH stability studies at long-term (5°C ± 3°C) and at accelerated (25°C ± 2°C) conditions have been initiated. Three manufacturing-scale production PHH-1V active substance batches were included in this study. So far, stability data up to 6-months at both long-term and accelerated conditions are available for these new ICH stability studies. The stability results indicate a certain susceptibility of this heterodimer to degradation. Based on the results provided from these stability studies, a maximum shelf-life claim of 5 months can be supported at this point in time.

In conclusion, based on the results from the aforementioned stability studies the claimed active substance shelf life of 5 months when stored at 2 ºC – 8 ºC is considered acceptable.

2.3.3. Finished Medicinal Product - COVID-19 Vaccine (recombinant, adjuvanted), 40 µg/dose, emulsion for injection

2.3.3.1. Description of the product and pharmaceutical development

Description and composition of the finished product

One dose (0.5 mL) of the finished product contains 40 micrograms (µg) of SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion heterodimer, comprising B.1.351-B.1.1.7 strains, adjuvanted with SQBA. Other ingredients are disodium phosphate dodecahydrate, potassium dihydrogen phosphate, sodium chloride, potassium chloride and water for injections; SQBA adjuvant containing squalene, polysorbate 80, sorbitan trioleate, sodium citrate, citric acid monohydrate and water for injections. All excipients comply with European Pharmacopoeia monographs.

The finished product (FP) is formulated with an SBQA oil-in-water adjuvant. The addition of an adjuvant to the composition of Bimervax, was considered necessary in order to generate a sufficient immune response to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older following primary immunisation with an mRNA vaccine. Based on the results of the non-clinical studies conducted in mice, the adjuvant selected was 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 dose of 0.5 mL.

The vaccine is supplied as 10 doses of vaccine per vial. An overfill is carried out to ensure that the correct volume can be withdrawn from the vials for all ten 0.5 ml doses.

The container closure system is a clear, sterilised Type I colourless 5 mL glass vial, stoppered with a sterilised Type I elastomeric stopper and an aluminium seal fitted with a plastic flip-off cap. Both bromobutyl or chlorobutyl stoppers can be used. These bromobutyl or chlorobutyl stoppers are classified as Type I rubber stoppers and comply with the specifications of Ph. Eur. 3.2.9. Suppliers of the primary packaging material need to be mentioned in the dossier and replacement or addition of a supplier should be handled via an appropriate variation **(Recommendation 8)**.

The finished product is supplied in one pack size of ten multidose vials.

Pharmaceutical development

The finished product is a 40 µg/dose SARS-CoV-2 virus recombinant spike (S) protein RBD fusion heterodimer (B.1.351-B.1.1.7 strains), adjuvanted vaccine presented as a sterile, preservative-free white homogeneous emulsion for injection for intramuscular use. The active substance is formulated with a phosphate-buffered saline (PBS) solution and with SQBA adjuvant, that is 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 dose of 0.5 mL.

Three dose levels of the recombinant RBD fusion dimer antigen were tested in the first-in human (FIH) randomised, controlled, observer-blinded, dose-escalation, multicentre Phase I/IIa clinical trial HIPRA-HH-1 conducted in 30 adult healthy volunteers distributed in three cohorts of ascending dose levels of antigen: 10 µg, 20 µg and 40 µg. Higher levels of binding antibodies were observed in subjects vaccinated with PHH-1V vaccine with an antigen dose of 40 µg, and a similar trend was observed for the levels of neutralising antibodies and T-cell response. These observations, together with the good safety and tolerability obtained for this higher antigen dose in terms of both local and systemic effects, supported the selection of PHH-1V with an antigen dose of 40 µg for further clinical development. Based on available interim results of the HIPRA-HH-2Phase IIb trial, the immunogenicity and safety of the selected dose of 40 µg/dose and PHH-1V formulation against VoCs was confirmed: PHH-1V showed a good safety profile and induced high neutralising levels against the D614G strain VoC and an improved immunogenicity response against Beta and Omicron variants compared to the comparator group. The Delta variant showed a non-inferior response to Comirnaty.

The adjuvant selected for Bimervax finished product formulation is an SQBA adjuvant. The adjuvant fraction in PHH-1V FP represents about a 50 % v/v of the final composition of the vaccine. The buffer selected for PHH-1V FP formulation is PBS solution.

The finished product material manufactured by previous manufacturing process 1, 2 and 3 was no longer available, which precluded a full new head-to-head analytical comparison using an improved analytical portfolio. No formal comparability study was performed to assess the impact on quality, efficacy and safety of the changes introduced in the manufacturing process of the PHH-1V FP due to the upscaling. Nonetheless, the applicant has conducted a retrospective analysis by comparison of all data available from material derived by the different processes. A comparability evaluation of the PHH-1V FP was primarily based on a comparison of batch release data. Data of all controlled parameters showed similar values within the three different manufacturing processes or low variability that can be associated with the inherent variability of the concerned analytical methods. A syringe extraction study to simulate the withdrawal of ten vaccine doses as the worst case has been conducted.

An in-use shelf life of 6 hours for PHH-1V vaccine at 2 ºC-8 ºC from the time of first needle puncture to administration has been demonstrated.

Finished Medicinal Product - SQBA adjuvant, emulsion for injection

Description and composition of the finished product

The SQBA adjuvant for Bimervax 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.

Pharmaceutical development

The SQBA adjuvant is a squalene-based adjuvant included in the formulation of Bimervax, whose qualitative and quantitative composition (9.75 mg squalene; 1.175 mg polysorbate-80; 1.175 mg sorbitan trioleate; 0.66 mg sodium citrate and 0.04 mg citric acid monohydrate per vaccine dose).

All components are compendial substances. No formal comparability of the SQBA adjuvant derived from a small scale (process 1) and the commercial scale (process 2) was performed. A summary of differences in the manufacturing process versions for the SQBA adjuvant was included and it is agreed that these differences are not expected to lead to any changes in the quality profile of the SQBA adjuvant. In addition, a statistical comparison of variability of SQBA adjuvant manufacturing process 1

versus process 2 has been performed. Results confirm the comparability of both processes as all parameters analysed for SQBA adjuvant batches produced with either Process 1 or 2 are within the mean ± 3SD.

Manufacturers

Appropriate valid GMP certificates have been provided for the manufacturer of the SQBA adjuvant.

Description of manufacturing process and process controls

The SQBA adjuvant is manufactured using standard manufacturing activities such as mixing, sterilising filtration, homogenization, and filtration. There is neither filling, stoppering nor storage of the SQBA adjuvant as the manufacturing process of Bimervax FP is designed as a continuous process.

Similarly to the manufacturing control strategy of the active substance discussed in the active substance section, the manufacturing control strategy for the SQBA adjuvant has been revised based on QTTP and CQAs to demonstrate that the manufacturing process is robust and capable of consistently leading to SQBA adjuvant with the defined quality attributes. New IPCs have been introduced and results of IPCs from new batches manufactured with this updated control strategy were submitted. The data provided demonstrated that the SQBA manufacturing process is robust and reproducible.

Process validation and/or evaluation

Initially, the applicant provided only lists of critical steps, process parameters and IPCs. No information was provided on CQAs, if and how they were identified, and how different manufacturing steps could impact on them. Even the composition of the adjuvant and its stability throughout the manufacturing process were not considered critical. IPCs were listed, but it was not explained how they are able to control quality of the finished product. Proposed acceptance ranges for process parameters and IPCs were extremely broad.

With the responses the proposed acceptance ranges for process parameters and IPCs have been tightened and are acceptable. The data presented is sufficient to confirm that the manufacturing process is able to deliver adjuvant with consistent quality.

Specification

The specifications for the SQBA adjuvant used in the production of Bimervax include general tests for appearance, pH, viscosity, particle size, squalene identification, squalene content, total emulsifying agents, purity/impurities, sterility and endotoxins.

The proposed specifications for the SQBA are considered acceptable. The characterisation of impurities includes the carbonyl content and potential extractables and leachables from the sterile single-use bag (biocontainer). The components of the SQBA adjuvant namely squalene, polysorbate 80 and sorbitan trioleate contain alcohols and/or double bounds in their structures that can be oxidized to carbonyl groups (C=O) forming oxidation products and therefore are controlled at the level of the SQBA adjuvant as well as at the level of the vaccine finished product. This is endorsed.

Reference standards

For squalene, polysorbate 80 and trioleate information on primary reference standards, storage and stability monitoring have been provided and is acceptable.

Container closure

SQBA adjuvant is packed in sterile single-use bag until its use for Bimervax finished product production.

Stability

A maximum holding time in the sterile single-use bag until its use for PHH-1V vaccine production has been demonstrated.

2.3.3.2. Manufacture of the product and process controls

Manufacturers

Valid GMP certificates were provided for the different sites involved in the manufacturing of the finished product.

Description of manufacturing process and process controls

Bimervax, COVID-19 vaccine (PHH-1V) is manufactured using standard manufacturing steps such as mixing and homogenisation of vaccine components, sterilising filtration, aseptic filling, capping, labelling and secondary packaging.
Briefly, the active substance RBD fusion heterodimer is added 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 to obtain the vaccine bulk. No reprocessing activities are considered for the finished product production.

Process validation and/or evaluation

The manufacturing process of the Bimervax finished product is carried out under aseptic conditions. Validation studies on the manufacturing process of PHH-1V vaccine with have demonstrated that the PHH-1V finished product manufacturing process is robust and capable of consistently leading to a PHH-1V FP vaccine that complies with the defined quality specifications.

The following points have been considered with the scope of the validation of PHH-1V FP manufacturing process:

- Media fills for validation of aseptic processing
- Validation of the PHH-1V manufacturing process
- Filter validations for filters used during PHH-1V manufacturing process
- Validation of bioburden testing
- Validation of sterility testing
- Validation of bacterial endotoxins testing
- Shipping validation studies

It should be noted that these validation studies were performed before the implementation of the updated control strategy of PHH-1V FP and SQBA adjuvant and hence, some of the control strategy proposals currently implemented were not included or assessed in those validations. Therefore, the applicant has informed that, as a result of the recently improved control strategy including the addition

of several IPCs and PPs, a complementary validation of the whole manufacturing process is currently on-going. This is accepted.

2.3.3.3. Product specification

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, container closure integrity test, visible and sub-visible particles and extractable volume.

A Major Objection was raised on the analytical portfolio applied to control the active substance and finished product. The applicant was asked to improve its analytical portfolio for release and shelf-life assessment to include validated state of the art methods to assess CQAs at the finished product levels, namely identity, potency, charge-variants, glyco-variants (consistency of glycosylation regarding side occupancy, amounts and structures), size-variants, degradation products and excipients (polysorbate 80 and sorbitan trioleate at the FP level). As discussed in the active substance section, the applicant improved the analytical portfolio used for AS and FP release and shelf-life determination. The methodological portfolio has been updated to control all the CQAs. Clinical material and especially its impurity profile were tested against the specifications valid at the time point of release by applying not fully validated methods, and thus not by applying the improved methodological portfolio. The following methods have been developed, validated and implemented to improve control of PHH-1V finished product at release and shelf-life:

1. Identification of RBD fusion heterodimer by peptide mapping using RP-HPLC-UV.

2. Control of product related substances and impurities using three different orthogonal methods: SDS-PAGE, CE-SDS and SEC-HPLC.

3. Control of charge variants by capillary isoelectric focusing (cIEF).

4. Thermal shift analysis (TSA) to confirm the intactness and proper structure of the RBD fusion heterodimer.

5. Determination of carbonyl content using a potentiometric method as indicator of oxidative processes of the components of the adjuvant.

6. Control of excipients as total emulsifying agents (polysorbate 80 (PS80) and sorbitan trioleate).

Peptide mapping was added as a method for assessment of identity, in combination with the already proposed methods ELISA and SEC-HPLC. This was endorsed, and AS and FP identity assessment is considered acceptable. The methodological portfolio to assess AS and PF purity, variants and impurities was improved by adding to the already proposed methodological portfolio SDS-PAGE under reducing conditions, charge variants by cIEF, and CE-SDS under reducing and non- reducing conditions.

The applicant implemented a thermal shift assay (TSA) to overcome potential limitations of the described ELISA to assess AS and FP potency. The proposed TSA assay was not considered a quantitative assay, nor it is specific for the mechanism of action of the vaccine. Thus, it did not contribute to the assessment of potency, but it would complement the methodological portfolio used to assess AS and FP integrity and its shelf-life. Thus, the implementation of the TSA assay as a supplementary, general test was proposed by the applicant to control AS and FP purity for release and shelf-life determination. A TSA has been included as general test at release and shelf-life specification of the AS and FP in order to confirm the correct structure of the heterodimer.

Regarding potency, new tightened acceptance criteria of RP for the FP were proposed. Manufacturing consistency, stability results from active substance/finished product, data from batches used in clinical studies and the method variability were considered in the recalculation of the potency acceptance criteria. The currently proposed acceptance criteria for potency are considered acceptable.

Carbonyl content as a stability indicating parameter was only being determined in the adjuvant and for the finished product at release and was not being assessed for shelf-life determination. Following responses, the carbonyl content is currently included in the specifications for release and shelf life. All the stability results obtained from three finished product batches show that the carbonyl content in finished product is below the acceptance limit. This is acceptable.

Initially the applicant did not have an analytical method able to separately get insight into PS80 and sorbitan trioleate concentrations in the adjuvant and at finished product level. The proposal to quantify both compounds as IPC's before being mixed together and filtrated, and the control of combined levels in the finished product was not considered acceptable, especially because further manipulation steps could affect PS80 and sorbitan trioleate levels in the finished product differently. The applicant provided finished product release and shelf-life data from a suitable number of representative FP batches and committed to substitute the current method for the combined assessment of PS80 and sorbitan trioleate by analytical method(s) enabling separate quantification of PS80 and sorbitan trioleate. This was considered acceptable **(Recommendation 4).**

In compliance with applicable regulations, a risk evaluation concerning the presence of nitrosamine impurities in the PHH-1V finished product has been conducted considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). 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.

In addition, elemental impurities risk assessment has been performed in accordance with ICH Q3D Guideline for Elemental Impurities. According to the results obtained in this evaluation, the predicted levels of elemental impurities under evaluation are below their control threshold. Therefore, it is not necessary to implement additional actions to ensure the PDE is not exceeded. The information on the control of elemental impurities is satisfactory.

Analytical methods

The presented set of analytical methods was considered sufficient to control the FP. Performance of the compendial methods in the respective FP-matrix was confirmed, and validation of product and process specific analytical methods sufficiently addressed in this and in the respective AS and adjuvant sections of the dossier.

An overview of the analytical procedures used for the Bimervax FP product as well as validation data for the analytical procedures have been provided. Method validation has been described for all non-compendial methods. The following analytical procedures have not been validated due to either being regarded as a compendial test (i.e., pH, osmolality, visible particles, extractable volume) or a technically simple analytical method (i.e., appearance, viscosity, particle size). Hence, no validation of the aforementioned analytical procedures is regarded as necessary. Nonetheless, it should be noted that although the general tests intended for the microbiological control (i.e., sterility and bacterial endotoxins) of the finished product are compendial tests, respective validation data were provided.

The suitability and applicability of the proposed compendial methods was confirmed and established with the FP matrix.

Batch analysis

Thirteen finished product batches have been manufactured at the commercial site and at the proposed commercial scale according to the commercial manufacturing Process 4 and filled in the proposed container closure system. The batch results provided are within the specifications and confirm the consistency of the manufacturing process.

Reference standards

Reference standards used for the control of squalene in the Bimervax finished product are the same standards used for the control of the adjuvant batches.

The same reference antigen standard used for the control of the active substance is used for the determination of recombinant protein receptor binding domain (RBD) fusion heterodimer and its biological activity in the Bimervax vaccine.

2.3.3.4. Stability of the product

A shelf life of 1 year when stored at 2°C – 8°C, protected from light, is claimed for the Bimervax finished product.

HIPRA has initiated an ICH stability study with primary batches fully representative of the manufacturing-scale production of Bimervax finished product. Long-term stability studies at 5°C ± 3°C are ongoing and accelerated stability studies at 25°C ± 2°C / 60% ± 5% RH have been completed with three GMP FP batches manufactured at the proposed commercial scale and in the proposed commercial manufacturing site and packaged in the proposed commercial container closure system.

12 months data from the ongoing ICH long-term and accelerated stability studies with three finished product lots representing the final commercial material are available. All results from the long-term stability study are within the acceptance criteria. The analytical portfolio for the finished product specifications has been recently extended. In this context, finished product batches under long-term stability have been tested with the complete validated analytical portfolio at after 9, 10, 11 and 12 months storage for two batches and after 8, 9, 10, 11 and 12 month storage for the third one.

Direct exposure to Ultraviolet (UV) light led to degradation of the protein; thus, protection from light is required for the storage of the finished product.

Based on the data a shelf-life claim of 1 year when stored at long-term storage condition 2°C – 8°C can be agreed. Chemical and physical in-use stability has been demonstrated for 6 hours at 2°C – 8°C from the time of first needle puncture. From a microbiological point of view, after first opening (first needle puncture), the vaccine should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Of note, the applicant missed to set the finished product vials in the inverted position in the first primary stability studies. A new stability study with finished product batches in the inverted position has been started very recently; however, currently no stability data from vials stored in the inverted position are available. Considering that the container closure components (Type I glass vials and rubber stoppers) comply with the respective Ph. Eur. monographs, no increased risk for the quality of the finished product stored in the described container closure system is expected. Nevertheless, the applicant is recommended to provide available stability data (including from vials stored in the inverted position) in a timeline of 3 months after the granting of the MA. **(Recommendation 3)**.

2.3.3.5. Adventitious agents

Transmissible Spongiform Encephalopathy / Bovine Spongiform Encephalopathy

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.

Viral safety

Master Cell Bank, Working Cell Bank (WCB) and Extended Cell Bank have been characterized. The protocol to establish new WCBs raise no concern. All unprocessed bulks will be tested for mycoplasma and adventitious viruses. This is acceptable.

The data on viral reduction studies which were performed with 4 model viruses in duplicate runs, show a safety margin that is considered sufficiently reassuring of the viral safety of the product.

In summary, the adventitious agents safety evaluation is considered acceptable.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The documentation initially included in the application dossier was overall considered to be insufficient to support the application for Bimervax (COVID-19 vaccine (recombinant, adjuvanted)) and a number of Major Objections and other concerns were identified during the procedure.

The major deficiencies identified during the procedure were summarised as follows:

- A first group of deficiencies related to the portfolio of the analytical methods which were considered insufficient for release testing of the active substance and the finished product, to assess its stability, and to compare products from different versions of the manufacturing process. The initial proposed panel of tests did not reflect the complexity of the molecule. The applicant only partially assessed the active substance physico-chemical and biological characteristics, and thus many CQAs were not adequately identified. The product QTPP and resulting CQAs were only taken into account very late in the development. Consequently, the proposed control strategy also did not focus on CQAs, and was largely insufficient. There was no link between the required finished product quality and the performance of the proposed manufacturing steps.

- The second group of deficiencies were related to the manufacturing control strategy of the active substance, the finished product and the adjuvant. The proposed strategy to also control the product-related variants/impurities was considered to be insufficient. During the procedure, the applicant was requested to implement suitable methods for the control of product-related variants/impurities.

- The third group of deficiencies were related to the control of viruses and host-cell proteins (HCP). Important virus safety measures like cell line qualification, bulk harvest testing and virus reduction validation were initially not in place and the manufacturing process (especially the downstream process) lacked the typical sequence of robust virus reduction steps, expected to be implemented in the manufacturing processes for biologics for human

medicines. Robust HCP reduction steps were also not in place as required. Therefore, the applicant was requested to prepare a risk assessment based on the outcome of the qualitative HCP assessment. The applicant was further asked to evaluate the potential impact of an induced HCP-specific immune response in light of treatment options with other therapeutic proteins.

- The purity of the active substance, including viral safety, was not considered appropriate: only two chromatography steps as proposed by the applicant were insufficient for the active substance to reduce process related impurities and product related impurities to acceptable levels. The specification of acceptable impurity levels at critical steps of the manufacturing process, which would ensure achieving the targeted quality profile, were initially not defined or not assessed at all. The active substance of the vaccine is a recombinant protein combining in a synthetic single molecule two different variants from the Spike-protein RBDs. It is a complex, post-translationally highly modified and relatively unstable recombinant protein. Nonetheless, initially the active substance was not characterised in depth, and there was no follow-up on the various impurities identified which were classified by the applicant as non-critical without providing any (experimental or clinical) justification.

- The proposed portfolio of active substance and finished product release and stability analytical methods was insufficient and many tests were not considered state of the art. The stability testing panel did not cover the most important quality attributes impacting on product safety and efficacy. The proposed potency-assay seemed only marginally related to the mechanism of action and its specificity/selectivity towards the RDB fusion protein was questionable. An adequate comparability evaluation of products manufactured by different versions of the manufacturing process was not possible as changes were implemented to critical manufacturing steps within one version of the manufacturing process, without any follow-up. Demonstration of comparability between processes was critical to ensure that the clinical data generated with previous processes can be considered representative of the commercial process.

Following several rounds of questions, sufficient data was generated and additional information and justifications were provided. Samples from the previous manufacturing processes were not available and therefore a direct comparison of the different manufacturing processes was not possible. Also, as the product QTPP and resulting CQAs were taken into account very late in the development process, the applicant justified the acceptance criteria in a holistic way as follows: a comparability evaluation at quality level focusing on the biological relevance of the observed differences and their potential impact on safety and efficacy. The comparability evaluation at the quality level was amended with a non-clinical comparability exercise including a specific bridging study as well as a comparison of data from different clinical trials using batches manufactured from different manufacturing processes (please refer to the active substance process development section for more information).

The applicant has introduced a number of improvements to the analytical methods portfolio and included the following additional methods and control parameters: identification of RBD fusion heterodimer by peptide mapping using RP-HPLC-UV; control of product related substances and impurities using three different orthogonal methods: SDS-PAGE, CE-SDS and SEC-HPLC; control of charge variants by capillary isoelectric focusing (cIEF); TSA to confirm the intactness and proper structure of the RBD fusion heterodimer; determination of carbonyl content using a potentiometric method as indicator of oxidative processes of the components of the adjuvant; control of excipients as

total emulsifying agents (polysorbate 80 (PS80) and sorbitan trioleate); Peptide mapping was added as a method for assessment of identity, in combination with the already proposed methods ELISA and SEC-HPLC.

The introduced changes to the portfolio of active substance and finished product release and stability analytical methods was considered to be sufficient and now covers important quality attributes impacting on product safety and efficacy. The manufacturing control strategy of the active substance, the finished product and the adjuvant is now considered acceptable. With the responses, the control strategy of the active substance manufacturing process was substantially improved. PP and IPCs for Process 4 (commercial process) for the upstream and downstream processes were further discussed and described taking into account the data on the QTPP and/or CQAs.

The deficiencies relating to viral and HCP safety have been appropriately addressed. The active substance and its purity profile has been characterised, and appropriate active substance and finished product release and stability specifications for purity, impurities and HCP have been set.

GMP post-authorisation inspections have been recommended and adopted by CHMP to be performed as soon as possible in order to confirm GMP compliance of the manufacturing sites that have recently implemented changes in the methods and manufacturing processes in the dossier.

Overall, the provided documentation to support the marketing authorisation application of Bimervax can be considered acceptable to address the quality of the active substance, the adjuvant and finished product in a satisfactory way.

The applicant has agreed with the CHMP to address a number of outstanding issues post-approval as follows: with regard to: the CE-SDS-DG-R method and its resolution (REC1); active substance and finished product specifications revision when additional batch data from 15 commercial AS and FP batches is available (REC2); additional finished product stability data (REC3); replacement of the current method for the combined assessment of PS80 and sorbitan trioleate by analytical method(s) enabling separate quantification of PS80 and sorbitan trioleate (REC4); complementary data in order to update the current active substance manufacturing process validation with the recently additional controls for the AS manufacturing process (REC5); the specificity of the potency assay in displacement experiments using monoclonal alpha- and beta-strain specific antibodies (REC6), an in-depth characterisation of the qualitative HCP profile (REC7) and suppliers of the primary packaging (REC8).

2.3.5. 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. Data has been presented to give assurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. For CE-SDS-DG-R, the applicant is recommended to identify the 2 identities in the major peak, as well as the 3 peaks related to product degradation of the active substance within 6 months of MA (from MO5).

2. For CE-SDS-DG-R, the applicant is recommended to revise the active substance (AS) and finished product (FP) CE-SDS-DG-R specifications after 15 commercial AS and FP batches have been manufactured.

3. The applicant is recommended to provide available finished product stability data (including from vials stored in the inverted position) within 3 months after the granting of the MA. In case of any significant trends observed in the ongoing and/or in the newly started stability studies (even if the stability results are within the shelf-life specifications) the applicant is recommended to inform the Agency and to provide a discussion and justification for this trend.

4. The applicant is recommended to substitute the current method for the combined assessment of PS80 and sorbitan trioleate by analytical method(s) enabling separate quantification of PS80 and sorbitan trioleate within 6 months after the granting of the MA.

5. The applicant's proposal to submit within 4 months after the marketing authorisation, additional and complementary data in order to update the current AS manufacturing process validation with the recently additional controls of the manufacturing process is endorsed.

6. The applicant is recommended to assess within 6 months after the granting of the MA, the specificity of the potency assay in displacement experiments using monoclonal alpha- and beta-strain specific antibodies.

7. An in-depth characterisation of the qualitative HCP profile of the AS should be performed in 2 months after the granting of the MA. A risk assessment based on the outcome of the qualitative HCP assessment should be included, in view of the potential impact of an induced HCP-specific immune response on further treatment options with other therapeutic proteins. Independently of their abundance, all identified HCPs should be classified (depending on their biological, cellular component and molecular function) and further described regarding their potential risk.

8. Suppliers of the primary packaging material should be mentioned in the dossier and replacement, or addition of a supplier should be handled via an appropriate variation.

2.4. Non-clinical aspects

2.4.1. Introduction

Bimervax or PHH1V consists of purified recombinant SARS-CoV-2 RBD heterologous dimer fusion protein derived from B.1.1.7 (alpha) and B.1.351 (beta) variants 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 dose of 0.5 mL. The vaccine is intended to boost immunogenicity in adults vaccinated at least 6 months before with mRNA or adenovirus vaccines in a homologous or heterologous primary vaccination to prevent COVID-19 caused by SARS-CoV-2 virus, following a single 0.5 mL intramuscular dose (40 µg recombinant RBD antigen and 50% (v/v) SBQA).

The mechanism of action of SBQA adjuvant is well described in the literature based on SQBA analogous 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 dose of 0.5 mL , including induction of chemokines for local recruitment of immune cells and enhanced antigen uptake by monocytes at the injection site, and enhanced monocytes differentiation into dendritic cells. The fixed 1:1 ratio of SBQA : RBD dimer in the PHH1 formulation was tested and an optimal ratio of adjuvant : antigen has not been explored.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The nonclinical pharmacology of PHH1V or PHH1V has been evaluated in 3 challenge models and in 6 immunogenicity studies using different doses of antigen ranging from 0.04 µg to 40 µg, formulated with SBQA adjuvant (v/v 50%). In general, a prime-boost regimen was used and the vaccine was administered intramuscularly (i.m.) at Day 0 and Day 21 of each study.

Challenge models

A challenge study in Cynomolgus monkeys (27-31 months of age) receiving 2 doses (40 µg) of PHH1V vaccine showed a strong effect against SARS-CoV-2 virus challenge (strain D614G, 2 x 106 PFU/animal, intranasal + intratracheal route on Day 36), including the prevention of infective virus load in lungs, a clear control of the infectious virus replication in the upper respiratory tract, as well as a prevention on bronchointerstitial lung inflammation at 6 days post challenge. In sera of vaccinated monkeys, not only the SARS-CoV-2 RBD-binding IgG antibodies, but also significantly high serum microneutralizing antibody titres against D614G, alpha, beta, gamma, delta and omicron SARS-CoV-2 variants, were elicited at Day 28 of the study. In addition, vaccination with PHH1V induced an activation of CD4+ and CD8+ T cells (Day 28) after re-stimulation with alpha + beta peptide mix or Omicron peptides, denoting overall a balanced Th1/Th2 response and the secretion of RBD-specific IgA in low respiratory airways (Day 28), which increased after the SARS-CoV-2 experimental infection (Day 42). The IgA supportive results were obtained using non-validated ELISA assay that enables to quantify BAL samples in a precise and linear manner.

Similarly, a challenge study in Golden Syrian hamsters (5-6 weeks old) vaccinated with 20 µg or 40 µg PHH1V dose demonstrated the efficacy of the vaccine against experimental infection with SARS-CoV-2 virus (SARS-CoV-2 Cat02 strain, 103.97 TCID50/animal, intranasal route on Day 35). Both doses of PHH1V vaccine reduced the infective viral load in lungs and elicited comparable SARS-CoV-2 RBD-binding IgG response at Days 35, 37, 39 and 42. However, relative to 20 µg dose, vaccination with 40 µg of PHH1V elicited the highest neutralizing antibody titres against D614G strain at Days 35 and 37 of the study, and provided a significant reduction in body weight loss and a better recovery of animals after challenge, and could also reduce the infective viral load and lesion severity in the upper respiratory. It is noteworthy that the results of viral titration and histopathology analysis of lungs of the vaccinated animals do not indicate the enhancement of respiratory disease associated with vaccine in this model.

The challenge study conducted in the humanized K18-hACE2 mice model (4-5 weeks old) found that vaccination with PHH1V vaccine (10 µg or 20 µg) conferred strong protection against the SARS-CoV-2 infection (SARS-CoV-2 Cat02, 103 TCID50/animal at Day 35), when assessed by weight loss or clinical signs (including mortality), infective viral load in main target organs (i.e. lungs, nasal turbinates and brain) as well as excretion of virus measured in the oropharyngeal swabs. Differences in viral load after experimental infection between vaccinated animals and control animals were also found in other respiratory (trachea, pharynx) or systemic (spleen and heart) organs. Moreover, in vaccinated animals, histopathological evaluation of lungs, nasal turbinates or brain showed no more than mild lesions after SARS-CoV-2 infection. Whereas moderate lesions were found in lungs and brain of some control animals, in line with high viral loads detected. In this study, PHH1V vaccinated animals showed significantly higher SARS-CoV-2 RBD-binding antibodies titres, and neutralizing titres against D614G strain at Days 35, 37 and 39, without significant difference between the 10 µg and 20 µg dose groups.

Taken together, PHH1V vaccine demonstrated immunogenic and its protective efficacy has been shown in three different models, including non-human primates (NHP). The applicant explained that division

of injection volumes between extremities in rodents is a common practice and has not been reported to have a negative impact on the animal's immune response. The applicant further explained that the negative serology immunological status (pre-vaccination) of animals used in these pharmacology studies was based on the fact of their breeding in isolated facilities and handling under barrier conditions, rather than serology testing pre-vaccination.

Immunogenicity studies

Two immunogenicity studies were performed in BALB/c mice (6-7 weeks at 1st vaccination) demonstrating a dose-dependent immunogenicity of PHH1V, including induction of SARS-CoV-2 RBD-binding IgG, neutralizing antibodies, and cellular immune responses. Neutralizing antibodies were elicited in mice with antigen doses as low as 0.2 µg at Day 21 and Day 35/Day 37 of the study. Vaccination with 20 µg PHH1V elicited pseudovirus-neutralizing titers (at Days 35 and 37) against alpha, beta, gamma and delta variants, orD614G strain, as well as a robust activation of CD4+ and CD8+ T cells (at Days 35 and 37) producing an RBD-specific Th1-dominant response after in vitro re-stimulation, and a balanced Th1/Th2 cytokines production until 48 hours post-stimulation, when analyzed in the intracellular cytokine staining (ICS) and ELISPot assays. Of note, in one study, the 20 µg vaccine dose (formulated with SQBA) was found efficient to induce saturated immune response, with no beneficial effect seen for addition of monophosphoryl lipid A (MPLA) or QS21 as immunostimulants to the vaccine formulation.

The immunogenicity of PHH1V was further demonstrated in three pig studies (8-9 weeks old). In addition to induction of SARS-CoV-2 RBD-binding IgG response, high titers of neutralizing antibodies were observed on Day 38 or Day 35 in two pig studies using 20 µg PHH1V dose and no dose-response effect in terms of neutralizing antibodies observed for the 10 µg, 20 µg and 40 µg vaccine doses in the third study. From the third pig study, broader cross-neutralizing antibody titres in sera of the vaccinated pigs were evident on Days 28, 35 and 42 of the study, against multiple SARS-CoV-2 Variants by the pseudovirus-based neutralization assays (PBNAs), including D614G strain, and alpha, beta, gamma, delta, delta plus, Mu and Omicron variants. The applicant provided evidence for detectable PBNA titers against alpha variant strain after first vaccination in some animals, but overall no data was reported of neutralizing antibodies against gamma, delta and omicron after one dose of vaccine.

Similarly, studies in pig model also revealed effect of PHH1V vaccine on cellular immune response in animals receiving 10 µg, 20 µg, or 40 µg dose, when analyzed on Day 35 and Day 42, and the analysis of the ratio IgG2a/IgG1 indicates a balanced Th1/Th2 response to SARS-COV-2 commercial RBD peptide pools of SARS-CoV-2 D614G strain sequence.

Additionally, a separate immunogenicity study in female Cynomolgus monkeys (30-35 months of age) showed that vaccination with 2 doses of PHH1V, at 20 µg or 40 µg, induced high levels of RBD binding IgG response and PBNA neutralizing antibody titres against pseudoviruses containing the SARS-CoV-2 variants of alpha, beta, gamma, and delta variants, on Days 29 and 36 of the study, and no significant differences were observed between the two tested doses. Neutralizing antibody titres against SARS-CoV-2 variants slightly decreased on Day 65, but were maintained stable until the end of the study (Day 84). The PBNA data from challenge study in NHP showed that all animals developed high titers against gamma variant and some animals started to develop neutralizing antibodies against the Omicron variant after the first dose of vaccine.

To sum up, results of these immunogenicity studies demonstrate that PHH1V vaccine, built on the fusion heterodimer RBDs of the B.1.1.7 (Alpha) and the B.1.351 (Beta) variants, is immunogenic and can elicit a cross-reactive response against different Variants of concern in different animal species including mice, pigs and NHPs.

2.4.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed with PHH1V vaccine, which can be acceptable, according to the applicable regulatory guidelines.

2.4.2.3. Safety pharmacology programme

Considering the nature of the PHH1V (local administration by i.m. route with limited systemic exposure) and the available nonclinical data, an effect on physiological functions (CNS, respiratory, cardiovascular, renal functions) other than the immune system are not expected. Still, FOB assessments were included in the GLP repeat dose toxicity studies AC25AA in mice (using PHH1 vaccine) and AC91AA in rats (using PHH1V vaccine). No other safety pharmacology assessments are planned, which is considered acceptable according to current guidelines.

2.4.2.4. Pharmacodynamic drug interactions

No studies on the pharmacodynamics drug interactions have been performed, which is in accordance with applicable guidelines.

2.4.3. Pharmacokinetics

In accordance with WHO guidelines on non-clinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), traditional absorption, distribution, metabolism, and excretion (ADME) evaluations are not generally needed for vaccines. The safety concerns associated with vaccines are generally not related to the pharmacokinetics but are related to the potential induction of immune response.

No PK studies were performed to assess the absorption, distribution, metabolism or excretion as well as the biodistribution and persistence of PHH1V vaccine or the SBQA adjuvant.

It is expected that the recombinant protein is degraded to small peptides and individual amino acids. In addition, several studies available in the literature address the distribution of MF59C.1 (equivalent to SQBA adjuvant) when administered i.m. to mice as part of a vaccine and show that the majority of the adjuvant is retained at the administration site before clearance and some distribution to other tissues. Additional non-clinical studies to assess the PK of the adjuvant are not deemed necessary, considering that MF59C.1 is recognised as an established adjuvant and it is already approved for use in other vaccines by the same route of administration. This is aligned with the applicable regulatory guidelines.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

No single dose toxicity studies were performed by the applicant, which is in accordance with applicable guidelines.

2.4.4.2. Repeat dose toxicity

The applicant conducted two pivotal GLP-compliant repeat-dose toxicity studies with PHH-1V adjuvanted with SBQA, one study in Sprague Dawley (SD) rats and one study in New Zealand White (NZW) rabbits. In both studies, three doses of the vaccine candidate were administered via the intramuscular route, the clinical human route. In general, both toxicity studies were adequately designed including sufficient animal numbers per study group. An adjuvant-only study group was not

included in these toxicity studies. This is acceptable because SBQA is comparable with the adjuvant MF59C.1 that is included in already approved products.

In both PHH-1V toxicity studies, the animals were treated with 40 µg antigen per dose with 50% SBQA of the total vaccine volume, equivalent to the human clinical dose. However, only in the rabbit study, the full human dose volume of 0.5 mL/dose was administered to the study animals. In the rat study, the 40 µg antigen were administered only in a 0.1 mL dose, the maximum possible volume for those animals. Thus, lower amount of SBQA was administered into the rats. Overall, three intramuscular doses of 40 µg PHH-1V adjuvanted with SBQA were well tolerated in rabbits and rats. No mortalities or unscheduled deaths occurred in both studies. Furthermore, no remarkable differences in body weight gain, grip strength and sensory reactivity were observed in the animals. However, the mean body temperature was slightly higher after the first and third dose of PHH-1V in rats compared to the control group. In contrast, no difference of mean body temperature was observed in rabbits between vaccinated and control groups. In both animal models, slight, transient local reactions at the injection sites were observed after vaccination with PHH-1V, such as swelling of the skin in rats and slight erythema in rabbits. These findings were not severe and are typical for adjuvanted vaccines. The haematology parameters were within the normal range in rats and rabbits. However, significantly higher eosinophil levels were observed in rats of the PHH-1V group, which only partly recovered. In addition, a transient increase in fibrinogen levels was observed in rats. In contrast, no remarkable changes were observed in haematology and coagulation parameters in rabbits during the study. In clinical chemistry analysis, a slight transient increase in globulin and decrease in albumin levels were recorded in rats and rabbits of the PHH-1V group at the end of the treatment period. These alterations could be related to the expected antibody generation, increased production of inflammatory cytokines and/or post-administration inflammation process after vaccination with PHH-1V. Remarkable vaccine-related organ weight changes were not observed in PHH-1V treated animals. However, only incidental slight differences were reported, such as greater kidney weights in female rats, lower weight of prostate and right mandibular gland in male rabbits. In addition, focal inflammation and fibroblastic proliferation were found in the subcutis at the injection sites of most male and female rabbits from the main PHH-1V group, which recovered only partly. Additionally, few animals had minimal to slight, multifocal inflammatory infiltrates into the skeletal muscle adjacent to the injection site associated with minor myofiber necrosis.

In addition, two pilot non-GLP toxicity studies with PHH-1V have been conducted. One pilot toxicity study was conducted in rabbits via the intramuscular administration route with 40 µg antigen/dose. The other study was performed in mice via the subcutaneous and intramuscular routes with different amounts of antigen (40 µg, 20 µg, 10 µg, 5 µg, 0 µg) at four doses. In general, the animals well-tolerated the vaccine. However, all rabbits of the pilot study suffered from encephalitozoon cuniculi infection and showed several adverse findings in different organs. Nevertheless, vaccine-related severe findings were not observed in the study animals.

Moreover, the applicant conducted a GLP-compliant repeat-dose toxicity study in CD-1 IGS mice with SBQA-adjuvanted PHH-1, a COVID-19 vaccine from the same vaccine platform as PHH-1V but specifically designed against the D614G strain. This study is only of supportive character. The mice were vaccinated intermuscular with three doses of 50 µg antigen in 0.1mL (0.05 mL for each injection site). Four PHH-1 vaccinated mice died shortly after vaccine administration. One female died after the first dose, another female after the second dose and two males after the third dose. Before these mice died, the two males showed cyanosis, dyspnea, and prostration. After the third dose, two other male mice of the PHH-1 group showed transient abnormal behaviour, such as cyanosis, reduced activity, hunched back, abnormal gait, partially closed eyes, spasms and circling. The female mouse that died after the first dose showed no relevant macroscopic findings. However, the deaths of both males and that of the other female might be due to a drug-induced anaphylactic reaction. These three animals

showed acute petechiae in the cerebellum together with acute congestion. Furthermore, anti-IgM and anti-IgG immunohistochemistry of the kidneys showed an increased thickening of the glomerular basement membranes from IgG deposits in treated mice compared to controls, which indicated the presence of circulating immunocomplexes associated with a type-III hypersensitivity immune reaction. In the remaining mice, no significant differences were observed compared to control mice regarding food consumption and body weight gain. However, higher body temperature and swollen skin at the injection sites were observed in the animals after every PHH-1 administration. The laboratory biochemistry parameters showed few alterations but they were still in a normal range. After the third PHH-1 dose, a significant increase in globulin levels was observed in vaccinated mice that could be related to the expected antibody generation after adjuvanted vaccine administration. Moreover, increased adrenal gland weight, increased spleen weight and decreased liver weight were observed in the PHH-1 group. At end of recovery, lower values in absolute brain weight were observed in males of the PHH-1 group. In addition, significantly higher values in absolute prostate weight was found in vaccinated males and significantly lower weight values of mandibular and sublingual glands were found in vaccinated females. At the end of the treatment, enlarged iliac and renal lymph nodes were observed in the PHH-1 treatment group, and few vaccinated mice showed abnormal coloration of stomach tissue. After the recovery period, some vaccinated mice still showed redness in different parts of the intestine, dark and reddish coloration in the mesenteric lymph nodes, reddish right uterine horn and/or pale liver. Although, PHH-1 caused these severe anaphylactic reactions in mice, which resulted even in few deaths, similar allergic reactions were not observed for PHH-1V in rats and rabbits.

2.4.4.3. Genotoxicity

No genotoxicity studies have been performed in accordance with the WHO Guidelines on Non-clinical Evaluation of Vaccines (2005) and Guidelines on the Non-clinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines (2014). The absence of these studies is considered acceptable.

2.4.4.4. Carcinogenicity

No carcinogenicity studies have been performed in accordance with the WHO Guidelines on Non-clinical Evaluation of Vaccines (2005) and Guidelines on the Non-clinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines (2014). The absence of these studies is considered acceptable.

2.4.4.5. Reproductive and developmental toxicity

Additionally, the applicant conducted a combined GLP-compliant reproductive and development toxicity study to analyse any effects of PHH-1V on embryo-foetal, pre- and post-natal development in SD rats. Male and female rats were injected with 40 µg (0.1 mL/dose) PHH-IV antigen via the intramuscular route. The males received three administrations, 35 and 28 and 6 days prior to mating, and the females received four administrations, 21 and 14 days prior to mating and on gestation days 9 and 19. Half of the female rats were subjected to caesarean section with full foetal examination performed at the end of gestation. The other half of the female rats were allowed to deliver and were monitored until the end of lactation. In ELISA experiments, the applicant could show that high anti-RBD IgG binding antibody titres were detected in foetus and pups of PHH-1V-immunized rats due to exposure of maternal antibodies. Immunisation with the vaccine candidate PHH-1V did not affect the reproductivity of female or male rats. The sperm count, motility and morphology of PHH-1V vaccinated males were comparable to the control group. No vaccine-related differences in mating performance of female rats were observed. Furthermore, the oestrus cycle length of the vaccinated females was comparable to the control group and no vaccine-dependent effects on mating length and mating index were observed. The fertility and gestational index, and gestation length did not differ between PHH-1V vaccinated and control females. Also, no vaccine-dependent differences were observed in prenatal and postnatal loss

or lactation index between vaccinated and control groups. Furthermore, the percentage of live pups of PHH-1V-vaccinated dams was comparable to the control group and within historical control data. In general, no severe vaccine-related clinical signs and changes in pre- and post-natal development were observed in the F1 litters. Furthermore, skeletal and visceral examinations of the foetuses did not show any vaccine-related malformations or severe variations, indicating that up to four doses of 40 µg PHH-1V did not cause teratogenic effects in rats.

2.4.4.6. Local Tolerance

No stand-alone local tolerance study was conducted. This is acceptable and in line with relevant guidance on non-clinical vaccine development since local tolerance was evaluated in repeated dose toxicity studies. No aspects were identified in the submitted toxicity studies that would warrant raising a concern on local tolerance after i.m. administration of PHH-1 and PHH-1V.

2.4.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100), due to their nature vaccines are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this application for Marketing Authorisation, which is considered acceptable.

2.4.6. Discussion on non-clinical aspects

Pharmacology

The immunogenicity of PHH1V vaccine has been demonstrated for a prime-boost regimen in mice, hamsters, pigs and NHPs, showing induction of serum RBD-specific IgG responses and antibodies that (cross-)neutralize pseudoviruses containing RBD of different SARS-CoV-2 strains, including alpha, beta, gamma, delta, delta plus, Mu, and Omicron. The induction of RBD-specific CD4 and CD8 T cells with a balanced Th1/Th2 response was evident, too, whenever analyzed. A clear effect of the second dose (the boost) has been observed for the RBD binding IgG, and relatively, the information on (cross-) neutralizing antibodies post primary vaccination (post dose 1) is limited from the nonclinical dossier.

The efficacy of PHH1V vaccine against SARS-CoV-2 experimental infection has been consistently demonstrated following a prime-boost regimen in 3 challenge models including humanized K18-hACE2 mice, hamsters and NHPs. Vaccination prevented infection of the lower and upper respiratory tracts and inflammation of the lungs in all studies, as well as prevented other consequences of the infection, such as virus spread to other organs/tissues like brains, spleens, hearts, etc (mice), body weight loss (mice, hamsters) and clinical signs including mortality (mice). A tendency of dose-response effect was revealed in hamster challenge model, with the highest dose (40 µg) of PHH1V conferring better efficacy and better recovery of the animals post experimental infection. Results of the hamster challenge model did not reveal any sign of enhanced respiratory disease associated with PHH1V vaccine.

Overall, testing of the primary pharmacodynamics of PHH1V is adequate.

There were no studies of second pharmacodynamics, pharmacodynamics drug interactions, or safety pharmacology performed with PHH1V vaccine. This is in line with currently applicable regulatory guidelines or justified by the absence of major finding in the completed repeat-dose toxicity studies.

Several points of other concerns identified for the primary pharmacodynamics aspect have been adequately addressed by the applicant during the rolling review procedure.

Pharmacokinetics

PK studies to assess the absorption, distribution, metabolism or excretion as well as biodistribution and persistence of the PHH1V vaccine or the SBQA adjuvant were not performed. The SBQA adjuvant is composed 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, whichhas been already included in the licensed vaccines. This is acceptable, according to the currently applicable regulatory guidelines on the non-clinical development of vaccine products.

Toxicology

The toxicity of SBQA adjuvanted PHH-1V was evaluated in two pivotal GLP-compliant repeat-dose toxicity studies in rats and rabbits, respectively. Overall, these studies revealed that three doses of 40 µg PHH-1V were safe and well tolerated in the study animals. The vaccine only caused slight transient local and systemic reactions, which recovered in general within short time. Furthermore, a GLP-compliant DART study with adjuvanted PHH-1V was conducted in rats. The applicant could demonstrate that the vaccine candidate induced no reproductive, teratogenic or developmental effects in rats. This study revealed also that foetuses and pups of PHH-1V-vaccinated rats had detectable RBD-specific binding antibodies. Thus, these data indicate that maternal anti-RBD binding antibodies were transferred to the foetuses and pups via umbilical cord and lactation.

A dedicated local tolerance study was not performed, which is acceptable since local tolerance assessment was part of repeat-dose toxicity study. There were no studies on genotoxicity and carcinogenicity and no environmental risk assessment was carried out, which is in line with applicable guidelines.

Overall, the safety profile of PHH-1V is acceptable.

2.4.7. Conclusion on the non-clinical aspects

No major non-clinical issues are identified in this application. Few points of other concerns were identified and have been properly addressed by the applicant.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The applicant has conducted a number of clinical studies which are indicated in the tabular overview below: HIPRA-HH-1, HIPRA-HH-2, HIPRA-HH-5, HIPRA-HH-10 and HAN-01. The clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies**

Table 1 Clinical development plan (CDP) to support marketing authorisation of COVID-19 Vaccine HIPRA (PHH-1V)

Reference / ID	Title	Phase and Design	Treatment / Route of administration / Dose	Duration / status	Country	Number of subjects	Primary endpoint(s)
HIPRA-HH-1 (EudraCT: 2021-001411-82; NCT05007509)	A phase I/IIa study to evaluate safety and immunogenicity of recombinant protein RBD fusion dimer candidate vaccine against SARS-CoV-2 in adult healthy volunteers	Phase I/IIa First-in-human, randomised, controlled, observer-blinded, dose-escalation, multicentre clinical trial	*PHH-1V*: 2 doses, 21 days apart at 10, 20 or 40 µg per dose. *Control vaccine (Comirnaty)*: 2 doses, 21 days apart at recommended dose (30 µg). Intramuscular	48 weeks follow-up On-going (initiated August 2021)	Spain	30 adults (18-39 years) (n=5:1 per group)	*Safety and tolerability:* • Number and percentage of solicited local and systemic reactogenicity adverse events for 7 days following each vaccination. • Number and percentage of unsolicited local and systemic reactogenicity adverse events for 28 days following each vaccination.
HIPRA-HH-2 (EudraCT: 2021-005226-26; NCT05142553)	A Phase IIb, double-blind, randomised, active controlled, multi-centre, non-inferiority trial followed by a Phase III, single arm, open label trial, to assess immunogenicity and safety of a booster vaccination with a recombinant protein RBD fusion dimer candidate (PHH-1V) against SARS-CoV-2, in adults fully vaccinated against COVID-19	Phase IIb: Double-blind, randomised, active controlled, multi-centre, non-inferiority clinical trial to assess immunogenicity and safety of COVID-19 Vaccine HIPRA compared with Pfizer–BioNTech (Comirnaty) vaccine	PHH-1V: one booster dose (40 µg) at least 182 days after full vaccination with Comirnaty. Control vaccine (only Phase IIb): one 30 µg booster dose with Comirnaty at least 182 days after full vaccination with Comirnaty. Intramuscular	52 weeks follow-up after booster vaccination of Day 0 On-going: started 16 November 2021	Up to 10 sites in Spain with competitive enrolment	862 screened adults (≥18 years). 765 safety population (513 PHH-1V; 252 Comirnaty). 752 subjects (504 PHH-1V and 248 Comirnaty) in the mITT and PP populations At least 10% >65 years Randomisation: 2:1	*Efficacy endpoint:* • Neutralisation titre measured as IC_{50} and reported as reciprocal concentration for each individual sample and geometric mean titre for group comparison at baseline and Day 14. IC_{50} measured by PBNA. *Safety primary endpoint:* • Number, percentage, and characteristics of solicited local reactions, for 7 days following vaccination. • Number, percentage, and characteristics of unsolicited local and systemic adverse events for 28 days following vaccination. • Number and percentage of serious adverse events throughout the trial duration. • Number and percentage of AESI throughout the trial duration. • Number and percentage of MAAE related to study vaccine throughout the trial duration • Change from baseline in safety laboratory parameters at 14 days following vaccination

HIPRA-HH-5 (EudraCT: 2022-000074-25)	A phase III, open label, single arm, multi-centre, international trial to assess the safety and immunogenicity of a booster vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults vaccinated against COVID-19.	Phase III Open label, single arm, multi-centre	PHH-1V: one booster dose (40 µg per dose) at least a minimum of 91 days and preferably a maximum of 240 days after the last dose or at least 30 days after the infection of COVID-19. Intramuscular.	For the immunogenicity assessment participants will be followed for 52 weeks. For the safety assessment participants will be followed for 26 weeks. On-going: started February 2022	Spain, Italy, Portugal	3,000 adults and adolescents (≥16 years)	*Safety:* • Number, percentage, and characteristics of solicited local reactions through Day 7 after vaccination. • Number, percentage, and characteristics of unsolicited local and systemic AEs through Day 28 after vaccination. • Number and percentage of SAEs through the end of the study. • Number and percentage of AESI through the end of the study. • Number and percentage of MAAE related to study vaccine through the end of the study. • Grade 3 and 4 change from baseline in safety laboratory parameters at Days 14, 91 and 182 after vaccination.
HIPRA-HH-10 (EudraCT: 2022-000795-19)	A Phase IIb, Double-Blind, Randomised, Active-Controlled, Multicentre, Non-Inferiority Trial Followed by a Phase III, Single-Arm, Open-Label Trial to Assess Immunogenicity and Safety of a Booster Vaccination with a Recombinant Protein RBD Fusion Dimer Candidate (PHH-1V) Against SARS-CoV-2 in Adults Fully Vaccinated Against COVID-19	Phase IIb Double-blind, randomised, active controlled, multi-centre, non-inferiority	PHH-1V: one booster dose (40 µg) at least 91 days after full vaccination with Vaxzevria. Intramuscular.	Each subject will be followed for 26 weeks (182 days) after the administration On-going: started March 2022	Spain	273 adults aged ≥18 years	*Efficacy:* • Neutralisation titre against Omicron measured as IC_{50} by PBNA and reported as reciprocal concentration for each individual sample and GMT for treatment group comparison at Baseline and Day 14. *Safety:* • Number, percentage, and characteristics of solicited local reactions through Day 7 after vaccination. • Number, percentage, and characteristics of unsolicited local and systemic AEs through Day 28 after vaccination. • Number and percentage of SAEs through the end of the study.

							• Number and percentage of AESI through the end of the study. • Number and percentage of MAAE related to study vaccine through the end of the study. • Change from Baseline in safety laboratory parameters at Days 14, 98 and 182 after vaccination.
HAN-01 (EudraCT: 2021-005722-24; ClinicalTrials.gov Identifier: NCT05142514)	A phase IIb study to evaluate safety and immunogenicity of recombinant protein RBD fusion dimer candidate vaccine against SARS-CoV-2 in adult healthy volunteers	Phase IIb Randomised, controlled, observer-blinded clinical trial. COVID-19 Vaccine HIPRA compared with Pfizer–BioNTech (Comirnaty) vaccine	*PHH-1V*: 2 doses (0.5 mL), 21 days apart at 40 µg per dose. *Comirnaty*: 2 doses (0.3 mL), 21 days apart at 30 µg mRNA per dose. Intramuscular.	Each subject will be followed for 24 weeks after the first dose. On-going	Vietnam	256 healthy adults aged 18-60 Randomisation: 1:1	*Safety:* • Number and percentage of solicited local and systemic reactogenicity adverse events for 7 days following each vaccination. • Number and percentage of unsolicited local and systemic reactogenicity adverse events for 28 days following each vaccination. • Change from baseline in safety laboratory parameters at 7 days following each vaccination. • Number and percentage of serious adverse events throughout the study duration. • Number and percentage of AESI throughout the study duration. • Number and percentage of MAAE related to study vaccine throughout the study duration. *Efficacy (immunogenicity):* • Neutralisation titer measured as IC_{50} and reported as reciprocal dilution/concentration for each individual sample, and GMT for group comparison at Day 21 and 35. IC_{50} measured by PBNA of different VoCs . • GMFR in neutralising antibodies titers from baseline at Day 21 and 35.
HIPRA-HH-4	A phase III, open label, single arm, multi-centre, trial to assess the safety	Phase III	PHH-1V: one booster dose (40 µg) at least 90	52 weeks follow-up after booster vaccination on Day	Spain, Turkey	Approximately 400 adults aged ≥18 years old	• Neutralisation titer against Omicron, Beta and Delta strains, and any other relevant VOC in the epidemiologic

(EudraCT:2022-000785-18)	and immunogenicity of a 2nd booster vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults with pre-existing immunosuppressive conditions vaccinated and boosted against COVID-19	Open label, single arm, multi-centre clinical trial	days after booster vaccination Intramuscular.	0 for safety and immunogenicity, respectively. Planned.		with pre-existing immunosuppressive conditions	moment, measured as IC_{50} by PBNA and reported as reciprocal concentration for each individual sample and GMT for descriptive statistics analysis at Baseline and at Day 14. For the HIV cohort, ID_{50} (reciprocal dilution inhibiting 50% of the infection) will be reported using a live virus assay (VNA) to measure cytopathic effect in Vero E6 cells. • GMFR in neutralising antibody titer from baseline to Day 14.
HIPRA-HH-3 (EudraCT: TBD)	Study title pending agreement of study design in PIP procedure	Phase I/II *Phase I/IIa*: Randomised (2:1), double-blind, active controlled, single-centre study *Phase IIb*: Open label uncontrolled multi-centre expansion cohort	*PHH-1V*: one booster dose (40 µg) at least 90 and <365 days after full vaccination. *Control*: one 30 µg booster dose of Comirnaty at least 90 and <365 days after full vaccination. Intramuscular	12 months (365 days) follow-up after booster vaccination at Day 0 Planned	Spain	*PHH-1V*: At least 227 evaluable subjects aged 12 to <16 years *Comirnaty*: At least 12 evaluable subjects aged 12 to <16 years	*Safety:* • Solicited local and systemic adverse events through Day 7 after booster dose. • Unsolicited local and systemic adverse events through Day 28 after booster dose. • AEs from booster dose throughout the study duration • SAEs from booster dose throughout the study duration • MAAEs from booster dose throughout the study duration.
HIPRA-HH-6 (EudraCT: TBD)	Study title pending agreement of study design in PIP procedure	Phase I/II *Phase I/IIa*: Randomised (2:1), double-blind, active controlled, single-centre study. *Phase IIb*: Open label uncontrolled multi-centre expansion cohort	*Phase I/IIa; Primary vaccination:* • Cohort 1: PHH-1V 10 µg (n=16) • Cohort 2: PHH-1V 20 µg (n=16) • Cohort 3: Comirnaty 10 µg (n=8) Phase IIb: *Booster vaccination:* • PHH-1V 10 or 20 µg (n=203) *Primary vaccination:* • PHH-1V 10 or 20 µg (n=126) Intramuscular	*Primary vaccine*: 6 months (182 days) follow-up after last dose) *Booster vaccine*: 6 months follow-up after vaccination at Day 0 Planned	Spain	*Primary vaccine PHH-1V*: At least 160 children aged 5 to <12 years old. *Booster vaccine PHH-1V*: At least 203 children aged 5 to <12 years old. *Control (Comirnaty)*: at least 8 children aged 5 to <12 years old.	*For primary vaccination* • Solicited local and systemic AEs for 7 following each vaccination. • Unsolicited local and systemic AEs for 28 days following each vaccination. • SAEs from dose 1 throughout the study duration. • MAAEs from dose throughout the study duration. • AESI from dose 1 throughout the study duration. *For booster dose* • Solicited local and systemic AEs through Day 7 after booster dose. • Unsolicited local and systemic AEs through Day 28 after booster dose. • SAEs from booster dose throughout the study duration. • MAAEs from booster dose throughout the study duration. • AESI from booster dose throughout the study duration.
HIPRA-HH-8 (EudraCT: TBD)	Study title pending agreement of study design in PIP procedure	Phase I/II *Phase I/IIa*: Randomised (1:1), double-blind, active controlled, single-centre study. *Phase IIb*: Open label uncontrolled multi-centre expansion cohort	*PHH-1V*: Administration of PHH-1V on Day 0 and Day 56 • Dose level 10 µg (16 subjects) • Dose level 20 µg (16 subjects) Phase IIb: *Booster vaccination:* • PHH-1V 10 or 20 µg (n=203) *Primary vaccination:* • PHH-1V 10 or 20 µg (n=126) Intramuscular	6 months (182 days) follow-up after last dose Planned	Spain	*Primary vaccine PHH-1V*: At least 142 subjects aged birth to <5 years old. *Booster vaccine PHH-1V*: At least 203 subjects aged birth to <5 years old. *Control (Comirnaty)*: at least 8 subjects aged birth to <5 years old.	*For primary vaccination* • Solicited local and systemic adverse events for 7 days following each vaccination. • Unsolicited local and systemic adverse events for 28 days following each vaccination. • Serious adverse events (SAEs) from dose 1 throughout the study duration. • Medically attended adverse events (MAAEs) from dose 1 throughout the study duration. • Adverse Events of Special Interest (AESI) from dose 1 throughout the study duration. *For booster dose* • Solicited local and systemic AEs through Day 7 after booster dose. • Unsolicited local and systemic AEs through Day 28 after booster dose. • SAEs from booster dose throughout the study duration. • MAAEs from booster dose throughout the study duration. • AESI from booster dose throughout the study duration.

AESI: adverse events of special interest; AR: adverse reaction; GMFR: Geometric mean fold rise; GMT: geometric mean titer; IC_{50}: Half-maximal inhibitory concentration; IT: Italy; MAAE: of medically attended adverse events; PBNA: pseudovirus-based neutralisation assay; RBD: receptor binding domain; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TBD: to be defined.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

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

2.5.2.2. 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-1V is a SARS-CoV-2 RBD heterologous dimer fusion protein derived from B.1.1.7 (alpha) and B.1.351 (beta) strains 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. Following administration, an immune response is generated, both at a humoral and cellular level, against the SARS-Co-V-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-1V induces antigen-specific T-cell immune response, which may contribute to protection to COVID-19.

Applied Assays

PBNA and VNA validation

Two methods were used in this application to measure neutralizing antibodies (nABs) in the sera of the subjects: one pseudovirion-based neutralisation assay (PBNA) and a virus neutralisation assay (VNA).

- For the PBNA, 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 VNA 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).

Initially only validation reports were submitted for the Alpha variant. Upon request, the Applicant submitted new validation reports of PBNAs specific to the SARS-CoV-2 variants B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617 (Delta) and B.1.1.259 (Omicron).

However, several concerns had to be addressed regarding the validation of both - PBNA and VNA. These issues included fundamental aspects required to ensure the validity and reliability of the obtained results.

Documentation of production and stability of pseudoviruses and viruses was missing. Upon request the lacking documentation could be supplied together with data supporting the Applicant's conclusion that the applied storage conditions of the pseudovirus and virus stocks enable stable storage for a prolonged time.

Initially no information regarding the positive and negative controls (a high specific antibody level serum and a pre-pandemic serum) used during validation was provided. The Applicant clarified that the

positive control test sera were obtained from patients having received two covid-19 vaccinations and a booster vaccination with PHH-1V. The negative control pre-pandemic serum was purchased at SigmaAldrich and originated from only one male donor (USA origin, AB blood type). This could be problematic, as one serum donor supposedly does not cover the neutralising capacity of the total population. Upon request the Applicant provided a scientific justification supported by assay data from the Phase 1/2a clinical trial HIPRA-HH-1 in which predominantly negative results were measured in Covid-19 naïve patient sera. It can be concluded that a sufficiently high number of negative sera was measured with the PBNA and the VNA to support the specificity.

Further, it was not clear how the expected titre IC50 of the positive control serum pool has originally been determined, and if this titre value has been determined by a validated method. From the Applicant's response to this concern, it is apparent that the IC50 values of the positive control sera used in the PBNAs and the VNA was determined with the same (yet non-validated) assays. Consequently, the applied PBNAs and the VNA are only capable of generating relative results of nABs in patient's sera. This however also means that throughout the clinical studies, only relative nAB titres were and can be measured with the established PBNAs (and the Alpha-variant VNA). The efficacy evaluation of PHH-1V therefore solely needs to rely on a relative comparison between nAB levels between different treatment arms.

The accuracy of both assays was determined by calculating the mean value of the analysed samples and expressing the variance of sub-groups of replicates (e.g. quadruplicate measured by Analyst A or B at day 1 or 2) to this mean value. This methodology is generally not supported. It should rather be determined by comparing the read-outs with their true value. However, it is acknowledged that this is currently not possible since no alternative analytical method was available to analyse the true value of the controls in the PBNA (and VNA) validations. Additionally, the Applicant argued that the final objective of the PBNA and VNA in the presented PHH-1V clinical studies is to compare levels of neutralizing antibodies between different treatments. Consequently, the true value of the positive control serum is not critical for the final evaluation of PHH-1V efficacy, which is acknowledged. In conclusion, the accuracy of the PBNA and VNA cannot be calculated, as no variance relative to a true value can be determined due to the lack of the latter. Consequently, the obtained results can only be compared within results obtained with the same assay.

Initially, it was questioned whether the analytical range of the PBNA (and VNA) might be too narrow to allow coverage of all possible nAB levels in patients. As consequence, the Applicant widened the range for all variants. The new upper limits in these PBNAs are: Alpha: 13327 IC50 (corresponding to 4.12 log10IC50); Beta: 39020 IC50 (4.59 log10IC50); Delta: 58848 IC50 (4.71 log10IC50); Omicron: 49220 IC50 (4.69 log10IC50). It is assumed that the new ranges cover the expectable nAB levels in clinical trials, as the upper limit of quantification is approximately one order of magnitude higher as applied in the previously submitted PBNA and VNA validation reports. In addition, the Applicant provided a validated approach to dilute high titre sera to reach the validated analysis range. Upon request, the Applicant presented an updated SOP implementing respective re-analyses of such saturated samples as standard procedure.

Originally, it was not clear if the claimed LOQ at 101.30 (20) IC50 of the Alpha variant PBNA and VNA has been experimentally determined, as no serum samples at this level were used in the validation studies. In response, the Applicant amended the Alpha variant validation, and incorporated low titre sera as LOQs in the Beta, Delta and Omicron variant PBNA validations. The new LOQs were as follows: Beta: 49 IC50 (1.69 log10IC50); Delta: 64 IC50 (1.80 log10IC50); Omicron: 61 IC50 (1.78 log10IC50); Alpha: 33 IC50 (1.52 log10IC50).

To conclude, validations of PBNAs of the main SARS-CoV-2 variants (Alpha, Beta, Delta and Omicron) and of the Alpha variant specific VNA support a robust and reliable use of these assays in the

determination of nABs throughout the clinical studies. Nevertheless, comparisons to results obtained with other assays cannot be made.

Apart from the PBNA and VNA, three additional assays are used to analyse patient sera: a commercial anti-SARS-CoV-2 S protein binding assay, an enzyme-linked immunospot (ELISpot) assay for the evaluation of T cell-mediated immunogenicity and an intracellular cytokine staining assay also to determine the cellular immunity responses towards PHH-1V. Only one of these assays was validated in-house (Elecsys Anti-SARS-CoV-2 S assay purchased from Roche). In a prior rapid scientific advice procedure (EMA/SA/0000078033), CHMP accepted this strategy. Nonetheless, for the non-validated assays, it is stressed that the data gathered in these assays cannot be regarded as reliable and should thus only be regarded as supplementary (but not pivotal) data.

Correlation study between PBNA and VNA

For the main conclusion of non-inferior or superior immunogenicity it is most important that differences between products obtained with PBNA correspond to comparable differences (in magnitude and scale) that would have been obtained using VNA. For this purpose, the Applicant was requested to provide Bland Altman plots of measurements obtained by either method for each variant and additional analyses from representative (or complete) samples from studies HIPRA-HH-1 and HIPRA-HH-2 evaluating the comparability of between product differences in post vaccination titres between assays.

The Applicant provided the requested Bland Altman plots comparing assay readouts from PBNA with corresponding measurements from VNA. Bland-Altman plots indicate close to 1:1 correspondence between assays for Alpha, Delta with higher absolute values obtained from PBNA (linear trend with slope 1 but positive intercept). For Omicron assays, a positive slope (indicating increasingly larger PBNA measurements for increasing average titres) was observed. For D614G strain, the estimated slope is negative (indicating increasingly lower PBNA values with increasing average titres). The latter however may be an artefact due to few outliers with large titre levels acting as leverage points. Overall, the variability between assay differences is within acceptable limits and importantly assay correspondence appears comparable between samples obtained from subjects vaccinated with different products.

In addition, the Applicant provided an analysis comparing post vaccination GMTs using either PBNA or VNA based on a subsample from study HIPRA-HH-2. The comparison between Day 14 GMTs obtained using VNA in the subset closely reproduced corresponding values obtained by PBNA.

Considering the information provided, the Applicant’s position that the measurements obtained by PBNA and VNA have adequate agreement is acknowledged.

2.5.3. 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 and assays have to be validated and the use of an assay for primary analysis needs to be adequately justified.

While several concerns had to be addressed during the assessment, it can be concluded that the presented validations of PBNAs of the main SARS-CoV-2 variants (Alpha, Beta, Delta and Omicron) and of the Alpha variant specific VNA support a robust and reliable use of these assays in the determination of nABs throughout the clinical studies. However, comparisons to results obtained with other assays cannot be made. The PBNAs (and the VNA) do not provide absolute determinations of the nAB content in patient’s sera, as none of the PBNAs (and the VNA) has been calibrated to adequate reference standards (e.g., sera with known nAB level). Consequently, throughout the clinical studies, only relative nAB titres were and can be measured with the established PBNAs and the Alpha-variant VNA.

The obtained results can therefore not be directly compared to other data sources. This means the efficacy evaluation of PHH-1V solely needs to rely on a relative comparison between nAB levels between different treatment arms.

2.5.4. 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 established PBNAs and the Alpha-variant VNA. The obtained results can therefore not be directly compared to other data sources. The efficacy evaluation of PHH-1V solely needs to rely on a relative comparison between nAB levels between different treatment arms.

2.5.5. Clinical efficacy

The clinical development is based on an immunobridging approach to extrapolate efficacy from the approved mRNA vaccine Comirnaty for which vaccine efficacy has been established.

2.5.5.1. Dose response study(ies)

Study HIPRA-HH-1

Study HH-1 is a Phase 1/2a, FIH, randomized (5:1), controlled (comparator Comirnaty 30 µg), observer-blinded, dose-escalation (2 doses 21 days apart, 3 cohorts receiving either 10, 20, or 40 µg), multicentre study (n=2, both in Spain) to evaluate safety, tolerability, and immunogenicity of PHH-1V in 30 healthy adults aged 18-39.

Immunogenicity objectives:

Immunogenicity was measured at baseline, 3-weeks after the first dose and 2-weeks after the second dose and in the long term i.e., 24 and 48 weeks after the second dose of COVID-19 HIPRA vaccine.

Measurements for all timepoints include:

- wild-type SARS-CoV-2 and SARS-CoV-2 pseudovirus neutralization,
- enzyme-linked immunosorbent assay (ELISA) to the SARS-CoV-2 spike glycoprotein
- T-cell mediated responses against the SARS-CoV-2 S glycoprotein

Results:

The following tables show the results for the endpoints:

- Neutralization titer measured as ID50 or IC50 and reported as reciprocal dilution/concentration for each individual sample and geometric mean titer (GMT) for group comparison at Day 21 and 35. IC50 measured by PBNA.
- Geometric mean fold rise (GMFR) in neutralizing antibodies titers from baseline at Day 21 and 35.

For results of other endpoints, please refer to the assessment report.

PBNA Alpha IC50:

Table 2 Neutralizing antibody immunogenicity. Descriptive and inferential analysis. Efficacy population. PBNA Alpha IC50

Summary table 5.2.1 Neutralizing antibody immunogenicity. Descriptive and inferential analysis. Efficcacy population. PBNA Alpha IC50.

Visit	Description	Statistics	Pfizer (n=5)	HIPRA (10 µg) (n=5)	HIPRA (20 µg) (n=10)	HIPRA (40 µg) (n=10)	Total (n=30)
Screening	Values	n	5	5	10	10	30
		Mean (SD)	10 (0)	10 (0)	10 (0)	22.6 (39.84)	14.2 (23)
		Median [P25 - P75]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]
		Min-Max	10-10	10-10	10-10	10 - 136	10 - 136
		GMT (SE) [95%CI]	10 (1.24) [6.4 - 15.63]	10 (1.24) [6.4 - 15.63]	10 (1.17) [7.29 - 13.71]	12.98 (1.17) [9.47 - 17.8]	10.67 (1.1) [8.8 - 12.95]
D2-21 days D1	Values	n	5	5	10	10	30
		Mean (SD)	1119.84 (1855.8)	1691.16 (2939.64)	270.38 (344.33)	2388.29 (6377.19)	1354.72 (3889.46)
		Median [P25 - P75]	222.73 [115.85 - 754.14]	217.98 [83.88 - 1274.68]	125.97 [36.73 - 379.82]	113.06 [43.52 - 1088.71]	156.52 [63.46 - 754.14]
		Min-Max	101.46 - 4405.01	10 - 6869.26	10 - 1134.82	10 - 20480	10 - 20480
		GMT (SE) [95%CI]	387.14 (2.42) [62.74 - 2389.01]	275.98 (2.42) [44.72 - 1703.03]	118.22 (1.87) [32.65 - 428.12]	204.95 (1.87) [56.6 - 742.17]	225.57 (1.47) [102.58 - 496.02]
	Contrast vs groups	Ref.: Pfizer #	Ref.	0.71 [0.05 - 9.35] ; 0.7890	0.31 [0.03 - 2.84] ; 0.2840	0.53 [0.06 - 4.92] ; 0.5625	-
		Ref.: HIPRA(10µg) #	-	Ref.	0.43 [0.05 - 3.98] ; 0.4414	0.74 [0.08 - 6.9] ; 0.7859	-
		Ref.: HIPRA(20µg) #	-	-	Ref.	1.73 [0.28 - 10.7] ; 0.5397	-
	Contrasts vs Screening	n	5	5	10	10	30
		Mean (SD)	1109.84 (1855.8)	1681.16 (2939.64)	260.38 (344.33)	2365.69 (6337.48)	1340.52 (3868.1)
		Median [P25 - P75]	212.73 [105.85 - 744.14]	207.98 [73.88 - 1264.68]	115.97 [26.73 - 369.82]	103.06 [33.52 - 1078.71]	146.52 [53.46 - 744.14]
		Min-Max	91.46 - 4395.01	0 - 6859.26	0 - 1124.82	0 - 20344	0 - 20344
		Ref.: Screening #	38.71 [7.42 - 202.04] ; 0.0001	27.6 [5.29 - 144.02] ; 0.0003	11.82 [3.68 - 38.03] ; 0.0002	15.79 [4.91 - 50.78] ; <.0001	-
14 days D2-D35	Values	n	5	5	10	10	30
		Mean (SD)	2699.33 (2067.66)	2479.38 (3058.96)	981.61 (1146.24)	2969.31 (6276.88)	2180.09 (3909.91)
		Median [P25 - P75]	1942.3 [1725.94 - 2906.96]	490.34 [260.25 - 4526.79]	550.12 [264.09 - 1275.54]	539.81 [247.22 - 1488.87]	714.5 [264.09 - 1942.3]
		Min-Max	779.52 - 6141.93	241.51 - 6878.04	196.07 - 3845.4	87.97 - 20480	87.97 - 20480
		GMT (SE) [95%CI]	2156.67 (1.79) [648.68 - 7170.26]	991.78 (1.79) [298.31 - 3297.36]	599.73 (1.51) [256.46 - 1402.47]	799.88 (1.51) [342.05 - 1870.51]	1006.46 (1.29) [598.23 - 1693.25]
	Contrast vs groups	Ref.: Pfizer #	Ref.	0.46 [0.08 - 2.51] ; 0.3560	0.28 [0.06 - 1.21] ; 0.0854	0.37 [0.09 - 1.62] ; 0.1776	-
		Ref.: HIPRA(10µg) #	-	Ref.	0.6 [0.14 - 2.63] ; 0.4885	0.81 [0.19 - 3.51] ; 0.7663	-
		Ref.: HIPRA(20µg) #	-	-	Ref.	1.33 [0.4 - 4.43] ; 0.6263	-
	Contrasts vs Screening	n	5	5	10	10	30
		Mean (SD)	2689.33 (2067.66)	2469.38 (3058.96)	971.61 (1146.24)	2946.71 (6237.82)	2165.89 (3889.59)
		Median [P25 - P75]	1932.3 [1715.94 - 2896.96]	480.34 [250.25 - 4516.79]	540.12 [254.09 - 1265.54]	529.81 [237.22 - 1478.87]	704.5 [254.09 - 1932.3]
		Min-Max	769.52 - 6131.93	231.51 - 6868.04	186.07 - 3835.4	77.97 - 20344	77.97 - 20344
		Ref.: Screening #	215.67 [75.83 - 613.34] ; <.0001	99.18 [34.87 - 282.05] ; <.0001	59.97 [28.64 - 125.58] ; <.0001	61.61 [29.42 - 129.01] ; <.0001	-

#: GMFR [95%CI] ; p-value
Not Apply: not available data.
Non-Est.: non estimable due to missing in all subjects in this group.
Brown cells shows the estimations of GMT by time point and the GMTR between-groups and intra-groups.
Source: table 29.1

PBNA Beta IC50

Table 3 Neutralizing antibody immunogenicity. Descriptive and inferential analysis. Efficacy population. PBNA Beta IC 50

Summary table 5.2.2 Neutralizing antibody immunogenicity. Descriptive and inferential analysis. Efficcacy population. PBNA Beta IC50.

Visit	Description	Statistics	Pfizer (n=5)	HIPRA (10 µg) (n=5)	HIPRA (20 µg) (n=10)	HIPRA (40 µg) (n=10)	Total (n=30)
Screening	Values	n	5	5	10	10	30
		Mean (SD)	10 (0)	10 (0)	10 (0)	19.4 (29.73)	13.13 (17.16)
		Median [P25 - P75]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]
		Min-Max	10-10	10-10	10-10	10 - 104	10 - 104
		GMT (SE) [95%CI]	10 (1.22) [6.7 - 14.93]	10 (1.22) [6.7 - 14.93]	10 (1.15) [7.53 - 13.27]	12.64 (1.15) [9.52 - 16.78]	10.6 (1.09) [8.91 - 12.61]
D2-21 days D1	Values	n	5	5	10	10	30
		Mean (SD)	690.1 (1184.75)	2654.57 (4933.46)	793.78 (1378.86)	4049.53 (6466.78)	2171.88 (4405.5)
		Median [P25 - P75]	132.05 [98.13 - 399.74]	203.72 [194.14 - 1444.7]	322.84 [53.79 - 798.13]	1180.57 [203.82 - 5478.26]	403.32 [120.5 - 1940.45]
		Min-Max	26.29 - 2794.31	10 - 11420.32	10 - 4568.95	120.5 - 20480	10 - 20480
		GMT (SE) [95%CI]	207.05 (2.42) [33.79 - 1268.67]	365.53 (2.42) [59.65 - 2239.73]	219.54 (1.87) [60.93 - 791.06]	1123.15 (1.87) [311.71 - 4046.92]	369.6 (1.47) [168.59 - 810.29]
	Contrast vs groups	Ref.: Pfizer #	Ref.	1.77 [0.14 - 22.92] ; 0.6524	1.06 [0.12 - 9.76] ; 0.9571	5.42 [0.59 - 49.95] ; 0.1295	-
		Ref.: HIPRA(10µg) #	-	Ref.	0.6 [0.07 - 5.53] ; 0.6409	3.07 [0.33 - 28.3] ; 0.3082	-
		Ref.: HIPRA(20µg) #	-	-	Ref.	5.12 [0.83 - 31.35] ; 0.0756	-
	Contrasts vs Screening	n	5	5	10	10	30
		Mean (SD)	680.1 (1184.75)	2644.57 (4933.46)	783.78 (1378.86)	4030.13 (6440.25)	2158.75 (4392.05)
		Median [P25 - P75]	122.05 [88.13 - 389.74]	193.72 [184.14 - 1434.7]	312.84 [43.79 - 788.13]	1170.57 [193.82 - 5468.26]	393.32 [110.5 - 1930.45]
		Min-Max	16.29 - 2784.31	0 - 11410.32	0 - 4558.95	110.5 - 20376	0 - 20376
		Ref.: Screening #	20.7 [3.66 - 117.18] ; 0.0013	36.55 [6.46 - 206.88] ; 0.0002	21.95 [6.44 - 74.79] ; <.0001	88.87 [26.09 - 302.72] ; <.0001	-
14 days D2-D35	Values	n	5	5	10	10	30
		Mean (SD)	1152.1 (733.78)	3730.46 (4965.7)	1466.24 (1201.16)	4625.34 (6661.18)	2844.29 (4480.11)
		Median [P25 - P75]	1289.26 [443.69 - 1563.15]	1109.49 [775.22 - 3996.32]	943.3 [770.02 - 2273]	1292.2 [583.07 - 8412.42]	1061.41 [583.07 - 2523.75]
		Min-Max	380.35 - 2084.05	517.96 - 12253.31	208.32 - 4009.55	90.93 - 20480	90.93 - 20480
		GMT (SE) [95%CI]	933.47 (1.77) [288.63 - 3019]	1852.47 (1.77) [572.78 - 5991.19]	1059.37 (1.5) [461.95 - 2429.42]	1541.96 (1.5) [672.38 - 3536.13]	1296.41 (1.28) [779.85 - 2155.14]
	Contrast vs groups	Ref.: Pfizer #	Ref.	1.98 [0.38 - 10.44] ; 0.4038	1.13 [0.27 - 4.78] ; 0.8578	1.65 [0.39 - 6.96] ; 0.4794	-
		Ref.: HIPRA(10µg) #	-	Ref.	0.57 [0.14 - 2.41] ; 0.4315	0.83 [0.2 - 3.5] ; 0.7951	-
		Ref.: HIPRA(20µg) #	-	-	Ref.	1.46 [0.45 - 4.71] ; 0.5167	-
	Contrasts vs Screening	n	5	5	10	10	30
		Mean (SD)	1142.1 (733.78)	3720.46 (4965.7)	1456.24 (1201.16)	4605.94 (6636.34)	2831.15 (4467.36)
		Median [P25 - P75]	1279.26 [433.69 - 1553.15]	1099.49 [765.22 - 3986.32]	933.3 [760.02 - 2263]	1282.2 [573.07 - 8402.42]	1051.41 [573.07 - 2513.75]
		Min-Max	370.35 - 2074.05	507.96 - 12243.31	198.32 - 3999.55	80.93 - 20376	80.93 - 20376
		Ref.: Screening #	93.35 [32.03 - 272.08] ; <.0001	185.25 [63.56 - 539.95] ; <.0001	105.94 [49.72 - 225.72] ; <.0001	122 [57.26 - 259.95] ; <.0001	-

#: GMFR [95%CI] ; p-value
Not Apply: not available data.
Non-Est.: non estimable due to missing in all subjects in this group.
Brown cells shows the estimations of GMT by time point and the GMTR between-groups and intra-groups.
Source: table 29.2

PBNA Gamma IC50

Table 4 Neutralizing antibody immunogenicity. Descriptive and inferential analysis. Efficacy population. PBNA Gamma IC50

Summary table 5.2.3 Neutralizing antibody immunogenicity. Descriptive and inferential analysis. Efficcacy population. PBNA Gamma IC50.

Visit	Description	Statistics	Pfizer (n=5)	HIPRA (10 µg) (n=5)	HIPRA (20 µg) (n=10)	HIPRA (40 µg) (n=10)	Total (n=30)
Screening	Values	n	5	5	10	10	30
		Mean (SD)	10 (0)	10 (0)	10 (0)	17.7 (24.35)	12.57 (14.06)
		Median [P25 - P75]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]
		Min-Max	10-10	10-10	10-10	10-87	10-87
		GMT (SE) [95%CI]	10 (1.2) [6.91 - 14.48]	10 (1.2) [6.91 - 14.48]	10 (1.14) [7.7 - 12.99]	12.42 (1.14) [9.56 - 16.13]	10.56 (1.08) [8.99 - 12.39]
D2-21 days D1	Values	n	5	5	10	10	30
		Mean (SD)	500.06 (764.9)	3342.17 (5921.01)	466.52 (741.15)	2588.22 (6336.32)	1658.62 (4365.2)
		Median [P25 - P75]	120.09 [109.01 - 343.08]	208.38 [201.49 - 2519.58]	102.49 [10 - 610.8]	138.49 [81.94 - 1233.72]	143.1 [73.06 - 1196.04]
		Min-Max	73.06 - 1855.05	10 - 13771.41	10 - 2391.39	35.46 - 20480	10 - 20480
		GMT (SE) [95%CI]	227.44 (2.53) [33.76 - 1532.16]	429.22 (2.53) [63.72 - 2891.44]	111.5 (1.93) [28.94 - 429.58]	341.95 (1.93) [88.75 - 1317.5]	247 (1.49) [108.14 - 564.18]
	Contrast vs groups	Ref.: Pfizer #	Ref.	1.89 [0.13 - 28.01] ; 0.6325	0.49 [0.05 - 5.07] ; 0.5360	1.5 [0.15 - 15.55] ; 0.7227	-
		Ref.: HIPRA(10µg) #	-	Ref.	0.26 [0.03 - 2.69] ; 0.2463	0.8 [0.08 - 8.24] ; 0.8430	-
		Ref.: HIPRA(20µg) #	-	-	Ref.	3.07 [0.46 - 20.66] ; 0.2381	-
	Contrasts vs Screening	n	5	5	10	10	30
		Mean (SD)	490.06 (764.9)	3332.17 (5921.01)	456.52 (741.15)	2570.52 (6312.17)	1646.05 (4353.76)
		Median [P25 - P75]	110.09 [99.01 - 333.08]	198.38 [191.49 - 2509.58]	92.49 [0 - 600.8]	128.49 [71.94 - 1223.72]	133.1 [63.06 - 1186.04]
		Min-Max	63.06 - 1845.05	0 - 13761.41	0 - 2381.39	25.46 - 20393	0 - 20393
		Ref.: Screening #	22.74 [3.8 - 136.07] ; 0.0013	42.92 [7.17 - 256.79] ; 0.0002	11.15 [3.15 - 39.5] ; 0.0006	27.54 [7.77 - 97.58] ; <.0001	-
14 days D2-D35	Values	n	5	5	10	10	30
		Mean (SD)	2263.5 (2127.21)	2109.4 (2576.1)	692.75 (616.11)	3400.2 (6230.35)	2093.13 (3869.68)
		Median [P25 - P75]	1353.66 [1273.78 - 2441.04]	671.4 [463.03 - 2631.18]	433.03 [163.65 - 1250.61]	1248.65 [424.27 - 2062.04]	751.17 [404.89 - 1882.88]
		Min-Max	406.18 - 5842.84	373.14 - 6408.22	135.3 - 1740.16	120.43 - 20480	120.43 - 20480
		GMT (SE) [95%CI]	1584.54 (1.74) [505.29 - 4969.01]	1143.59 (1.74) [364.67 - 3586.21]	459.19 (1.48) [204.65 - 1030.32]	1128.2 (1.48) [502.81 - 2531.45]	984.32 (1.27) [600.07 - 1614.62]
	Contrast vs groups	Ref.: Pfizer #	Ref.	0.72 [0.14 - 3.63] ; 0.6817	0.29 [0.07 - 1.17] ; 0.0805	0.71 [0.18 - 2.89] ; 0.6221	-
		Ref.: HIPRA(10µg) #	-	Ref.	0.4 [0.1 - 1.63] ; 0.1919	0.99 [0.24 - 4] ; 0.9843	-
		Ref.: HIPRA(20µg) #	-	-	Ref.	2.46 [0.78 - 7.7] ; 0.1180	-
	Contrasts vs Screening	n	5	5	10	10	30
		Mean (SD)	2253.5 (2127.21)	2099.4 (2576.1)	682.75 (616.11)	3382.5 (6206.9)	2080.57 (3857.07)
		Median [P25 - P75]	1343.66 [1263.78 - 2431.04]	661.4 [453.03 - 2621.18]	423.03 [153.65 - 1240.61]	1238.65 [414.27 - 2052.04]	741.17 [394.89 - 1872.88]
		Min-Max	396.18 - 5832.84	363.14 - 6398.22	125.3 - 1730.16	110.43 - 20393	110.43 - 20393
		Ref.: Screening #	158.45 [57.27 - 438.38] ; <.0001	114.36 [41.34 - 316.38] ; <.0001	45.92 [22.36 - 94.3] ; <.0001	90.87 [44.25 - 186.61] ; <.0001	-

#: GMFR [95%CI] ; p-value
Not Apply: not available data.
Non-Est.: non estimable due to missing in all subjects in this group.
Brown cells shows the estimations of GMT by time point and the GMTR between-groups and intra-groups.
Source: table 29.3

PBNA Delta IC50

Table 5 Neutralizing antibody immunogenicity. Descriptive and inferential analysis. Efficacy population. PBNA Delta IC50

Summary table 5.2.4 Neutralizing antibody immunogenicity. Descriptive and inferential analysis. Efficcacy population. PBNA Delta IC50.

Visit	Description	Statistics	Pfizer (n=5)	HIPRA (10 µg) (n=5)	HIPRA (20 µg) (n=10)	HIPRA (40 µg) (n=10)	Total (n=30)
Screening	Values	n	5	5	10	10	30
		Mean (SD)	10 (0)	10 (0)	13.9 (12.33)	17.3 (23.08)	13.73 (14.89)
		Median [P25 - P75]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]
		Min-Max	10-10	10-10	10-49	10-83	10-83
		GMT (SE) [95%CI]	10 (1.25) [6.36 - 15.72]	10 (1.25) [6.36 - 15.72]	11.72 (1.17) [8.51 - 16.14]	12.36 (1.17) [8.97 - 17.02]	10.97 (1.1) [9.02 - 13.35]
D2-21 days D1	Values	n	5	5	10	10	30
		Mean (SD)	2634.68 (4586.18)	1588.8 (2843.21)	276.99 (400.99)	2781.15 (6368.01)	1723.29 (4231.37)
		Median [P25 - P75]	663.11 [326.27 - 1254.08]	609.73 [56.11 - 620.03]	100.14 [10 - 410.68]	127.93 [22.02 - 2446.24]	159.38 [24.02 - 739.91]
		Min-Max	126.94 - 10803.01	10 - 6648.11	10 - 1204.18	10 - 20480	10 - 20480
		GMT (SE) [95%CI]	820.59 (2.73) [104 - 6474.59]	269.07 (2.73) [34.1 - 2122.99]	82.81 (2.04) [19.22 - 356.81]	194.46 (2.04) [45.13 - 837.85]	244.19 (1.55) [99.83 - 597.28]
	Contrast vs groups	Ref.: Pfizer #	Ref.	0.33 [0.02 - 6.09] ; 0.4398	0.1 [0.01 - 1.27] ; 0.0737	0.24 [0.02 - 2.97] ; 0.2527	-
		Ref.: HIPRA(10µg) #	-	Ref.	0.31 [0.02 - 3.86] ; 0.3472	0.72 [0.06 - 9.07] ; 0.7940	-
		Ref.: HIPRA(20µg) #	-	-	Ref.	2.35 [0.3 - 18.53] ; 0.4034	-
	Contrasts vs Screening	n	5	5	10	10	30
		Mean (SD)	2624.68 (4586.18)	1578.8 (2843.21)	263.09 (403.58)	2763.85 (6345.47)	1709.56 (4220.76)
		Median [P25 - P75]	653.11 [316.27 - 1244.08]	599.73 [46.11 - 610.03]	79.93 [0 - 400.68]	117.93 [12.02 - 2436.24]	149.38 [12.02 - 729.91]
		Min-Max	116.94 - 10793.01	0 - 6638.11	0 - 1194.18	0 - 20397	0 - 20397
		Ref.: Screening #	82.06 [11.47 - 587.3] ; <.0001	26.91 [3.76 - 192.57] ; 0.0020	7.06 [1.76 - 28.41] ; 0.0077	15.74 [3.91 - 63.29] ; 0.0004	-
14 days D2-D35	Values	n	5	5	10	10	30
		Mean (SD)	4441.51 (3601.04)	1973.17 (3392.19)	646.4 (625.44)	3068.8 (6247.62)	2307.51 (4191.25)
		Median [P25 - P75]	3007.03 [2600.42 - 5910.08]	605.23 [307.26 - 826.62]	418.16 [173.64 - 989.9]	845 [102 - 1754]	755 [307.26 - 2150.64]
		Min-Max	728 - 9962	105.55 - 8021.2	144.34 - 2150.64	55 - 20480	55 - 20480
		GMT (SE) [95%CI]	3199.27 (1.88) [870.73 - 11754.85]	665.1 (1.88) [181.02 - 2443.73]	444.17 (1.56) [176.98 - 1114.77]	752.85 (1.56) [299.97 - 1889.49]	918.44 (1.32) [522.79 - 1613.52]
	Contrast vs groups	Ref.: Pfizer #	Ref.	0.21 [0.03 - 1.31] ; 0.0911	0.14 [0.03 - 0.68] ; 0.0171	0.24 [0.05 - 1.16] ; 0.0734	-
		Ref.: HIPRA(10µg) #	-	Ref.	0.67 [0.14 - 3.29] ; 0.6070	1.13 [0.23 - 5.57] ; 0.8742	-
		Ref.: HIPRA(20µg) #	-	-	Ref.	1.69 [0.46 - 6.23] ; 0.4122	-
	Contrasts vs Screening	n	5	5	10	10	30
		Mean (SD)	4431.51 (3601.04)	1963.17 (3392.19)	632.5 (626.27)	3051.5 (6225.02)	2293.78 (4180.91)
		Median [P25 - P75]	2997.03 [2590.42 - 5900.08]	595.23 [297.26 - 816.62]	408.16 [163.64 - 979.9]	835 [92 - 1744]	745 [297.26 - 2140.64]
		Min-Max	718 - 9952	95.55 - 8011.2	134.34 - 2140.64	45 - 20397	45 - 20397
		Ref.: Screening #	319.93 [97.05 - 1054.68] ; <.0001	66.51 [20.18 - 219.26] ; <.0001	37.89 [16.3 - 88.08] ; <.0001	60.93 [26.21 - 141.62] ; <.0001	-

#: GMFR [95%CI] ; p-value
Not Apply: not available data.
Non-Est.: non estimable due to missing in all subjects in this group.
Brown cells shows the estimations of GMT by time point and the GMTR between-groups and intra-groups.
Source: table 29.4

Overall, PHH-1V has demonstrated to be immunogenic in adult subjects vaccinated with antigen doses of 10 µg, 20 µg or 40 µg in a prime-boost regime. Specifically, high levels of SARS-CoV-2 neutralising are produced against Alpha, Beta, Gamma and Delta variants. The sample size of this clinical trial was very low as it was a FIH. So, data from the immunogenicity could only be taken as a trend as the statistical analysis was not always able to confirm a significant difference with this sample size.
There was no evidence of a clear dose-response relationship between the three PHH-1V vaccine doses.

2.5.5.2. Main study(ies)

Study HIPRA-HH-2

Study HIPRA-HH-2 is a double-blind, randomized (2:1), active controlled (comparator Comirnaty 30 µg), multi-centre (10 sites in Spain), non-inferiority trial to evaluate immunogenicity and safety of a single PHH-1V dose (40 µg) as a booster vaccination in in adults (18, at least 10% >65 years). This study is planned to be followed by a Phase 3 single-arm, open-label trial to assess further immunogenicity and safety.

The latest report provides the interim analysis (version 5.0; dated 10 March 2023) and presents results from all enrolled subjects who completed Day 14, Day 28, and Day 182 assessments, and also a subset of subjects who completed Day 98 assessments.

Methods

- **Study Participants**

Adults aged 18 years of age or older previously primed with 2 doses of Pfizer/BioNTech vaccine vaccine at least 182 days and with a maximum of 365 days prior to the booster injection.

Inclusion criteria:

Subjects must have met all the following criteria to be considered eligible for the study:

1 Male or female, by birth, ≥ 18 years old at Screening.

2. Was willing and able to comply with scheduled visits, laboratory tests, complete diaries, and other study procedures.

3. Body Mass Index (BMI) between 18 to 40 kg/m2.

4. Had received a complete COVID-19 vaccination programme (two administrations, prime and boosting) at least 182 days and with a maximum of 365 days before booster vaccination with Comirnaty vaccine.

5. Had a negative COVID-19 polymerase chain reaction (PCR) test at Screening.

6. Was willing to avoid all other vaccines within 4 weeks before and after vaccination in this study (Day 0). Seasonal influenza vaccination was allowed if it was received at least 14 days before or after Day 0.

7. Was willing to refrain from blood donation during the study.

8. Women of childbearing potential must have had a negative blood or urine pregnancy test at Screening and Day 0 (before vaccination).

9. Women of childbearing potential must have been willing to use highly effective contraceptive methods or had practiced sexual abstinence from the screening visit until 8 weeks after the vaccination (Day 0). Highly effective contraceptive methods included oral,

intravaginal, or transdermal combined (containing oestrogen and progestogen) hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomised partner; condom and sexual abstinence.

NOTE: A woman was considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods included hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state was defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may have been used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement was insufficient.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods (LAM) were not acceptable methods of contraception.

10. Males who were not sterilised, must have been willing to avoid impregnating female partners from Screening until 8 weeks after vaccination (Day 0).

11. Was willing and able to provide written informed consent prior the initiation of any study procedures.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from participation in this study:

1. Pregnant or lactating or intending to become pregnant or planned to breastfeed during the study.

2. Positive pregnancy test at Screening or Day 0.

3. Any medical disease (acute, subacute, intermittent, or chronic) or condition that in the opinion of the Investigator compromised the subject's safety, preclude vaccination or compromised interpretation of the results.

4. Ongoing serious psychiatric condition likely to affect participation in the study (e.g., ongoing severe depression, recent suicidal ideation, bipolar disorder, personality disorder, alcohol and drug dependency, severe eating disorder, psychosis, use of mood stabilisers or antipsychotic medication).

5. History of respiratory disease (e.g., chronic obstructive pulmonary disease [COPD]) requiring daily medications currently or any treatment of respiratory disease exacerbations (e.g., asthma exacerbation) in the last 6 months.

6. History of significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease) or history of myocarditis or pericarditis as an adult. Controlled hypertension was permitted at the discretion of the Investigator.

7. History of neurological or neurodevelopmental conditions (e.g., epilepsy, stroke, seizures in the last 3 years, encephalopathy, focal neurologic deficits, Guillain-Barré syndrome, encephalomyelitis, or transverse myelitis).

8. Ongoing malignancy or recent diagnosis of malignancy in the last five years excluding basal cell and squamous cell carcinoma of the skin, which were allowed.

9. Any confirmed or suspected autoimmune, immunosuppressive or immunodeficiency disease/condition (iatrogenic or congenital), including human immunodeficiency virus (HIV) infection, asplenia, or recurrent severe infections.

NOTE: Mild psoriasis, well controlled autoimmune thyroid disease, vitiligo, stable coeliac disease not requiring immunosuppressive or immunomodulatory therapy and any stable endocrine disorders that have a confirmed autoimmune aetiology (e.g., thyroid, pancreatic), including controlled diabetes, were permitted at the discretion of the Investigator.

10. Acute illness within 72 hours before Day 0 that, in the opinion of the Investigator may have interfered the evaluation of safety parameters.

11. Received an investigational drug within 90 days before Screening or planned to participate in another interventional clinical study (drug/biologic/device) within 12 months after vaccination (Day 0).

12. History of hypersensitivity or severe allergic reactions, including anaphylaxis, generalised urticarial, angioedema and other significant reactions related to food, drugs, vaccines, or pharmaceutical agents, which were likely to be exacerbated by any component of PHH-1V (including the oil in water adjuvant equivalent to MF59C.1).

13. Use of any immunosuppressant, glucocorticoids, or other immune-modifying drugs within 2 months before Day 0; or anticipation of the need for immunosuppressive treatment within 182 days after vaccination (Day 0). NOTE: The use of topical, inhaled, and nasal routes were not permitted. Short courses of ≤5 days of topical and inhaled corticoids were permitted.

14. Received immunoglobulin, blood-derived products, or other immunosuppressant drugs within 90 days before vaccination (Day 0).

15. Known disturbance of coagulation (iatrogenic or congenital) or blood dyscrasias.

16. Known bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder), (iatrogenic or congenital), blood dyscrasias, or prior history of significant bleeding or bruising following intramuscular (IM) injections or venepuncture.

NOTE: The use of ≤325 mg of aspirin per day as prophylaxis was permitted, but the use of other platelet aggregation inhibitors, thrombin inhibitors, Factor Xa inhibitors, or warfarin derivatives was exclusionary, regardless of bleeding history, because these implied treatment or prophylaxis of known cardiac or vascular disease.

17. Chronic liver disease.

18. Positive test for HIV types 1 or 2 infection, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibodies (HCV Abs) at Screening.

19. Suspected or known current alcohol abuse or any other substances abuse (except tobacco).

NOTE: Abuse was defined if consumption exceeded an average of 14 units/week (daily dose of 24 g, weekly dose of 168 g). One unit (12 g) corresponded to 0.3 L of beer/day or 0.12 L of wine/day or 1 glass (at 2 cL) of spirits/day.

20. History of COVID-19 infection.

21. Ever been included in a trial with an experimental vaccine against COVID-19.

22. Close contact with anyone known to have SARS-CoV-2 infection within 15 days before

Screening.

23. Scheduled elective surgery during the study.

24. Life expectancy of less than 12 months.

25. Any condition and/or laboratory finding that, in the Investigators opinion, would have interfered with the study or placed the subject at risk.

- **Treatments**

Subjects were randomly assigned to the following two treatment arms in a 2:1 ratio of PHH 1V:Comirnaty ratio:

- Cohort 1: single booster dose of PHH-1V on Day 0 (COVID-19 HIPRA's vaccine (PHH-1V) 0.5 mL (40 µg), single intramuscular administration. Batch number: 70Z2111)
- Cohort 2: single booster dose of Comirnaty on Day 0 ((COVID-19 Pfizer–BioNTech's vaccine (Comirnaty) 0.3 mL (30 µg), single intramuscular administration. Several commercial batches have been used during the study.)

Additionally, randomisation was stratified by age group (18-64 versus 65+ years) with approximately 10% of the sample enrolled in the older age group.

- **Objectives**

Primary objectives:

- To determine and compare the changes in immunogenicity measured by pseudovirus neutralisation against the D614G strain (also known as L strain) at Baseline and Day 14 after PHH-1V vaccination versus subjects who have received complete vaccination, including homologous booster, with the Comirnaty vaccine at least 182 days and with a maximum of 365 days before booster vaccination.
- To assess the safety and tolerability of PHH-1V as a booster dose in healthy adult subjects fully vaccinated against COVID-19 with the Comirnaty vaccine.

Secondary objectives:

- To determine and compare the changes of the immunogenicity measured by SARS-CoV-2 pseudovirion-based neutralisation assay (PBNA) against the Variants of Concern (VOC) at Baseline and at Day 14, 28, extra visit (if applicable), 98 (only in a subset of approximately 20% of the total subjects included in the study), 182, and 364 in subjects who have received two doses of Comirnaty vaccine and PHH 1V as a booster versus subjects who have received three vaccinations with the Comirnaty vaccine.
- To determine and compare the changes in immunogenicity measured by wild-type SARS CoV-2 neutralisation test (VNA) at Baseline and Days 14, 28, extra visit (if applicable), 182, and 364 in a subset of subjects (ie. 20% of the total subjects in the study) who have received two doses of Comirnaty vaccine and PHH-1V as a booster versus subjects who have received three vaccinations with the Comirnaty vaccine.
- To evaluate the immunogenicity measured by enzyme-linked immunosorbent assay (ELISA) to the SARS-CoV-2 spike glycoprotein at Baseline and Days 14, 28, extra visit (if applicable), 98 (only in a subset of approximately 20% of the total subjects included in the study), 182, and 364 in subjects who have received two doses of Comirnaty vaccine and PHH-

1V as a booster versus subjects who have received three vaccinations with the Comirnaty vaccine.

- To evaluate T-cell mediated responses against the SARS-CoV-2 S glycoprotein at Baseline and Day 14 in a subset of subjects (ie. 20% of the total subjects in the study) who have received two doses of Comirnaty vaccine and PHH-1V as a booster versus subjects who have received three vaccinations with the Comirnaty vaccine.

- To assess Th-1/Th-2 T-cell mediated responses against the SARS-CoV-2 S glycoprotein at Baseline and Day 14 in a subset of subjects (ie. 20% of the total subjects in the study) who have received two doses of Comirnaty vaccine and PHH 1V as a booster versus subjects who have received three vaccinations with the Comirnaty vaccine.

Exploratory objectives:

- To assess the number of subjects with SARS-CoV-2 infections ≥14 days after PHH-1V booster in subjects who had no evidence of infection before participating in the study.

- To assess the number of SARS-CoV-2 severe infections ≥14 days after receiving PHH-1V.

- **Outcomes/endpoints**

Primary endpoints:

- Neutralisation titre against D614G strain measured as inhibitory concentration 50 (IC50) by a PBNA and reported as reciprocal concentration for each individual sample and geometric mean titre (GMT) for treatment group comparison at Baseline and Day 14.

Secondary endpoints:

- Neutralisation titre against VoC measured as IC50 by PBNA and reported as reciprocal concentration for each individual sample and GMT for treatment group comparison at Baseline and Days 14, 28, extra visit (if applicable), 98 (only in a subset of approximately 20% of the total subjects included in the study), 182, and 364.
- Geometric mean fold ratios (GMFR) in neutralising antibodies titres for treatment group comparison at Baseline and Days 14, 28, extra visit (if applicable), 98 (only in a subset of approximately 20% of the total subjects included in the study), 182, and 364.
- Neutralisation titre measured as inhibitory dilution 50 (ID50) by a VNA and reported as reciprocal dilution for each individual sample, and GMT for treatment group comparison at Baseline and Days 14, 28, extra visit (if applicable), 182, and 364. This analysis will be performed in a subset of subjects.
- Binding antibodies titre measured for each individual sample and GMT for treatment group comparison at Baseline and Days 14, 28, extra visit (if applicable), 98 (only in a subset of approximately 20% of the total subjects included in the study),182, and 364.
- GMFR in binding antibodies titre from Baseline and Days 14, 28, extra visit (if applicable), 98 (only in a subset of approximately 20% of the total subjects included in the study), 182, and 364.
- Percentage of subjects that, after a booster dose, have a ≥4-fold change in binding antibodies titre from Baseline and Days 14, 28, extra visit (if applicable), 98 (only in a subset of approximately 20% of the total subjects included in the study),182, and 364.

- T-cell-mediated response to the SARS-CoV-2 S protein as measured by whole PBMC stimulation by enzyme-linked immune absorbent spot (ELISpot) at Baseline and at Day 14. This analysis will be performed in a subset of subjects.
- CD4+/CD8+ T-cell response to the SARS-CoV-2 S protein as measured by in vitro PBMC stimulation by cytokine staining assays at Baseline and at Day 14. This analysis will be performed in a subset of subjects.

Exploratory endpoints:

- Number and percentage of subjects with SARS-CoV-2 infections according to COVID 19 infection criteria throughout the study duration.
- Number and percentage of COVID-19 severe infections through Day 364.
- Number and percentage of hospital admissions associated with COVID-19 through Day 364.
- Number and percentage of intensive care unit admissions associated with COVID 19 through Day 364.
- Number and percentage of deaths associated with COVID-19 through Day 364.

- **Sample size**

In accordance with the FDA Guidance for Industry on Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, non-inferiority for a new influenza vaccine product could be claimed if the upper bound of a two-sided 95% CI surrounding the ratio of GMT for the control to investigational product does not exceed 1.5. Given the uncertainty in the immune response and variability, this study was planned with a reduced non-inferiority margin of 1.4 to ensure sufficient sample size for safety and immunogenicity assessments. Considering these assumptions, and with a 2:1 randomisation ratio, group sample sizes of 301 and 151, respectively, would have achieved 90% power to detect non-inferiority using a one-sided 2.5% significance level, two-sample t-test using a SDlog=0.45 for both treatments.

Assuming a 25% withdrawal rate, a total of 602 subjects (401 in PHH-1V group, 201 in the Comirnaty active control group) were planned to be randomised in this study.

The 602 planned subjects enrolled into the study were stratified 2:1 for the following age groups: 18 to 64 years and ≥65 years.

- **Randomisation and Blinding (masking)**

Subjects were allocated to treatment using an Interactive Response Technology (IRT). Randomisation was stratified by age group: 18 to 64 years and ≥65 years with approximately 10% enrolled among the ≥65 group. Subjects were randomly assigned to treatment (PHH-1V or Comirnaty) in a 2:1 ratio. Randomisation could have taken place prior to the Baseline visit (Day 0) but the inclusion and exclusion criteria needed to be reviewed again during the randomisation visit to ensure that the subject was eligible.

This study was double-blinded; subjects, site staff, the Sponsor, and the CRO were blinded to subject treatment. At each site, an unblinded pharmacist or other qualified personnel prepared the booster dose, depending on treatment allocation. In addition, an identified, unblinded site staff member, who was not otherwise involved with the study procedures (except for blood collection), may have administered treatment to subjects. A label was used to mask the syringe because the two treatments

were visually different. An unblinded Clinical Research Associate (CRA), who was not otherwise involved with monitoring study data, reviewed study drug accountability.

- **Statistical methods**

Analysis populations

As of protocol version 5.0 the following analyses populations were defined in this study:

- **Enrolled (EP):** All subjects who have signed the Informed Consent Form (ICF).
- **Intent-to-treat (ITT):** All subjects who are randomly assigned to treatment, regardless of the treatment status in the study. Subjects will be grouped as randomised.
- **Modified Intent-to-treat (mITT):** All subjects in the ITT who meet the inclusion/exclusion criteria and received a dose of study drug.
- **Per-protocol (PP):** All subjects in the mITT who received a dose of study drug and have no major protocol deviations, as determined and documented by Sponsor prior to data base lock (DBL) and unblinding that impact critical or key study data. Subjects will be analysed according to the treatment they actually received.
- **Immunogenicity (IGP):** All subjects in the mITT who had a valid immunogenicity test result before receiving study drug and at least one valid result after dosing. Subjects will be grouped as randomised.
- **Safety (SP):** All randomised subjects who received the study drug. This population will be used for all analyses of safety. Subjects will be analysed according to the treatment they actually received.

The efficacy analysis was to be performed using the mITT and PP populations. Immunogenicity was to be further analysed using the IGP population.

Due to concerns raised during the rolling review an additional analysis population"mITT3" was defined that excluded confirmed COVID-19 cases: All subjects in the mITT without COVID-19 infections recorded via adverse event reporting prior to their 6 month visit date, for the evaluation of long-term immunogenicity.

Efficacy Analysis:

To show non-inferiority the treatment group difference (Comirnaty active control vs PHH-1V) the efficacy analyses tested the following hypothesis (FDA Guidance for Industry on Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines):

- Null hypothesis, H0: The ratio of the GMTs (Licensed product: Investigational product) 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).

The NIm for this study is 1.4, whereby the upper bound of the 95% CI must be lower to reject the null hypothesis and is defined for each endpoint separately.

According to the interim CSR:

The following subject populations were evaluated and used for presentation and analysis of the data:

- **Enrolled (EP)**: All subjects who had signed the ICF.
- **Intent-to-treat (ITT)**: All subjects who were randomly assigned to treatment, regardless of the subject's treatment status in the study. Subjects were grouped as treated.
- **Modified ITT (mITT)**: All subjects in the ITT who met the inclusion/exclusion criteria and received a dose of study drug. Subjects who tested positive for COVID-19 within 14 days of receiving study drug were excluded. Subjects were grouped as treated.
- **Per-protocol (PP)**: All subjects in the mITT and had no important protocol deviations, as determined, and documented by Sponsor prior to data base lock (DBL) and unblinding that impacted critical or key study data. Subjects were analysed according to the treatment they actually received.
- **Immunogenicity (IGP)**: All subjects in the mITT who had a valid immunogenicity test result before receiving study drug and at least one valid result after dosing. Subjects were grouped as treated.
- **Safety (SP)**: All randomised subjects who received the study drug. This population was used for all analyses of safety. Subjects were analysed according to the treatment they actually received.

The mITT population was the primary population for the analysis of efficacy parameters. Subsets of efficacy parameters were evaluated for the PP and IGP populations. The Safety population was the primary population for the analysis of safety endpoints.

In Addition interim CSR Version 4.0:

In version 4.0 of the Interim Study Report the Applicant additionally defines:

• mITT3 (excluding confirmed COVID-19 cases): All subjects in the mITT without COVID-19 infections recorded via adverse event reporting prior to their 6 month visit date, for the evaluation of long-term immunogenicity.

Estimand

According to the SAP:

The primary estimand for the study which follows the 'While On Treatment' strategy is:

The ratio of the geometric mean titres (GMTs) for the two treatment groups in the target subject population for the neutralising antibody titres measured as inhibitory concentration 50 (IC50) by PBNA for D614G strain at Day 14 after the booster dose, regardless of study discontinuation and COVID-19 infections.

Estimand components:

A. The population is restricted to the modified intent-to-treat (mITT) above.

B. The variable is the neutralising antibody titres measured as IC50 by PBNA for D614G strain and reported as GMT at Day 14 after the booster dose.

C. The intervention effect is regardless of study discontinuation and COVID-19 infections.

D. The population-level summary measure is the ratio of the GMTs for the two treatment groups.

Secondary estimands will follow a similar strategy as above.

Analysis Methods

According to the protocol:
The following statistical methods were carried out:

- The continuous variables related to immunogenicity were analysed using analysis of variance (ANOVA) with previously log-transformed data. Estimates for each treatment group were presented with the associated 95% CIs of the geometric means. The treatment group difference (Comirnaty active control vs PHH-1V) was also presented with the corresponding 95% CI and p-value.
- The binary variables related to the immunogenicity endpoints (e.g., proportion of subjects with a >=4-fold change in binding antibodies titre from Baseline) were described by frequency proportion and 95% CI using exact methods based on binomial, Clopper- Pearson method by treatment group. A logistic regression was used to evaluate the treatment comparisons and estimate the differences between groups and their 95% CI.
- Assessment of the subjects with COVID-19 infections and severity was described using incidence of cases and frequencies (%).

All statistical tests were performed using a two-tailed 5% overall significance level, unless otherwise stated. The efficacy analysis was performed using the mITT and PP populations. Immunogenicity analysis was further analysed using the IGP population.

To investigate the primary endpoint of neutralisation titre against D614G strain as measured by IC50 by a PBNA at Day 14, a mixed effects model for repeated measures (MMRM) was used.

The MMRM model will be carried out on log transformed data and will include the following effects:

- Fixed effects: treatment group, age group, visit (Baseline and Day 14) and treatment-by-visit interaction
- Random effect: site
- Repeated measures structure: visits within subject.

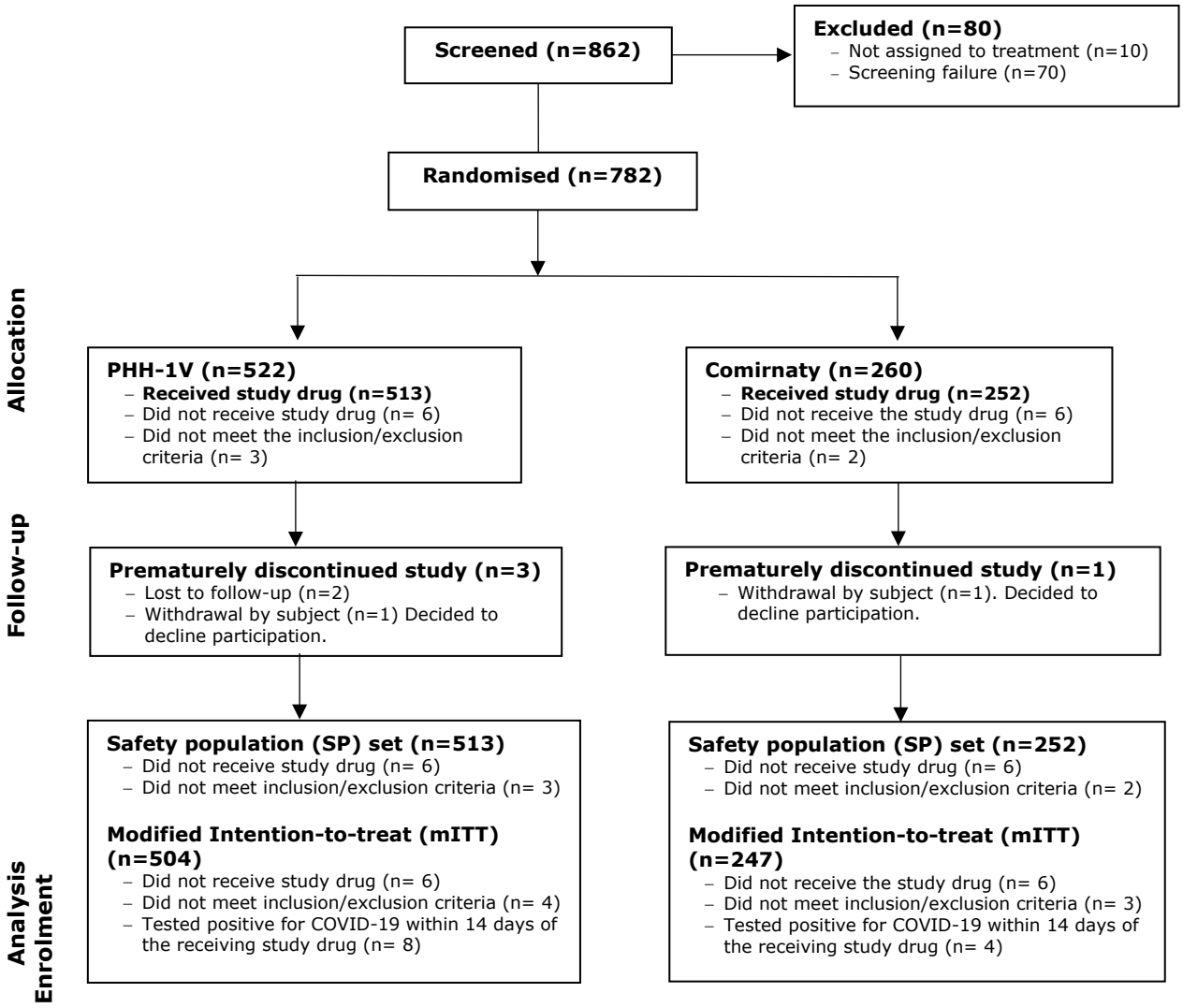
A compound symmetry covariance matrix structure was used. The denominator degrees of freedom were computed using the Kenward-Roger method.

The model assumptions for each model were assessed, for example via visual inspection of the diagnostic plots. Alternative covariance matrix structures were explored and if necessary, transformation of the endpoint was considered as a sensitivity analysis. Alternative methods may be considered if assumptions on transformed data are also not met.

The Least Squared (LS) mean ratio estimates for each treatment group were presented with the associated 95% CIs. The back-transformed treatment group difference in LS Means ratio (GMT) (Comirnaty active control vs PHH-1V) was also presented with the corresponding 95% CI and p-value.

Results

- **Participant flow**



- **Recruitment**

Date first subject enrolled: 15 November 2021

Date last subject completed: Pending

Datacut-off date: 18 July 2022

Release date of report: 10 March 2023

- **Conduct of the study**

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with Good Clinical Practice (GCP) guidelines as denoted in the International Council for Harmonisation (ICH) E6 requirements.

Changes in the Conduct of the Study

Protocol version 2.0 (30 September 2021) was the protocol version in the original submissions to Agencia Española del Medicamento (AEMPS) Spanish Agency of Medicines and the ethics committee. There have been several amendments to the protocol since Protocol version 2.0. A summary of substantial changes to the protocol follows.

Only key changes are reported here. For the full list of changes please refer to the study report.

Protocol Version 3.0 (29 November 2021):

- The sample size decreased, from 1075 to 602 subjects.
- The percentage of subjects randomised in the 65+ age group decreased from 20% to 10%.
- A phone call at 72 hours post vaccination was added for the first 30 subjects to collect safety data to be sent to the DSMB.
- The non-inferiority margin increased to 1.4 from 1.25.
- Modified intent-to-treat (mITT) population was added, which was to be used for the PP and IGP populations.
- Infections (COVID-19) was added to the list of AESI's potential immune-mediated medical conditions.

Protocol Version 4.0 (20 December 2021):

- The unblinding date was updated from Day 182 to Day 28. Once the subject was aware of which vaccine they received, they were able to decide if they wanted to receive a commercial COVID-19 vaccine (three months after receiving PHH-1V).
- This was added as an extra visit between Day 28 and Day 182.

Protocol Version 5.0 (14 February 2022):

- Day 98 was added to the schedule of events for only a subset of approximately 20% of the total number of subjects included in the study.
- The exploratory endpoint was updated to collect the number and percentage of subjects with SARS-CoV-2 infections ≥14 days after PHH-1V booster vaccination.
- Infections (COVID-19) was updated in the list of AESI's potential immune-mediated medical conditions to COVID-19 cases happening ≥14 days post-booster.
- *Changes in the Planned Analysis of the Study*

Changes between the protocol-defined statistical analyses and those presented in the SAP:

- Addition of the Estimands Framework per ICH E9 (R1) addendum.
- Clarification of analysis of the exploratory endpoints relating to COVID-19 infections
- Update to secondary endpoint text for GMFR to correct terminology as this endpoint cannot be analysed at Baseline as this is used to calculate the fold rise.
- Amendments to the summary statistics for immunogenicity data to only list raw and reciprocal data and summarise the log10 transformations.

Protocol Version 8.0 (20 July 2022):

This latest protocol version submitted with sequence 4 (October 2022) incorporates the Applicant's intent to investigate a fourth dose administration of PHH-1V.

- **Baseline data**

For all analyses, Baseline was defined as the most recent measurement prior to the first

administration of study drug.

For an overview of baseline demographic data please refer to the safety section of this report (Table 50).

- **Numbers analysed**

Table 6. Subject enrolment and disposition

	Statistics	PHH-1V	Comirnaty	Overall
Enrolled population	n			862
Intention-to-treat (ITT)	n	522	260	782
Modified Intention-to-treat (mITT)	n (%)	504 (100.0)	247 (100.0)	751 (100.0)
mITT excluding all subjects with COVID-19 infections (mITT3 (excluding confirmed COVID-19 cases)	n (%)	347 (68.8)	167 (67.6)	514 (68.4)
Per-protocol set (PP)	n (%)	504 (100.0)	247 (100.0)	751 (100.0)
Immunogenicity population	n (%)	503 (99.8)	246 (99.6)	749 (99.7)
Safety population (SP) set	n (%)	513 (101.8)	252 (102.0)	765 (101.9)
Subjects who completed the study	n (%)	0	0	0
Subjects who prematurely discontinued study	n (%)	3 (0.6)	1 (0.4)	4 (0.5)
Reason for study withdrawal	n (%)			
Lost to follow-up		2 (0.4)	0	2 (0.3)
Withdrew consent to participate in study		0	1 (0.4)	1 (0.1)
Withdrawal by subject		1 (0.2)	0	1 (0.1)

- **Outcomes and estimation**

Primary efficacy endpoint

- Neutralisation titre against the D614G strain measured as half maximal inhibitory concentration (IC50) by a PBNA and reported as reciprocal concentration for each individual sample and geometric mean titre (GMT) for treatment group comparison at Baseline and Day 14.

Geometric mean values of the neutralisation titres against the D614G strain strain for the PHH-1V treatment group were 87.93, 2003.03, 2280.78, 1114.42 and 1234.04 on Days 14, 28, 98, and 182, respectively.

Geometric mean values of the neutralisation titres against the D614G strain strain for the Comirnaty treatment group were 85.80, 3387.16, 2984.40, 988.51 and 763.10 on Days 14, 28, 98, and 182, respectively.

Table 7 Summary of IC50 against D614G strain (mITT Population)
Log10 Data

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
		Observed value	Observed value	Observed value
Baseline	n	504	247	751
	Geometric mean	87.93	85.80	87.23
	Geometric SD	2.73	2.62	2.69
	Minimum	1.29	1.30	1.29
	Q1	1.61	1.64	1.63
	Median	1.91	1.90	1.91
	Q3	2.21	2.17	2.20
	Maximum	4.01	3.79	4.01
Day 14	n	500	241	741
	Geometric mean	2003.03	3387.16	2376.23
	Geometric SD	2.97	2.50	2.90
	Minimum	1.66	1.95	1.66
	Q1	3.00	3.31	3.12
	Median	3.33	3.54	3.42
	Q3	3.60	3.78	3.67
	Maximum	4.69	4.63	4.69
Day 28	n	496	244	740
	Geometric mean	2280.78	2984.40	2492.22
	Geometric SD	3.12	2.68	2.99
	Minimum	1.72	2.32	1.72
	Q1	3.02	3.20	3.09
	Median	3.37	3.47	3.41
	Q3	3.70	3.76	3.73
	Maximum	5.07	4.74	5.07
Day 98	n	78	42	120
	Geometric mean	1114.42	988.51	1068.62
	Geometric SD	2.48	2.18	2.37
	Minimum	1.97	2.30	1.97
	Q1	2.87	2.74	2.80
	Median	3.06	2.98	3.05
	Q3	3.31	3.17	3.25
	Maximum	3.88	3.90	3.90
Day 182	n	492	242	734
	Geometric mean	1234.04	763.10	1053.18
	Geometric SD	3.72	3.32	3.66
	Minimum	1.30	1.30	1.30
	Q1	2.73	2.54	2.64
	Median	3.13	2.93	3.05

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
		Observed value	Observed value	Observed value
	Q3	3.50	3.25	3.40
	Maximum	4.31	4.31	4.31

Abbreviations: IC_{50} = Inhibitory Concentration 50, N = the number of subjects in the population, mITT = modified intent-to-treat population; SD = standard deviation.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Table 14.2.1.1.1.1

Table 8 Analysis of IC50 agaisnt D614G strain (mITT Population)
Analysis of IC_{50} against Wuhan (mITT Population)

	PHH-1V (N=504)	Comirnaty (N=247)
Baseline		
Number of subjects with data n (%)	504 (100.0)	247 (100.0)
Adjusted treatment mean (LS Mean) [1]	1.93	1.92
Standard error	0.033	0.039
95% CI	1.864, 2.002	1.845, 2.003
GMT for adjusted treatment mean [2]	85.75	84.02
95% CI	73.180, 100.483	70.044, 100.785
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.98
95% CI for adjusted ratio		0.83, 1.16
p-value for ratio = 1		0.8080
Day 14		
Number of subjects with data n (%)	500 (99.2)	241 (97.6)
Adjusted treatment mean (LS Mean) [1]	3.29	3.52
Standard error	0.033	0.039
95% CI	3.222, 3.360	3.444, 3.603
GMT for adjusted treatment mean [2]	1953.89	3336.54
95% CI	1667.165, 2289.932	2778.559, 4006.568
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		1.71
95% CI for ratio		1.45, 2.02
p-value for ratio = 1		<0.0001
Day 28		
Number of subjects with data n (%)	496 (98.4)	244 (98.8)

	PHH-1V (N=504)	Comirnaty (N=247)
Adjusted treatment mean (LS Mean) [1]	3.35	3.47
Standard error	0.033	0.039
95% CI	3.280, 3.417	3.392, 3.550
GMT for adjusted treatment mean [2]	2230.95	2958.40
95% CI	1903.291, 2615.005	2465.002, 3550.550
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		1.33
95% CI for ratio		1.12, 1.56
p-value for ratio = 1		0.0008
Day 98		
Number of subjects with data n (%)	78 (15.5)	42 (17.0)
Adjusted treatment means (LS Mean) [1]	3.08	3.02
Standard error	0.057	0.074
95% CI	2.964, 3.189	2.876, 3.165
GMT for adjusted treatment mean [2]	1193.35	1048.32
95% CI	921.235, 1545.849	750.901, 1463.540
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.88
95% CI for adjusted ratio		0.60, 1.29
p-value for ratio = 1		0.5101
Day 182		
Number of subjects with data n (%)	492 (97.6)	242 (98.0)
Adjusted treatment means (LS Mean) [1]	3.08	2.88
Standard error	0.033	0.039
95% CI	3.012, 3.150	2.797, 2.955
GMT for adjusted treatment mean [2]	1205.49	751.64
95% CI	1028.216, 1413.329	626.022, 902.456
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.62
95% CI for adjusted ratio		0.53, 0.74
p-value for ratio = 1		<0.0001

Abbreviations: CI = confidence interval; GMT = Geometric Mean Titre; IC_{50} = Inhibitory Concentration 50; LS mean = least square mean; N = the number of subjects in the population; mITT = modified intent-to-treat population; MMRM = mixed model repeated measures.

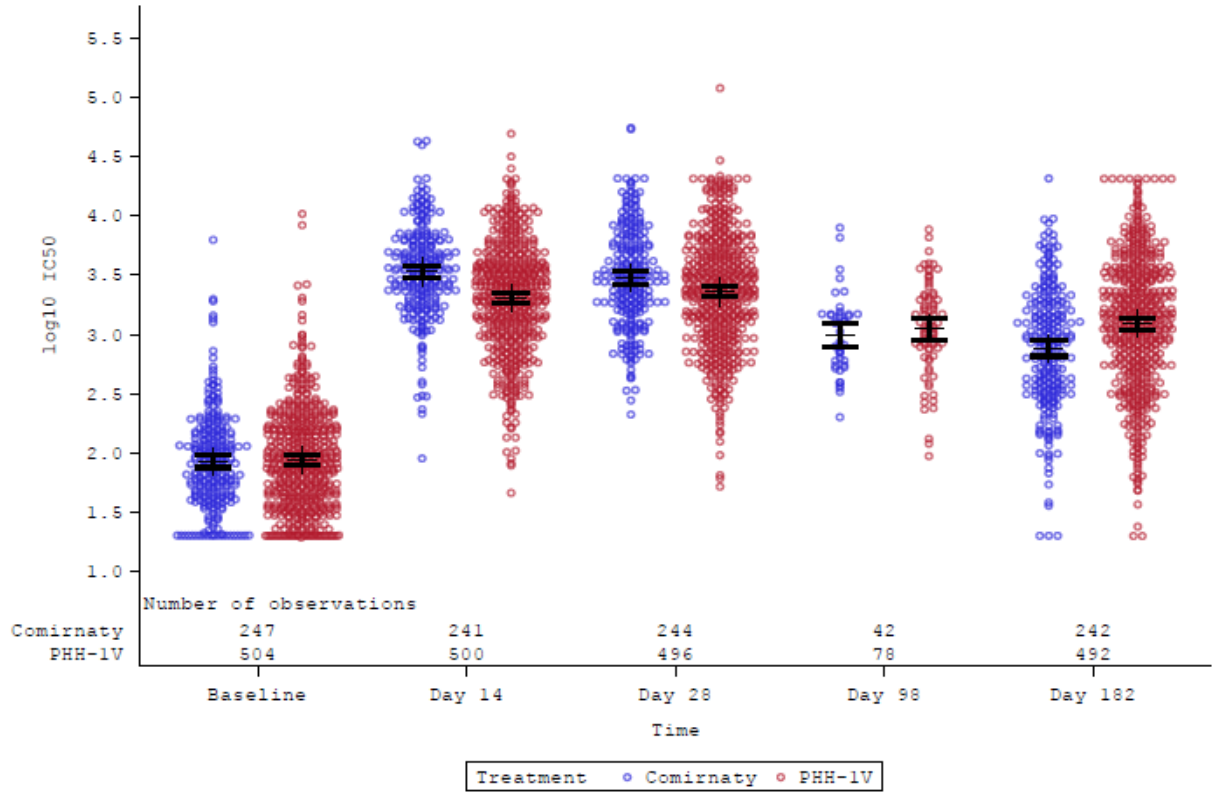
[1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group, age group (18-64, >64), visit (Baseline, Days 14 and 98), and the treatment-by-visit interaction term as fixed effects. Site was included as a random effect. A compound symmetry covariance matrix 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 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 analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis. Transformations have been made on the imputed data.

Source: Table 14.2.1.2.1.1

Figure 2. Log10 IC50 against D614G strainOver time (mITT Population)



Abbreviations: IC_{50} = Inhibitory Concentration 50; mITT = modified intent-to-treat population.

Baseline will be defined as the most recent measurement prior to the first administration of study drug.

Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.

Source: Figure 14.2.1.1.1.1

Figure 3. Reverse cumulative distribution curves of log_{10} neutralizing antibody titres at Day 14.

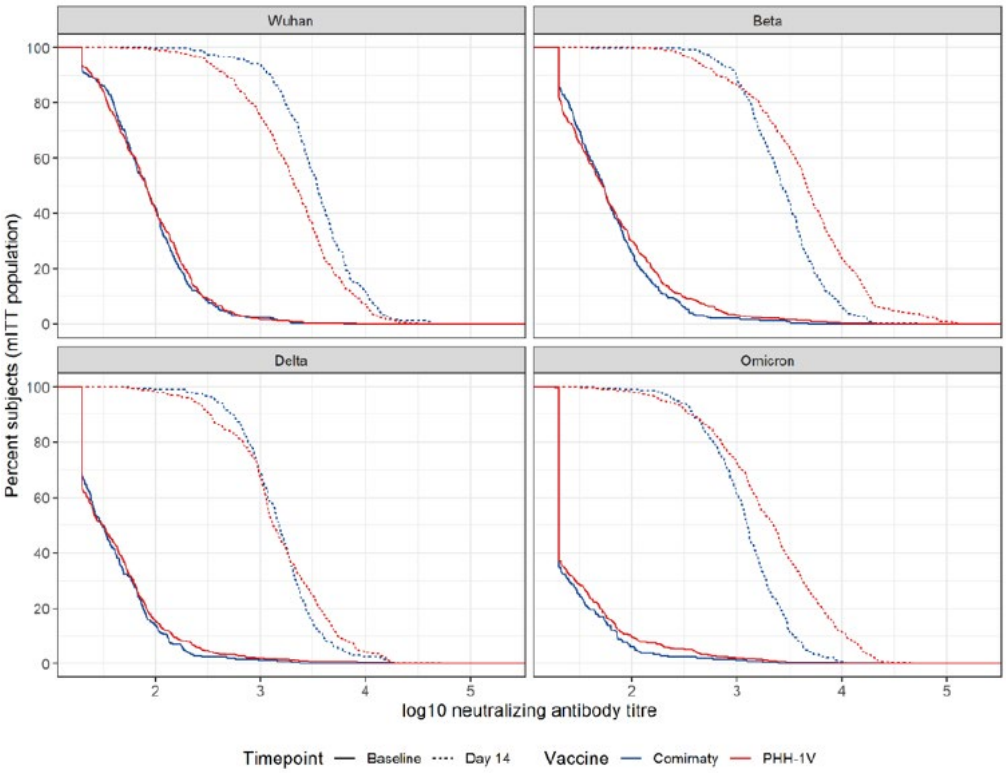


Figure 1. Reverse cumulative distribution curves of log_{10} neutralizing antibody titres. Plots depicting the reverse empirical cumulative distribution functions of the log_{10} neutralizing antibody titres for the primary endpoint (Wuhan) and VOCs (Beta, Delta and Omicron variants) at two timepoints (Baseline and Day 14 after vaccination), splitting by treatment arm (Comirnaty and PHH-1V). Solid lines refer to titres at baseline conditions and dashed lines refer to titres at day 14. Blue lines correspond to subjects vaccinated with Comirnaty and red lines to subjects vaccinated with PHH-1V. A total of 504 and 500 individuals have been plotted for the PHH-1V arm at baseline and day 14 timepoints, respectively; and 247 and 241 individuals have been plotted for the Comirnaty arm at baseline and day 14, respectively.

Secondary efficacy endpoints

- Neutralisation titre against VOC measured as IC50 by PBNA and reported as reciprocal concentration for each individual sample and GMT for treatment group comparison at Baseline and Days 14, 28, extra visit (if applicable), 98 (only in a subset of approximately 20% of the total subjects included in the study), 182, and 364.

BETA strain

Geometric mean values of the neutralisation titres against the Beta strain for the PHH-1V treatment group were 66.79, 4332.46, 3805.27, 1820.75 and 2601.95 on Days 0, 14, 28, 98, and 182, respectively.

Geometric mean values of the neutralisation titres against the Beta strain for the Comirnaty treatment group were 61.13, 2663.88, 2473.63, 996.93 and 1794.99 on Days 0, 14, 28, 98, and 182, respectively.

Table 9 Summary of IC50 against Beta (mITT Population)
Log10 Data

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
		Observed value	Observed value	Observed value
Baseline	n	504	247	751
	Geometric mean	66.79	61.13	64.87
	Geometric SD	3.38	2.69	3.15
	Minimum	1.28	1.30	1.28
	Q1	1.37	1.44	1.40
	Median	1.72	1.73	1.73
	Q3	2.09	2.01	2.06
	Maximum	4.72	3.68	4.72
Day 14	n	500	241	741
	Geometric mean	4332.46	2663.88	3698.61
	Geometric SD	3.62	2.41	3.29
	Minimum	2.01	1.60	1.60
	Q1	3.30	3.16	3.24
	Median	3.67	3.42	3.59
	Q3	3.99	3.65	3.89
	Maximum	5.32	4.73	5.32
Day 28	n	496	244	740
	Geometric mean	3805.27	2473.63	3301.48
	Geometric SD	3.44	2.74	3.26
	Minimum	1.30	1.75	1.30
	Q1	3.25	3.10	3.18
	Median	3.65	3.39	3.55
	Q3	3.98	3.67	3.88
	Maximum	4.81	4.31	4.81
Day 98	n	78	42	120
	Geometric mean	1820.75	996.93	1474.67
	Geometric SD	3.53	2.95	3.43
	Minimum	1.72	2.04	1.72
	Q1	2.90	2.70	2.83
	Median	3.28	2.96	3.17
	Q3	3.70	3.30	3.54
	Maximum	4.31	4.18	4.31
Day 182	n	492	242	734
	Geometric mean	2601.95	1794.99	2302.18
	Geometric SD	3.58	4.52	3.92

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
		Observed value	Observed value	Observed value
	Minimum	1.30	1.30	1.30
	Q1	3.08	2.80	2.97
	Median	3.47	3.26	3.43
	Q3	3.81	3.76	3.80
	Maximum	4.41	4.31	4.41

Abbreviations: IC_{50} = Inhibitory Concentration 50, mITT = modified intent-to-treat, N = the number of subjects in the population, SD = standard deviation.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Table 14.2.2.1.1.1

Table 10 Analysis of IC50 agasint Beta (mITT population)

	PHH-1V (N=504)	Comirnaty (N=247)
Baseline		
Number of subjects with data n (%)	504 (100.0)	247 (100.0)
Adjusted treatment mean (LS Mean) [1]	1.82	1.78
Standard error	0.032	0.039
95% CI	1.753, 1.885	1.703, 1.861
GMT for adjusted treatment mean [2]	65.93	60.55
95% CI	56.621, 76.771	50.454, 72.656
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.92
95% CI for ratio		0.77, 1.10
p-value for ratio = 1		0.3595
Day 14		
Number of subjects with data n (%)	500 (99.2)	241 (97.6)
Adjusted treatment mean (LS Mean) [1]	3.64	3.42
Standard error	0.032	0.040
95% CI	3.565, 3.698	3.345, 3.504
GMT for adjusted treatment mean [2]	4278.92	2659.02
95% CI	3673.992, 4983.460	2213.045, 3194.858
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.62
95% CI for ratio		0.52, 0.75

	PHH-1V (N=504)	Comirnaty (N=247)
p-value for ratio = 1		<0.0001
Day 28		
Number of subjects with data n (%)	496 (98.4)	244 (98.8)
Adjusted treatment mean (LS Mean) [1]	3.58	3.39
Standard error	0.032	0.040
95% CI	3.511, 3.643	3.313, 3.472
GMT for adjusted treatment mean [2]	3774.87	2467.06
95% CI	3240.633, 4397.184	2054.583, 2962.354
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.65
95% CI for ratio		0.54, 0.79
p-value for ratio = 1		<0.0001
Day 98		
Number of subjects with data n (%)	78 (15.5)	42 (17.0)
Adjusted treatment mean (LS Mean) [1]	3.31	3.07
Standard error	0.059	0.077
95% CI	3.196, 3.428	2.920, 3.224
GMT for adjusted treatment mean [2]	2051.21	1179.68
95% CI	1571.505, 2677.335	831.770, 1673.107
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.58
95% CI for ratio		0.38, 0.87
p-value for ratio = 1		0.0088
Day 182		
Number of subjects with data n (%)	492 (97.6)	242 (98.0)
Adjusted treatment mean (LS Mean) [1]	3.41	3.25
Standard error	0.032	0.040
95% CI	3.343, 3.476	3.172, 3.332
GMT for adjusted treatment mean [2]	2569.17	1786.38
95% CI	2204.981, 2993.516	1487.001, 2146.028
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.70

	PHH-1V (N=504)	Comirnaty (N=247)
95% CI for ratio		0.58, 0.84
p-value for ratio = 1		0.0001

Abbreviations: CI = confidence interval; GMT = Geometric Mean Titre; IC_{50} = Inhibitory Concentration 50; LS mean = least square mean; N = the number of subjects in the population; mITT = modified intent-to-treat population; MMRM = mixed model repeated measures.

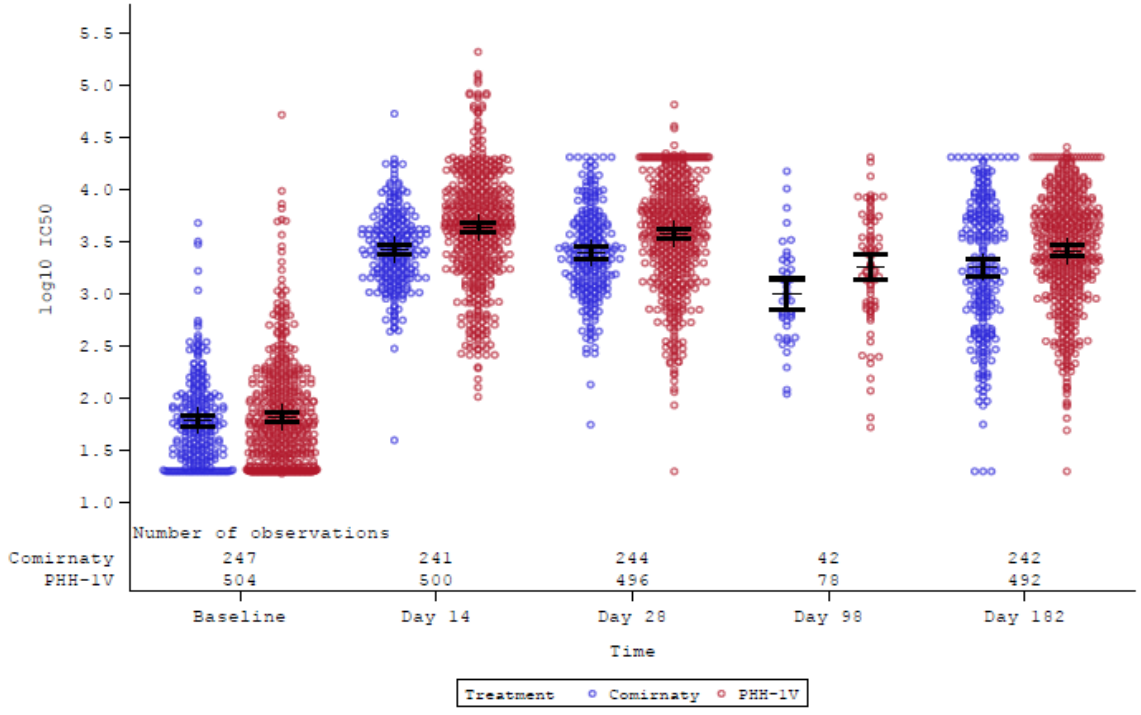
[1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group, age group (18-64, >64), visit (Baseline, Days 14 and 98), and the treatment-by-visit interaction term as fixed effects. Site was included as a random effect. A compound symmetry covariance matrix 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 are estimated using Least Square (LS) Means from the fitted model on the log10 scale and back-transformed.

Raw data provided as <20 have been imputed as 20 for analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis. Transformations have been made on the imputed data.

Source: Table 14.2.2.2.1.1

Figure 4. Log10 IC50 Against Beta Over time (mITT Population)



Abbreviations: IC_{50} = Inhibitory Concentration 50; mITT = modified intent-to-treat population.

Baseline will be defined as the most recent measurement prior to the first administration of study drug.

Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.

Source: Figure 14.2.2.1.1.1

DELTA strain

Geometric mean values of the neutralisation titres against the Delta strain for the PHH-1V treatment group were 44.49, 1455.10, 1692.90, 1665.97 and 2287.66 on Days 0, 14, 28, 98, and 182, respectively.

Geometric mean values of the neutralisation titres against the Delta strain for the Comirnaty treatment group were 41.14, 1474.22, 1494.21, 831.15 and 1245.99 on Days 0, 14, 28, 98, and 182, respectively.

Table 11: Summary of IC50 against Delta (mITT Population)
Log10 Data

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
		Observed value	Observed value	Observed value
Baseline	n	504	247	751
	Geometric mean	44.49	41.14	43.36
	Geometric SD	2.87	2.38	2.71
	Minimum	1.30	1.30	1.30
	Q1	1.30	1.30	1.30
	Median	1.49	1.49	1.49
	Q3	1.84	1.84	1.84
	Maximum	4.27	3.38	4.27
Day 14	n	500	241	741
	Geometric mean	1455.10	1474.22	1461.29
	Geometric SD	3.03	2.36	2.81
	Minimum	1.72	1.76	1.72
	Q1	2.92	2.95	2.94
	Median	3.12	3.18	3.15
	Q3	3.50	3.38	3.44
	Maximum	4.73	4.27	4.73
Day 28	n	496	244	740
	Geometric mean	1692.90	1494.21	1624.63
	Geometric SD	3.28	2.52	3.03
	Minimum	1.71	1.92	1.71
	Q1	2.94	2.93	2.93
	Median	3.20	3.14	3.18
	Q3	3.55	3.40	3.51
	Maximum	4.87	4.31	4.87
Day 98	n	78	42	120
	Geometric mean	1665.97	831.15	1306.09
	Geometric SD	3.32	2.61	3.21
	Minimum	1.85	1.94	1.85

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
		Observed value	Observed value	Observed value
	Q1	2.95	2.64	2.75
	Median	3.27	2.91	3.13
	Q3	3.55	3.13	3.43
	Maximum	4.40	4.21	4.40
Day 182	n	491	242	733
	Geometric mean	2287.66	1245.99	1871.85
	Geometric SD	3.61	4.41	3.98
	Minimum	1.30	1.30	1.30
	Q1	3.00	2.64	2.92
	Median	3.42	3.10	3.34
	Q3	3.78	3.60	3.73
	Maximum	4.44	4.31	4.44

Abbreviations: IC_{50} = Inhibitory Concentration 50, mITT = modified intent-to-treat, N = the number of subjects in the population, SD = standard deviation.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Table 14.2.2.1.1.1

Table 12 Analysis of the IC50 agasint Delta (mITT Population)

	PHH-1V (N=504)	Comirnaty (N=247)
Baseline		
Number of subjects with data n (%)	504 (100.0)	247 (100.0)
Adjusted treatment mean (LS Mean) [1]	1.65	1.62
Standard error	0.033	0.039
95% CI	1.582, 1.721	1.538, 1.698
GMT for adjusted treatment mean [2]	44.84	41.47
95% CI	38.235, 52.577	34.504, 49.837
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.92
95% CI for ratio		0.78, 1.10
p-value for ratio = 1		0.3672
Day 14		
Number of subjects with data n (%)	500 (99.2)	241 (97.6)
Adjusted treatment mean (LS Mean) [1]	3.17	3.17
Standard error	0.033	0.040
95% CI	3.097, 3.236	3.093, 3.254

	PHH-1V (N=504)	Comirnaty (N=247)
GMT for adjusted treatment mean [2]	1466.65	1490.42
95% CI	1250.515, 1720.135	1238.773, 1793.198
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		1.02
95% CI for ratio		0.86, 1.21
p-value for ratio = 1		0.8539
Day 28		
Number of subjects with data n (%)	496 (98.4)	244 (98.8)
Adjusted treatment mean (LS Mean) [1]	3.23	3.18
Standard error	0.033	0.040
95% CI	3.164, 3.303	3.101, 3.261
GMT for adjusted treatment mean [2]	1711.24	1515.79
95% CI	1458.851, 2007.286	1260.559, 1822.706
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.89
95% CI for ratio		0.75, 1.05
p-value for ratio = 1		0.1640
Day 98		
Number of subjects with data n (%)	78 (15.5)	42 (17.0)
Adjusted treatment mean (LS Mean) [1]	3.32	3.04
Standard error	0.057	0.075
95% CI	3.207, 3.433	2.892, 3.186
GMT for adjusted treatment mean [2]	2089.64	1093.64
95% CI	1609.517, 2712.990	780.275, 1532.866
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.52
95% CI for ratio		0.35, 0.77
p-value for ratio = 1		0.0012
Day 182		
Number of subjects with data n (%)	491 (97.4)	242 (98.0)
Adjusted treatment mean (LS Mean) [1]	3.36	3.10
Standard error	0.033	0.040

	PHH-1V (N=504)	Comirnaty (N=247)
95% CI	3.293, 3.432	3.019, 3.180
GMT for adjusted treatment mean [2]	2303.74	1257.77
95% CI	1963.439, 2703.031	1045.543, 1513.073
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.55
95% CI for ratio		0.46, 0.65
p-value for ratio = 1		<0.0001

Abbreviations: CI = confidence interval; GMT = Geometric Mean Titre; IC_{50} = Inhibitory Concentration 50; LS mean = least square mean; N = the number of subjects in the population; mITT = modified intent-to-treat population; MMRM = mixed model repeated measures.

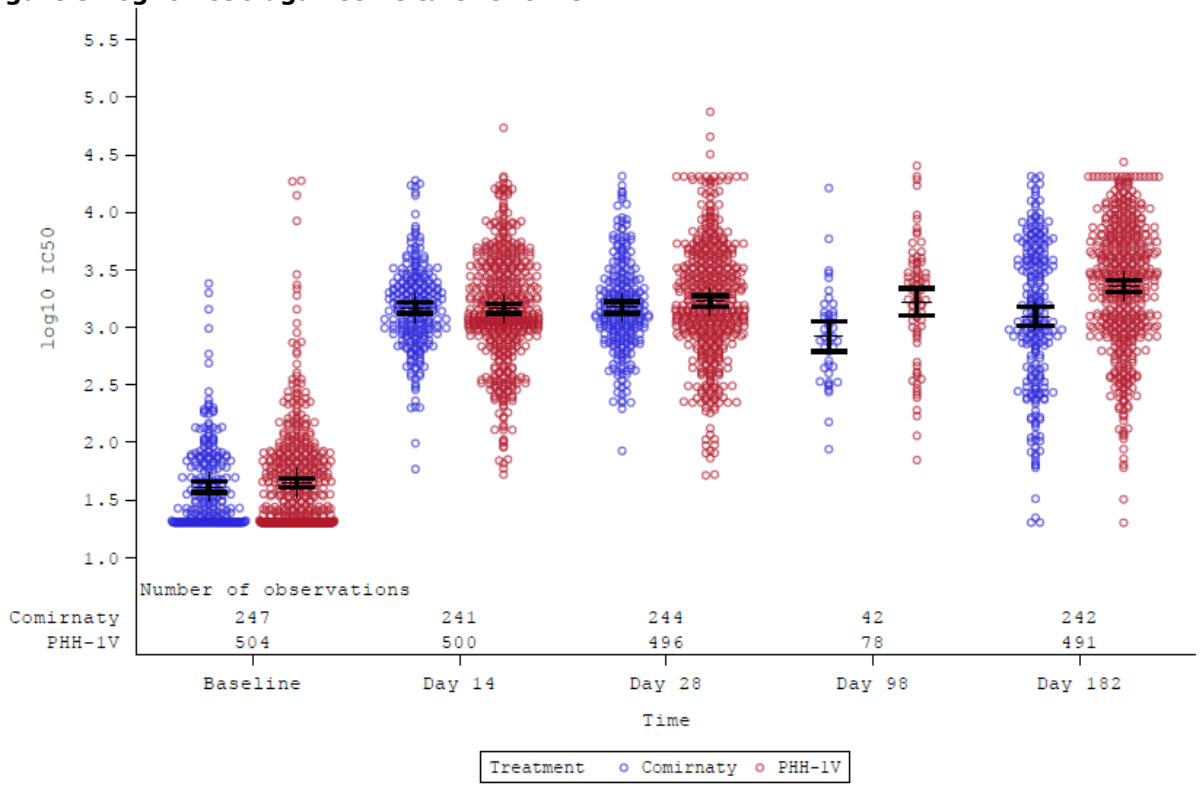
[1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group, age group (18-64, >64), visit (Baseline, Days 14 and 98), and the treatment-by-visit interaction term as fixed effects. Site was included as a random effect. A compound symmetry covariance matrix 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 are estimated using Least Square (LS) Means from the fitted model on the log10 scale and back-transformed.

Raw data provided as <20 have been imputed as 20 for analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis. Transformations have been made on the imputed data.

Source: Table 14.2.2.2.1.1

Figure 5 Log10 IC50 against Delta Over time



Abbreviations: IC_{50} = Inhibitory Concentration 50; mITT = modified intent-to-treat population.
Baseline will be defined as the most recent measurement prior to the first administration of study drug.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Figure 14.2.2.1.1.1

OMICRON BA.1 strain

Geometric mean values of the neutralisation titres against the Omicron strain for the PHH-1V treatment group were 32.88, 2058.68, 1526.41, 624.52 and 890.94 on Days 0, 14, 28, 98, and 182, respectively.

Geometric mean values of the neutralisation titres against the Omicron strain for the Comirnaty treatment group were 29.14, 1217.13, 998.47, 343.03 and 670.38 on Days 0, 14, 28, 98, and 182, respectively.

Table 13 Summary of IC50 against Omicron (mITT Population)
Log10 Data

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
		Observed value	Observed value	Observed value
Baseline	n	504	247	751
	Geometric mean	32.88	29.14	31.60
	Geometric SD	2.71	2.16	2.54
	Minimum	1.27	1.30	1.27
	Q1	1.30	1.30	1.30
	Median	1.30	1.30	1.30
	Q3	1.59	1.50	1.56

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
		Observed value	Observed value	Observed value
	Maximum	4.40	3.39	4.40
Day 14	n	500	241	741
	Geometric mean	2058.68	1217.13	1735.22
	Geometric SD	3.67	2.41	3.34
	Minimum	1.48	1.66	1.48
	Q1	2.96	2.85	2.91
	Median	3.35	3.11	3.22
	Q3	3.71	3.34	3.58
	Maximum	4.67	4.03	4.67
Day 28	n	496	244	740
	Geometric mean	1526.41	998.47	1327.06
	Geometric SD	3.82	2.54	3.44
	Minimum	1.30	1.71	1.30
	Q1	2.81	2.74	2.78
	Median	3.21	2.99	3.12
	Q3	3.54	3.22	3.47
	Maximum	4.55	4.21	4.55
Day 98	n	78	42	120
	Geometric mean	624.52	343.03	506.37
	Geometric SD	3.76	2.90	3.56
	Minimum	1.26	1.57	1.26
	Q1	2.39	2.30	2.35
	Median	2.80	2.49	2.70
	Q3	3.21	2.73	3.11
	Maximum	3.89	3.70	3.89
Day 182	n	492	242	734
	Geometric mean	890.94	670.38	811.19
	Geometric SD	3.88	4.86	4.22
	Minimum	1.30	1.30	1.30
	Q1	2.56	2.28	2.49
	Median	2.98	2.91	2.96
	Q3	3.35	3.37	3.35
	Maximum	4.31	4.29	4.31

Abbreviations: IC_{50} = Inhibitory Concentration 50, mITT = modified intent-to-treat, N = the number of subjects in the population, SD = standard deviation.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Table 14.2.2.1.1.1

Table 14 Analysis of IC50 against Omicron (mITT Population)

	PHH-1V (N=504)	Comirnaty (N=247)
Baseline		
Number of subjects with data n (%)	504 (100.0)	247 (100.0)
Adjusted treatment mean (LS Mean) [1]	1.51	1.46
Standard error	0.029	0.037
95% CI	1.452, 1.574	1.388, 1.537
GMT for adjusted treatment mean [2]	32.59	29.00
95% CI	28.343, 37.469	24.408, 34.444
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.89
95% CI for ratio		0.74, 1.07
p-value for ratio = 1		0.2057
Day 14		
Number of subjects with data n (%)	500 (99.2)	241 (97.6)
Adjusted treatment mean (LS Mean) [1]	3.31	3.09
Standard error	0.030	0.038
95% CI	3.249, 3.371	3.010, 3.161
GMT for adjusted treatment mean [2]	2042.36	1217.90
95% CI	1775.901, 2348.789	1023.840, 1448.754
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.60
95% CI for ratio		0.50, 0.72
p-value for ratio = 1		<0.0001
Day 28		
Number of subjects with data n (%)	496 (98.4)	244 (98.8)
Adjusted treatment mean (LS Mean) [1]	3.18	3.00
Standard error	0.030	0.038
95% CI	3.120, 3.241	2.923, 3.074
GMT for adjusted treatment mean [2]	1515.40	996.73
95% CI	1317.429, 1743.129	838.485, 1184.828
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.66
95% CI for ratio		0.55, 0.79
p-value for ratio = 1		<0.0001
Day 98		
Number of subjects with data n (%)	78 (15.5)	42 (17.0)

	PHH-1V (N=504)	Comirnaty (N=247)
Adjusted treatment mean (LS Mean) [1]	2.82	2.60
Standard error	0.058	0.077
95% CI	2.704, 2.933	2.446, 2.749
GMT for adjusted treatment mean [2]	658.87	395.69
95% CI	506.161, 857.655	279.035, 561.104
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.60
95% CI for ratio		0.40, 0.91
p-value for ratio = 1		0.0170
Day 182		
Number of subjects with data n (%)	492 (97.6)	242 (98.0)
Adjusted treatment mean (LS Mean) [1]	2.95	2.82
Standard error	0.030	0.038
95% CI	2.885, 3.007	2.750, 2.900
GMT for adjusted treatment mean [2]	882.92	668.32
95% CI	767.339, 1015.907	561.923, 794.852
GMT for treatment ratio (Comirnaty vs. PHH-1V) [2]		
Ratio		0.76
95% CI for ratio		0.63, 0.91
p-value for ratio = 1		0.0028

Abbreviations: CI = confidence interval; GMT = Geometric Mean Titre; IC_{50} = Inhibitory Concentration 50; LS mean = least square mean; N = the number of subjects in the population; mITT = modified intent-to-treat population; MMRM = mixed model repeated measures.

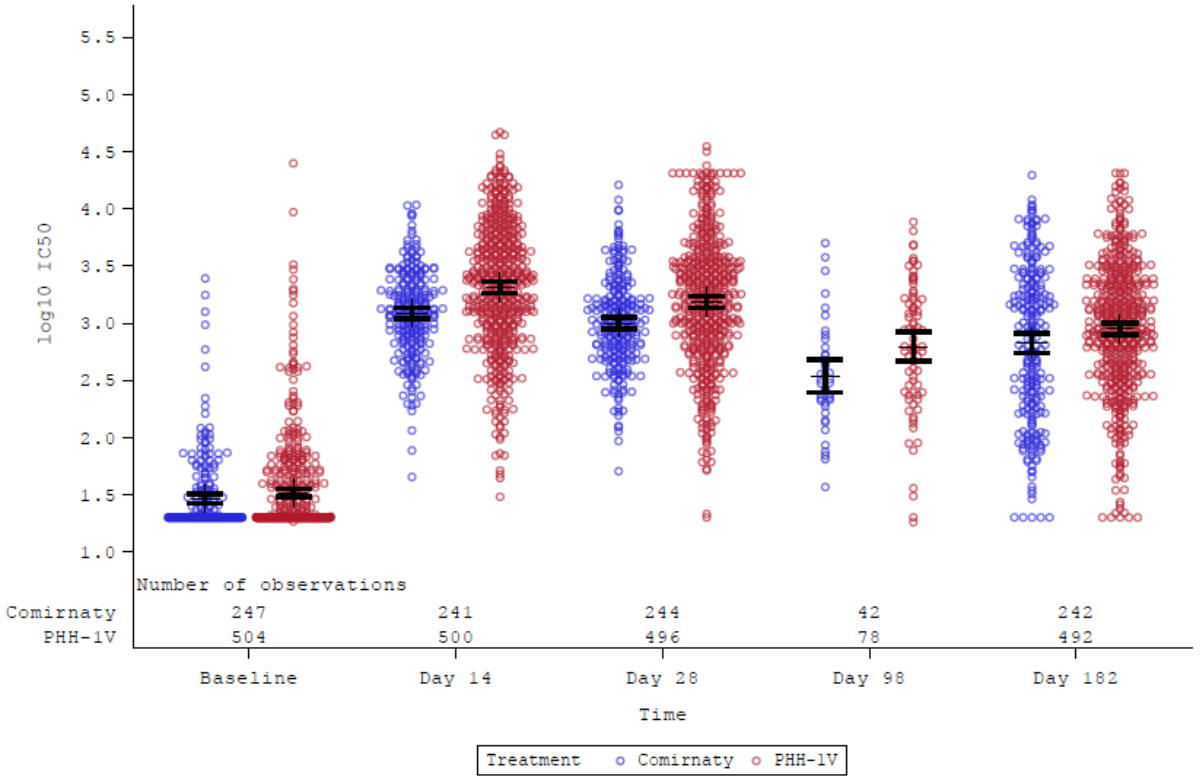
[1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group, age group (18-64, >64), visit (Baseline, Days 14 and 98), and the treatment-by-visit interaction term as fixed effects. Site was included as a random effect. A compound symmetry covariance matrix 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 are estimated using Least Square (LS) Means from the fitted model on the log10 scale and back-transformed.

Raw data provided as <20 have been imputed as 20 for analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis. Transformations have been made on the imputed data.

Source: Table 14.2.2.2.1.1

Figure 6: Log 10 Against Omicron over time



Abbreviations: IC_{50} = Inhibitory Concentration 50; mITT = modified intent-to-treat population.
Baseline will be defined as the most recent measurement prior to the first administration of study drug.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Figure 14.2.2.1.1.1

OMICRON BA.4/5 strain

Geometric mean values of the neutralisation titres against the Omicron BA.4/5 strain for the PHH-1V treatment group were 20.38 and 705.60 on Days 0, and 14, respectively.

Geometric mean values of the neutralisation titres against the Omicron strain for the Comirnaty treatment group were 16.00 and 524.28 on Days 0, and 14, respectively.

Table 15. Summary of PBNA IC50 against Omicron BA4/5 (subset)

Visit	Statistics	PHH-1V (N = 504)	Comirnaty (N = 248)	Overall (N = 752)
		Observed value	Observed value	Observed value
Baseline	n	15	9	24
	Geometric mean	20.38	16.00	18.61
	Geometric SD	1.90	1.00	1.67
	Minimum	1.20	1.20	1.20
	Q1	1.20	1.20	1.20
	Median	1.20	1.20	1.20
	Q3	1.20	1.20	1.20
	Maximum	2.01	1.20	2.01
Day 14	n	50	24	74
	Geometric mean	705.60	524.28	640.80
	Geometric SD	3.46	2.82	3.25
	Minimum	1.20	1.20	1.20
	Q1	2.53	2.63	2.58
	Median	2.96	2.69	2.78
	Q3	3.16	3.03	3.11
	Maximum	4.00	3.38	4.00

Abbreviations: n = number of subjects in the population, SD = Standard deviation.

Raw data provided as <16 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.

Table 16 Analysis of PBNA IC50 against Omicron BA4/5 (subset)

Visit	Statistics	PHH-1V (N = 504)	Comirnaty (N = 248)
Baseline	Number of subjects with data n (%)	15 (3.0)	9 (3.6)
	Adjusted treatment mean (LS Mean) [1]	1.20	1.08
	Standard error	0.117	0.147
	95% CI	0.960, 1.438	0.781, 1.370
	GMT for adjusted treatment mean	15.83	11.90
	95% CI	9.130, 27.445	6.039, 23.440
	GMT for treatment ratio (Comirnaty vs PHH-1V) [2]		
	Ratio		0.75
	95% CI for ratio		0.34, 1.67
	p-value for ratio = 1		0.4768
Day 14	Number of subjects with data n (%)	50 (9.9)	24 (9.7)
	Adjusted treatment mean (LS Mean) [1]	2.86	2.73
	Standard error	0.084	0.111
	95% CI	2.676, 3.052	2.496, 2.955
	GMT for adjusted treatment mean	730.84	531.47
	95% CI	474.110, 1126.580	313.541, 900.872
	GMT for treatment ratio (Comirnaty vs PHH-1V) [2]		
	Ratio		0.73
	95% CI for ratio		0.42, 1.24
	p-value for ratio = 1		0.2422

Abbreviations: CI = confidence interval, GMT = Geometric Mean Titre, IC50 = Inhibitory Concentration 50, LS mean = least square mean, n = number of subjects in the population
[1] A mixed effects model was fitted to assess the endpoint on the log10 scale. The model included the treatment group, the visit (Baseline and Day 14) and the treatment-by-visit interaction as fixed effects and 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 are on the log10 scale.
[2] 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 <16 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 for treatment group comparison at Baseline and Days 14, 28, extra visit (if applicable), 98 (only in a subset of approximately 20% of the total subjects included in the study), 182, and 364.

Table 17. Summary of Fold Rise in Neutralizing antibodies titres (mITT Population, D614G strain)

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
Day 14	n	500	241	741
	Mean	49.24	84.88	60.83
	SD	79.05	172.78	119.06
	Minimum	0.58	1.00	0.58
	Q1	9.56	17.28	11.48
	Median	22.98	41.99	29.26
	Q3	56.70	85.14	66.56
	Maximum	1024.00	1956.59	1956.59
Day 28	n	496	244	740

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
	Mean	60.06	79.01	66.31
	SD	101.72	128.99	111.72
	Minimum	0.54	0.43	0.43
	Q1	10.77	15.81	12.18
	Median	25.75	37.51	29.82
	Q3	66.25	80.78	70.48
	Maximum	976.81	959.49	976.81
Day 98	n	78	42	120
	Mean	25.71	16.57	22.51
	SD	38.28	26.77	34.84
	Minimum	0.30	1.36	0.30
	Q1	5.80	6.45	6.41
	Median	13.22	9.37	11.65
	Q3	33.03	17.34	24.21
	Maximum	250.50	175.06	250.50
Day 182	n	492	242	734
	Mean	42.61	24.54	36.65
	SD	85.25	44.57	74.79
	Minimum	0.09	0.08	0.08
	Q1	4.57	3.86	4.21
	Median	16.20	9.47	12.71
	Q3	45.08	26.89	38.44
	Maximum	876.88	430.21	876.88

Abbreviations: IC_{50} = Inhibitory Concentration 50, mITT = modified intent-to-treat, N = the number of subjects in the population, SD = standard deviation.
Fold rise is calculated as post-baseline titre/baseline titre.
Baseline will be defined as the most recent measurement prior to the first administration of study drug.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Table 14.2.3.1.1.1

Table 18 Analysis of GMFR in neutralizing antibodies titres (mITT Population, , D614G strain)

	PHH-1V (N=504)	Comirnaty (N=247)
Day 14		
Number of subjects included in the analysis n (%)	500 (99.2)	241 (97.6)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.33	1.59
Standard error	0.064	0.069
95% CI	1.189, 1.473	1.444, 1.741
GMFR adjusted treatment mean [3]	21.42	39.13
95% CI	15.452, 29.696	27.826, 55.034
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		1.83
95% CI for ratio		1.49, 2.24
p-value for ratio = 1		<0.0001
Day 28		
Number of subjects included in the analysis n (%)	496 (98.4)	244 (98.8)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.39	1.54
Standard error	0.064	0.069
95% CI	1.246, 1.530	1.394, 1.690
GMFR adjusted treatment mean [3]	24.45	34.85
95% CI	17.633, 33.890	24.785, 48.991
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		1.43
95% CI for ratio		1.17, 1.74
p-value for ratio = 1		0.0006
Day 98		
Number of subjects included in the analysis n (%)	78 (15.5)	42 (17.0)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.15	1.10
Standard error	0.080	0.095
95% CI	0.984, 1.314	0.915, 1.295
GMFR adjusted treatment mean [3]	14.08	12.73
95% CI	9.637, 20.583	8.221, 19.717

	PHH-1V (N=504)	Comirnaty (N=247)
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.90
95% CI for ratio		0.60, 1.37
p-value for ratio = 1		0.6313
Day 182		
Number of subjects included in the analysis n (%)	492 (97.6)	242 (98.0)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.12	0.94
Standard error	0.064	0.069
95% CI	0.981, 1.265	0.797, 1.093
GMFR adjusted treatment mean [3]	13.26	8.81
95% CI	9.567, 18.392	6.262, 12.383
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.66
95% CI for ratio		0.54, 0.81
p-value for ratio = 1		<0.0001

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; IC_{50} = inhibitory concentration 50; LS mean = least square mean; N = the number of subjects in the population; mITT = modified intent-to-treat population; MMRM = mixed model repeated measures.

[1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group, age group (18-64, >64), visit (Baseline, Days 14 and 98) as fixed effects, and the treatment-by-visit interaction term. Site was included as a random effect. A compound symmetry covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used 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 GMT for treatment 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. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.

Source: Table 14.2.3.2.1.1

Table 19 Summary of fold rise in neutralizing antibodies titres (mITT Population, Beta)

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
Day 14	n	500	241	741
	Mean	176.38	75.73	143.64
	SD	367.09	81.63	308.63
	Minimum	0.29	1.79	0.29
	Q1	26.87	22.60	24.92
	Median	67.89	47.27	60.05
	Q3	174.34	100.57	147.19
	Maximum	3940.13	555.40	3940.13
Day 28	n	496	244	740
	Mean	128.91	86.71	115.00
	SD	218.34	126.97	193.97
	Minimum	0.39	0.84	0.39
	Q1	24.63	18.77	22.35
	Median	65.29	38.59	54.80
	Q3	148.57	87.94	126.20
	Maximum	3048.63	886.68	3048.63
Day 98	n	78	42	120
	Mean	70.97	41.09	60.51
	SD	90.10	84.99	89.14
	Minimum	1.09	1.84	1.09
	Q1	16.67	8.44	11.03
	Median	39.28	15.76	30.16
	Q3	90.80	34.82	78.26
	Maximum	627.04	510.25	627.04
Day 182	n	492	242	734
	Mean	105.99	95.86	102.65
	SD	168.23	156.54	164.43
	Minimum	0.02	0.11	0.02
	Q1	15.67	8.30	14.17
	Median	41.10	36.97	39.88
	Q3	124.17	99.90	113.34
	Maximum	1024.00	1024.00	1024.00

Abbreviations: mITT = modified intent-to-treat, N = the number of subjects in the population, SD = standard deviation.
Fold rise is calculated as post-baseline titre/baseline titre.
Baseline will be defined as the most recent measurement prior to the first administration of study drug.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Table 14.2.3.1.1.1

Table 20. Analysis of GMFR in neutralizing Antibodies titres (mITT Population, Beta)

	PHH-1V (N=504)	Comirnaty (N=247)
Day 14		
Number of subjects included in the analysis n (%)	500 (99.2)	241 (97.6)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.80	1.64
Standard error	0.056	0.062
95% CI	1.676, 1.919	1.512, 1.774
GMFR adjusted treatment mean [3]	62.74	43.98
95% CI	47.386, 83.063	32.540, 59.440
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.70
95% CI for ratio		0.56, 0.87
p-value for ratio = 1		0.0014
Day 28		
Number of subjects included in the analysis n (%)	496 (98.4)	244 (98.8)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.74	1.61
Standard error	0.056	0.062
95% CI	1.622, 1.865	1.480, 1.741
GMFR adjusted treatment mean [3]	55.41	40.80
95% CI	41.848, 73.365	30.198, 55.120
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.74
95% CI for ratio		0.59, 0.92
p-value for ratio = 1		0.0059
Day 98		
Number of subjects included in the analysis n (%)	78 (15.5)	42 (17.0)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.48	1.29
Standard error	0.075	0.092
95% CI	1.325, 1.628	1.107, 1.473
GMFR adjusted treatment mean [3]	29.95	19.50
95% CI	21.113, 42.476	12.806, 29.693

	PHH-1V (N=504)	Comirnaty (N=247)
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.65
95% CI for ratio		0.42, 1.01
p-value for ratio = 1		0.0537
Day 182		
Number of subjects included in the analysis n (%)	492 (97.6)	242 (98.0)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.58	1.47
Standard error	0.056	0.062
95% CI	1.455, 1.699	1.339, 1.601
GMFR adjusted treatment mean [3]	37.77	29.53
95% CI	28.522, 50.017	21.852, 39.910
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.78
95% CI for ratio		0.63, 0.97
p-value for ratio = 1		0.0273

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; IC_{50} = inhibitory concentration 50; LS mean = least square mean; N = the number of subjects in the population; mITT = modified intent-to-treat population; MMRM = mixed model repeated measures.

[1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group, age group (18-64, >64), visit (Baseline, Days 14 and 98) as fixed effects, and the treatment-by-visit interaction term. Site was included as a random effect. A compound symmetry covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used 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 GMT for treatment 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. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.

Source: Table 14.2.3.2.1.1

Table 21. Summary of Fold Rise in Neutralizing Antibodies Titres (mITT Population, Delta)

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
Day 14	n	500	241	741
	Mean	69.49	59.32	66.19
	SD	108.97	81.93	101.03
	Minimum	0.23	0.64	0.23
	Q1	14.28	20.91	15.97
	Median	38.52	39.99	39.15

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
	Q3	70.91	69.97	70.54
	Maximum	823.85	850.87	850.87
Day 28	n	496	244	740
	Mean	97.48	65.63	86.98
	SD	232.06	92.51	197.76
	Minimum	0.26	0.98	0.26
	Q1	16.58	17.74	17.04
	Median	41.82	40.07	41.09
	Q3	89.73	75.82	84.04
	Maximum	3442.67	1024.00	3442.67
Day 98	n	78	42	120
	Mean	89.14	33.93	69.82
	SD	132.06	47.32	112.94
	Minimum	1.36	2.53	1.36
	Q1	18.73	14.25	15.90
	Median	52.92	20.50	36.56
	Q3	101.12	37.68	81.47
	Maximum	788.19	292.06	788.19
Day 182	n	491	242	733
	Mean	129.96	85.70	115.35
	SD	186.41	126.33	170.15
	Minimum	0.05	0.11	0.05
	Q1	19.19	10.95	16.11
	Median	57.18	35.39	49.71
	Q3	150.16	108.13	138.34
	Maximum	1024.00	875.91	1024.00

Abbreviations: IC50 = Inhibitory Concentration 50, mITT = modified intent-to-treat, N = the number of subjects in the population, SD = standard deviation.

Fold rise is calculated as post-baseline titre/baseline titre.
Baseline will be defined as the most recent measurement prior to the first administration of study drug.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Table 14.2.3.1.1.1

Table 22 Analysis of GMFR in neutralizing antibodies titres (mITT Population, Delta)

	PHH-1V (N=504)	Comirnaty (N=247)
Day 14		
Number of subjects included in the analysis n (%)	500 (99.2)	241 (97.6)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.51	1.56
Standard error	0.044	0.051
95% CI	1.415, 1.604	1.455, 1.666
GMFR adjusted treatment mean [3]	32.32	36.33
95% CI	25.978, 40.214	28.488, 46.335
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		1.12
95% CI for ratio		0.91, 1.38
p-value for ratio = 1		0.2668
Day 28		
Number of subjects included in the analysis n (%)	496 (98.4)	244 (98.8)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.58	1.57
Standard error	0.044	0.051
95% CI	1.481, 1.671	1.464, 1.675
GMFR adjusted treatment mean [3]	37.70	37.11
95% CI	30.300, 46.913	29.115, 47.312
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.98
95% CI for ratio		0.80, 1.21
p-value for ratio = 1		0.8811
Day 98		
Number of subjects included in the analysis n (%)	78 (15.5)	42 (17.0)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.69	1.46
Standard error	0.066	0.083
95% CI	1.558, 1.820	1.295, 1.624
GMFR adjusted treatment mean [3]	48.86	28.82
95% CI	36.108, 66.113	19.718, 42.115

	PHH-1V (N=504)	Comirnaty (N=247)
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.59
95% CI for ratio		0.39, 0.90
p-value for ratio = 1		0.0144
Day 182		
Number of subjects included in the analysis n (%)	491 (97.4)	242 (98.0)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.71	1.49
Standard error	0.044	0.051
95% CI	1.611, 1.801	1.382, 1.593
GMFR adjusted treatment mean [3]	50.82	30.71
95% CI	40.831, 63.244	24.083, 39.163
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.60
95% CI for ratio		0.49, 0.74
p-value for ratio = 1		<0.0001

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; IC_{50} = inhibitory concentration 50; LS mean = least square mean; N = the number of subjects in the population; mITT = modified intent-to-treat population; MMRM = mixed model repeated measures.

[1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group, age group (18-64, >64), visit (Baseline, Days 14 and 98) as fixed effects, and the treatment-by-visit interaction term. Site was included as a random effect. A compound symmetry covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used 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 GMT for treatment 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. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.

Source: Table 14.2.3.2.1.1

Table 23. Summary of Fold Rise in neutralizing antibodies titres (mITT Population, Omicron)

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
Day 14	n	500	241	741
	Mean	148.58	66.51	121.89
	SD	244.81	69.42	208.46
	Minimum	0.56	0.50	0.50
	Q1	29.04	23.75	26.58
	Median	70.14	48.46	60.95
	Q3	166.21	83.50	131.87

Visit	Statistics	PHH-1V (N=504)	Comirnaty (N=247)	Overall (N=751)
	Maximum	2334.54	540.27	2334.54
Day 28	n	496	244	740
	Mean	113.49	60.86	96.14
	SD	184.65	80.02	159.87
	Minimum	0.56	0.27	0.27
	Q1	19.63	20.27	19.67
	Median	50.74	38.19	45.34
	Q3	131.03	68.30	105.90
	Maximum	1753.67	807.81	1753.67
Day 98	n	78	42	120
	Mean	50.34	26.62	42.04
	SD	62.70	45.30	58.14
	Minimum	0.78	1.85	0.78
	Q1	10.55	7.05	8.85
	Median	30.16	13.69	19.67
	Q3	67.84	23.43	50.26
	Maximum	307.23	250.53	307.23
Day 182	n	492	242	734
	Mean	75.71	70.31	73.93
	SD	132.00	100.79	122.55
	Minimum	0.02	0.08	0.02
	Q1	11.30	5.53	8.97
	Median	33.02	23.78	31.88
	Q3	78.51	86.36	83.05
	Maximum	1024.00	541.85	1024.00

Abbreviations: IC_{50} = Inhibitory Concentration 50, mITT = modified intent-to-treat, N = the number of subjects in the population, SD = standard deviation.
Fold rise is calculated as post-baseline titre/baseline titre.
Baseline will be defined as the most recent measurement prior to the first administration of study drug.
Raw data provided as <20 have been imputed as 20 for the purposes of analysis. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.
Source: Table 14.2.3.1.1.1

Table 24. Analysis of GMFR in neutralizing antibodies titres (mITT population, Omicron)

	PHH-1V (N=504)	Comirnaty (N=247)
Day 14		
Number of subjects included in the analysis n (%)	500 (99.2)	241 (97.6)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.79	1.62
Standard error	0.047	0.055
95% CI	1.685, 1.887	1.510, 1.735
GMFR adjusted treatment mean [3]	61.06	41.93
95% CI	48.384, 77.058	32.344, 54.362
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.69
95% CI for ratio		0.55, 0.85
p-value for ratio = 1		0.0007
Day 28		
Number of subjects included in the analysis n (%)	496 (98.4)	244 (98.8)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.66	1.54
Standard error	0.047	0.055
95% CI	1.554, 1.756	1.423, 1.648
GMFR adjusted treatment mean [3]	45.19	34.30
95% CI	35.804, 57.035	26.467, 44.440
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.76
95% CI for ratio		0.61, 0.94
p-value for ratio = 1		0.0128
Day 98		
Number of subjects included in the analysis n (%)	78 (15.5)	42 (17.0)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.29	1.14
Standard error	0.071	0.089
95% CI	1.144, 1.426	0.961, 1.314
GMFR adjusted treatment mean [3]	19.28	13.71
95% CI	13.936, 26.669	9.134, 20.592

	PHH-1V (N=504)	Comirnaty (N=247)
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.71
95% CI for ratio		0.45, 1.12
p-value for ratio = 1		0.1385
Day 182		
Number of subjects included in the analysis n (%)	492 (97.6)	242 (98.0)
Fold rise adjusted treatment mean (LS Mean) [1][2]	1.42	1.36
Standard error	0.047	0.055
95% CI	1.321, 1.523	1.249, 1.475
GMFR adjusted treatment mean [3]	26.43	23.02
95% CI	20.934, 33.361	17.761, 29.845
GMFR for treatment ratio (Comirnaty vs. PHH-1V) [3]		
GMFR ratio		0.87
95% CI for ratio		0.70, 1.08
p-value for ratio = 1		0.2142

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; IC_{50} = inhibitory concentration 50; LS mean = least square mean; N = the number of subjects in the population; mITT = modified intent-to-treat population; MMRM = mixed model repeated measures.

[1] A MMRM model was fitted to the assess the endpoint on the log10 scale. The model included treatment group, age group (18-64, >64), visit (Baseline, Days 14 and 98) as fixed effects, and the treatment-by-visit interaction term. Site was included as a random effect. A compound symmetry covariance matrix was used to model the within-subject error and the Kenward-Roger approximation was used 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 GMT for treatment 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. Any zero values have been imputed to 10 (half the LLOQ) for analysis purposes. Transformations have been made on the imputed data.

Source: Table 14.2.3.2.1.1

Table 25 Analysis of GMFR in PBNA IC50 against BA4/5 (subset)

Visit	Statistics	PHH-1V (N = 504)	Comirnaty (N = 248)
Day 14	Number of subjects with data n (%)	50 (9.9)	24 (9.7)
	Adjusted treatment mean (LS Mean) [1][2]	1.66	1.65
	Standard error	0.108	0.133
	95% CI	1.444, 1.885	1.377, 1.923
	GMFR for adjusted treatment mean	46.17	44.67
	95% CI	27.799, 76.677	23.799, 83.837
	GMFR for treatment ratio (Comirnaty vs PHH-1V) [3]		
	Ratio		0.97
	95% CI for ratio		0.43, 2.16
	p-value for ratio = 1		0.9336

Abbreviations: CI = confidence interval, GMT = Geometric Mean Titre, IC50 = Inhibitory Concentration 50, LS mean = least square mean, n = number of subjects in the population, GMFR = geometric mean fold rise
[1] A mixed effects model was fitted to assess the endpoint on the log10 scale. The model included the treatment group, the visit (Baseline and Day 14) and the treatment-by-visit interaction as fixed effects and 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 are on the log10 scale.
[2] The adjusted treatment means are estimated using the Least Square Means from the fitted model on the log10 scale.
[3] The GMT for treatment 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 <16 have been imputed as 20 for the purposes of analysis. Transformations have been made on the imputed data.

Table 26 Analysis of Fold change in binding antibodies titres (mITT Population)

	PHH-1V (N=504)	Comirnaty (N=247)
Day 14		
Number of subjects included in the analysis n (%)	498 (98.8)	241 (97.6)
Number of responders n (%) [1]	490 (98.4)	238 (98.8)
Responders 95% CI [2]	(0.969, 0.993)	(0.964, 0.997)
Adjusted treatment odds ratio (LS Mean) [3]	61.52	83.62
Standard error	0.352	0.595
95% CI	30.872, 122.591	26.053, 268.388
Treatment Difference in LS Means Odds Ratios (Comirnaty – PHH-1V) [4]		
Ratio		1.36
95% CI for ratio		0.35, 5.25
p-value for ratio = 1		0.6562
Day 28		
Number of subjects included in the analysis n (%)	496 (98.4)	244 (98.8)
Number of responders n (%) [1]	484 (97.6)	240 (98.4)
Responders 95% CI [2]	(0.958, 0.987)	(0.959, 0.996)

	PHH-1V (N=504)	Comirnaty (N=247)
Adjusted treatment odds ratio (LS Mean) [3]	41.74	59.01
Standard error	0.293	0.489
95% CI	23.490, 74.156	22.617, 153.961
Treatment Difference in LS Means Odds Ratios (Comirnaty – PHH-1V) [4]		
Ratio		1.41
95% CI for ratio		0.46, 4.31
p-value for ratio = 1		0.5425
Day 98		
Number of subjects included in the analysis n (%)	78 (15.5)	42 (17.0)
Number of responders n (%) [1]	74 (94.9)	41 (97.6)
Responders 95% CI [2]	(0.874, 0.986)	(0.874, 0.999)
Adjusted treatment odds ratio (LS Mean) [3]	24.61	37.24
Standard error	0.473	0.826
95% CI	9.746, 62.130	7.374, 188.060
Treatment Difference in LS Means Odds Ratios (Comirnaty – PHH-1V) [4]		
Ratio		1.51
95% CI for ratio		0.24, 9.72
p-value for ratio = 1		0.6624
Day 182		
Number of subjects included in the analysis n (%)	493 (97.8)	242 (98.0)
Number of responders n (%) [1]	468 (94.9)	224 (92.6)
Responders 95% CI [2]	(0.926, 0.967)	(0.885, 0.955)
Adjusted treatment odds ratio (LS Mean) [3]	19.27	12.77
Standard error	0.208	0.247
95% CI	12.806, 28.990	7.868, 20.720
Treatment Difference in LS Means Odds Ratios (Comirnaty – PHH-1V) [4]		
Ratio		0.66
95% CI for ratio		0.35, 1.24
p-value for ratio = 1		0.1992

Abbreviations: CI = Confidence interval, LS mean = least square mean, mITT = modified intent-to-treat, N = the number of subjects in the population, n = the number of subjects meeting the criterion.
[1] % = n / number of subjects in the analysis. A responder is defined as those subjects with a fold change in binding antibodies of 4 or greater.
[2] Exact CI for the proportion of responders has been calculated using the Clopper-Pearson method.
[3] A generalised estimating equations model for repeated measures was fitted to the assess the endpoint. The model included treatment group, age group (18-64, >64), visit (Baseline, Days 14 and 98) as fixed effects, and the treatment-by-visit interaction term. The model will assume a binomial family with logit link and an exchangeable working correlation matrix was used to model the within-subject error.
[4] The adjusted treatment mean odds ratios and the treatment difference in odds ratio are estimated using Least Square (LS) Means from the fitted model on the log10 scale and back-transformed.
Source: Table 14.2.7.1.1.1

T-cell-mediated response to the SARS-CoV-2 S protein as measured by whole peripheral blood mononuclear cell (PBMC) stimulation by enzyme-linked immune absorbent spot (ELISpot) at Baseline and at Day 14. This analysis was performed in a subset of subjects.

To evaluate the severe acute respiratory coronavirus 2 (SARS-CoV-2)-specific T-cell responses, 6 peptide pools overlapping SARS-CoV-2 Spike protein (2 pools), receptor binding domain (RBD) and RBD alpha, RBD beta, and RBD delta variants, were used.

The peptides used in the simulations are as follows:

SPIKE_SA: 194 peptides overlapping the S1-2016 to S1-2196 region of the Spike protein;

SPIKE_SB: 168 peptides overlapping the S1-2197 to S2-2377 region of the Spike protein;

RBD: 84 peptides overlapping the RBD region of the Spike protein (D614G strain sequence);

RBD_B.1.1.7: 84 peptides overlapping the RBD region of the SARS-CoV-2 Alpha variant;

RBD_B.1.351: 84 peptides overlapping the RBD region of the SARS-CoV-2 Beta variant;

RBD_B.1617.2: 84 peptides overlapping the RBD region of the SARS-CoV-2 Delta variant.

Table 27. IFN-γ responses determined by ELIspot assay in PBMC from groups immunised with PHH-1V and Comirnaty after a primary vaccination with Comirnaty

	PHH-1V (n=36)		Comirnaty (n=12)	
	Baseline	Day 14	Baseline	Day 14
RBD	29 (80.6%)	34 (94.4%)	12 (100%)	12 (100%)
RBD.B.1.1.7	29 (80.6%)	34 (94.4%)	12 (100%)	12 (100%)
RBD.B.1.351	30 (83.3%)	34 (94.4%)	12 (100%)	12 (100%)
RBD.B.1617.2	26 (72.2%)	33 (91.7%)	11 (91.7%)	12 (100%)
Spike SA	33 (91.7%)	35 (97.2%)	12 (100%)	12 (100%)
Spike SB	35 (97.2%)	34 (94.4%)	12 (100%)	12 (100%)
Responders*	36 (100%)	36 (100%)	12 (100%)	12 (100%)
Non-Responders	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations: ELISpot = Enzyme-Linked Immune Absorbent Spot; IFN-γ = interferon gamma; PBMC = Peripheral Blood Mononuclear Cell; RBD = receptor binding domain.

*Responders are subjects with at least one positive IFN-γ response against any of the SARS-CoV-2 peptides pools at any time and Non-responder if ELISpot responses were all negative.

PBMC were isolated before the booster vaccination (Baseline) and at Day 14 post vaccination with PHH-1V and Comirnaty vaccines, stimulated with RBD (RBD, RBD B.1.1.7, RBD 1.351) and Spike (SA, SB) peptide pools, and analysed by IFN-γ-specific ELISpot assay. Results show the number and percentage of positive subjects at Baseline and 14 days after booster vaccination with PHH-1V or Comirnaty. The numbers at Baseline are the controls.

$CD4^+/CD8^+$ T-cell response to the SARS-CoV-2 S protein as measured by in vitro PBMC stimulation by cytokine staining assays at Baseline and at Day 14. This analysis was performed in a subset of subjects.

The frequency of $CD4^+$ and $CD8^+$ T-cells expressing IFN-γ, interleukin-2 (IL-2), and interleukin-4 (IL-4) was assessed by intracellular cytokine staining (ICS) in a subgroup of approximately 30% randomly and blindly selected subjects previously determined as positive by ELISpot.

Table 28. IFN-y+ CD4+ and IFN-y+ CD8+ T cell responses in PBMCs from groups immunised with PHH-1V and Comirnaty after a primary vaccination with Comirnaty

		PHH-1V (n=8)		Comirnaty (n=7)	
		Baseline	Day 14	Baseline	Day 14
CD4-INF	RBD	0 (0%)	6 (75%)	0 (0%)	3 (42.86%)
	RBD.B.1.1.7	0 (0%)	7 (87.5%)	0 (0%)*	4 (57.14%)
	RBD.B.1.351	1 (12.5%)	6 (75%)	0 (0%)	4 (57.14%)
	Spike SA	3 (37.5%)	7 (87.5%)	4 (57.14%)	5 (71.43%)
	Spike SB	6 (75%)	4 (50%)	2 (28.57%)	6 (85.71%)
CD8-IFN	RBD	1 (12.5%)	3 (37.5%)	2 (28.57%)	3 (42.86%)
	RBD.B1.1.7	1 (12.5%)	3 (37.5%)	1 (16.67%)*	3 (42.86%)
	RBD.B.1.351	1 (12.5%)	3 (37.5%)	2 (28.57%)	3 (42.86%)
	Spike SA	3 (37.5%)	5 (62.5%)	1 (14.29%)	4 (57.14%)
	Spike SB	1 (12.5%)	1 (12.5%)	0 (0%)	4 (57.14%)
Responders** CD4-IFN		6 (75%)	7 (87.5%)	4 (57.14%)	6 (85.71%)
Non- Responders CD4-IFN		2 (25%)	1 (12.5%)	3 (42.86%)	1 (14.29%)
Responders CD8-IFN		3 (37.5%)	6 (75%)	1 (14.29%)	4 (57.14%)
Non- Responders CD8-IFN		5 (62.5%)	2 (25%)	6 (85.71%)	3 (42.86%)

Abbreviations: ELISpot = Enzyme-Linked Immune Absorbent Spot; ICS = intracellular cytokine staining; IFN-γ = interferon gamma; PBMC = Peripheral Blood Mononuclear Cell; RBD = receptor binding domain.

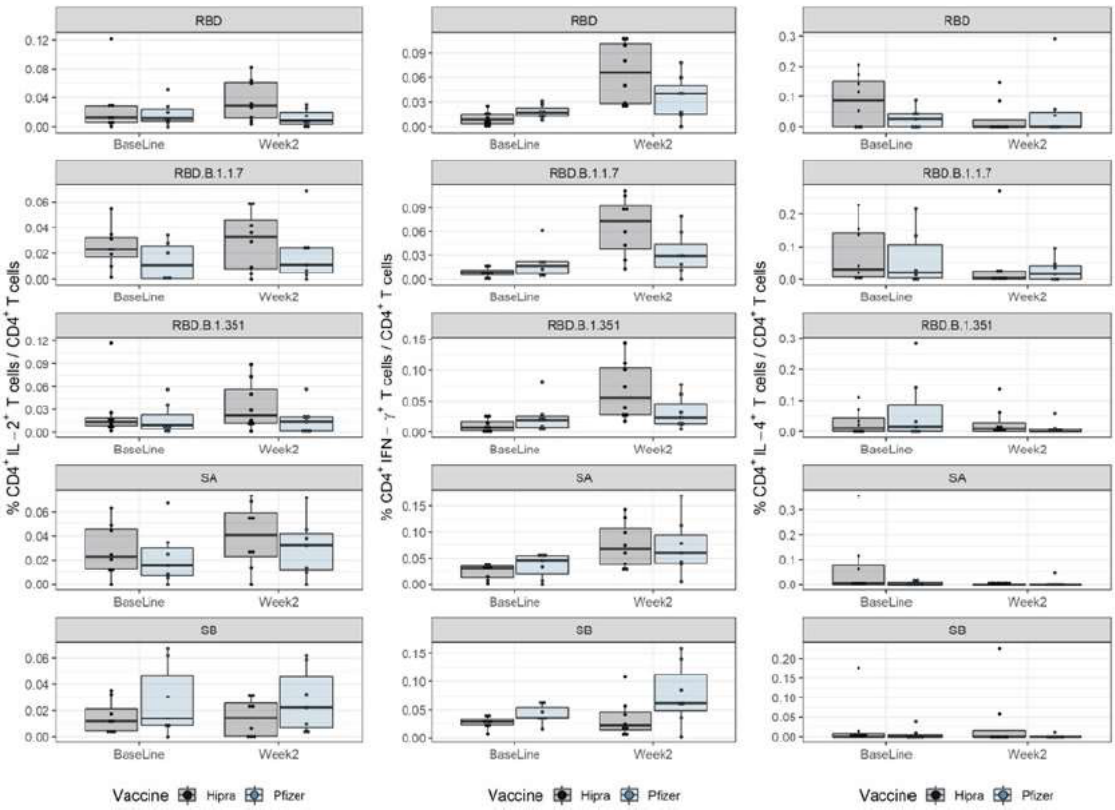
* It was not possible to determine the value of activation for one sample of PBMC against the RBD.B.1.1.7 stimulation (n=6).

** Responders are subjects with at least one positive IFN-γ ICS response against any of the SARS-CoV-2 peptide pools at each timepoint and Non-Responders are subjects whose responses at these timepoints were all negative. An ICS was considered positive if the percentages of cytokine-positive cells in the stimulated samples were three times more than the values obtained in the unstimulated controls and if the background-subtracted magnitudes were higher than 0.02%.

PBMC were isolated before the booster vaccination (Baseline) and at Day 14 post vaccination with PHH-1V and Comirnaty vaccines, stimulated with RBD (RBD, RBD B.1.1.7, RBD 1.351) and Spike (SA, SB) peptide pools, and analysed by intracellular cytokine staining. Results show the number and percentage of positive subjects at Baseline and 14 days after booster vaccination with PHH-1V or Comirnaty. The numbers at Baseline are the controls

As IL-4 expression was not detected in the activated $CD4^+$-T cells after the in vitro re-stimulation, the ICS results suggest that the PHH-1V booster vaccine induced a Th1-biased T-cell response.

Figure 7 CD4+-T-cell responses in PBMC from groups immunized with PHH-1V and Comirnaty booster dose after a primary vaccination with Comirnaty



Abbreviations: IL-2 = interleukin-2; IL-4 = interleukin-4; IFN-γ = interferon gamma; PBMC = Peripheral Blood Mononuclear Cell; RBD = receptor binding domain.

PBMC were isolated before the booster vaccination (Baseline) and at Day 14 (Week 2) post vaccination with PHH-1V and Comirnaty vaccines, stimulated with RBD (RBD, RBD B.1.1.7, RBD 1.351) and Spike (SA, SB) peptide pools, and analysed by intracellular cytokine staining. The frequencies of cytokine expressing CD4+ T cells are shown. The cytokine expression in PBMC stimulated with the medium was considered the background value and this was subtracted from peptide-specific responses.

Exploratory endpoints

Number and percentage of subjects with SARS-CoV-2 infections ≥14 days after PHH-1V booster according to COVID-19 infection criteria throughout the study duration.

Table 29 summary of COVID-19 cases (Safety Population)

	PHH-1V (N=513)		Comirnaty (N=252)		Overall (N=765)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Total number COVID-19 cases	21	21 (4.1)	12	12 (4.8)	33	33 (4.3)

Source: Table 14.3.1.2

So far none of events defined as other exploratory endpoints were reported:

- Number and percentage of severe COVID-19 infections through Day 364.
- Number and percentage of hospital admissions associated with COVID-19 through Day 364.
- Number and percentage of intensive care unit (ICU) admissions associated with COVID-19 through Day 364.

- Number and percentage of deaths associated with COVID-19 through Day 364.

- **Ancillary analyses**

Percentage of subjects achieving at least 4-fold rise in nAbs:

Table 30 Percentage of subjects achieving at least 4-fold rice in neutralising antibodies at day 14 (mITT, HIPRA-HH-2)

Variant	Statistics	PHH-1V (N=504)	Comirnaty (N=248)
Wuhan	Number of subjects included in the analysis n (%)	500 (99.2)	241 (97.2)
	Number of subjects ≥4 fold-rise n (%) [1]	456 (91.2)	232 (96.3)
	subjects ≥4 fold-rise 95% CI [2]	88.37, 93.53	93.03, 98.28
Beta	Number of subjects included in the analysis n (%)	500 (99.2)	241 (97.2)
	Number of subjects ≥4 fold-rise (%)	482 (96.4)	234 (97.1)
	Subjects ≥4 fold-rise 95% CI	94.37, 97.85	94.11, 98.82
Delta	Number of subjects included in the analysis n (%)	500 (99.2)	241 (97.2)
	Number of subjects ≥4 fold-rise n (%)	473 (94.6)	234 (97.1)
	Subjects ≥4 fold-rise 95% CI	92.24, 96.41	94.11, 98.82
Omicron BA.1	Number of subjects included in the analysis n (%)	500 (99.2)	241 (97.2)
	Number of individuals with fold-rise ≥4 n (%)	480 (96.0)	232 (96.3)
	Individuals ≥4 fold-rise 95% CI	93.89, 97.54	93.03, 98.28

Abbreviations: CI = confidence interval, N = the number of subjects in the population, n = the number of subjects meeting the criterion, mITT = modified intention-to-treat.

[1] % = n / number of subjects in the analysis. A responder is defined as those subjects with a fold change in the antibody titre of 4 or greater.
[2] Exact CI for the proportion of responders has been calculated using the Clopper-Pearson method.

Table 31 Percentage of subjects achieving at least 4-fold rice in neutralising antibodies at day28 (mITT, HIPRA-HH-2)

Variant	Statistic	PHH-1V (N=504)	Comirnaty (N=248)
Wuhan	Number of subjects included in the analysis n (%)	496 (98.4)	243 (98)
	Number of subjects ≥4 fold-rise n (%) [1]	462 (93.1)	228 (93.8)
	subjects ≥4 fold-rise 95% CI [2]	90.55, 95.21	90.02, 96.50
Beta	Number of subjects included in the analysis n (%)	496 (98.4)	244 (98.4)
	Number of subjects ≥4 fold-rise (%)	477 (96.2)	232 (95.1)
	Subjects ≥4 fold-rise 95% CI	94.08, 97.68	91.57, 97.43
Delta	Number of subjects included in the analysis n (%)	496 (98.4)	244 (98.4)
	Number of subjects ≥4 fold-rise n (%)	468 (94.4)	237 (97.1)
	Subjects ≥4 fold-rise 95% CI	91.94, 96.22	94.18, 98.84
Omicron BA.1	Number of subjects included in the analysis n (%)	496 (98.4)	244 (98.4)
	Number of individuals with fold-rise ≥4 n (%)	467 (94.2)	233 (95.5)
	Individuals ≥4 fold-rise 95% CI	91.71, 96.05	92.08, 97.73

Abbreviations: CI = confidence interval, N = the number of subjects in the population, n = the number of subjects meeting the criterion, mITT = modified intention-to-treat.
[1] % = n / number of subjects in the analysis. A responder is defined as those subjects with a fold change in the antibody titre of 4 or greater.
[2] Exact CI for the proportion of responders has been calculated using the Clopper-Pearson method.

mITT3 analyses:

Table 32 Summary of GMT and GMFR at baseline, day 14, day 28, day 98 and day 182 for the mITT population, and baseline and day 182 for the mITT3 population (HIPRA-HH-2)

Variant	Time point	Analysis	PHH-1V mITT	Comirnaty mITT	PHH-1V mITT3	Comirnaty mITT3
Wuhan	Baseline	GMT	85.75	84.02	92.17	85.98
	Day 14	GMT GMFR	1953.89 21.42	3336.54 39.13	NA	NA
	Day 28	GMT GMFR	2230.95 24.45	2958.40 34.85	NA	NA
	Day 98 (subset)	GMT GMFR	1193.35 14.08	1048.32 12.73	NA	NA
	Day 182	GMT GMFR	1205.49 13.26	751.64 8.81	1113.77 11.17	606.85 6.64
Beta	Baseline	GMT	65.93	60.55	74.59	63.19
	Day 14	GMT GMFR	4278.92 62.74	2659.02 43.98	NA	NA
	Day 28	GMT GMFR	3774.87 55.41	2467.06 40.80	NA	NA
	Day 98 (subset)	GMT GMFR	2051.21 29.95	1179.68 19.50	NA	NA
	Day 182	GMT GMFR	2569.17 37.77	1786.38 29.53	2228.40 29.12	1193.19 18.34
Delta	Baseline	GMT	44.84	41.47	49.58	42.09
	Day 14	GMT GMFR	1466.65 32.32	1490.42 36.33	NA	NA
	Day 28	GMT GMFR	1711.24 37.70	1515.79 37.11	NA	NA
	Day 98 (subset)	GMT GMFR	2089.64 48.86	1093.64 28.82	NA	NA
	Day 182	GMT GMFR	2303.74 50.82	1257.77 30.71	2058.37 41.25	877.58 20.83
BA.1	Baseline	GMT	32.59	29.00	35.48	29.67
	Day 14	GMT GMFR	2042.36 61.06	1217.90 41.93	NA	NA
	Day 28	GMT GMFR	1515.40 45.19	996.73 34.30	NA	NA
	Day 98 (subset)	GMT GMFR	658.87 19.28	395.69 13.71	NA	NA
	Day 182	GMT	882.92	668.32	723.89	401.85

Variant	Time point	Analysis	PHH-1V mITT	Comirnaty mITT	PHH-1V mITT3	Comirnaty mITT3
		GMFR	26.43	23.02	20.14	13.45

NA: Not applicable, as the relevant data for these time points is from the mITT population.
Source: HIPRA-HH-2 - Interim Results Report, Version 4.0, 30th September 2022 - Table 14.2.1.2.1.1 (mITT); HIPRA-HH-2 - Interim Results Report, Version 4.0, 30th September 2022 - Table 14.2.1.2.7.1 (mITT3)

- **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 33.Summary of Efficacy for trial HH-2

Title: A Phase IIb, double-blind, randomised, active-controlled, multi-centre, non-inferiority trial followed by a Phase III, single-arm, open-label trial, to assess immunogenicity and safety of a booster vaccination with a recombinant protein RBD fusion dimer candidate (PHH-1V) against SARS-CoV-2, in adults fully vaccinated against COVID-19.			
Study identifier	HIPRA-HH-2 EudraCT number: 2021-005226-26 ClinicalTrials.gov ID: NCT05142553		
Design	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks not applicable not applicable
Hypothesis	Non-inferiority of Comirnaty versus PHH-1V vaccine for immunogenicity		
Treatments groups	Comirnaty (tozinameran) group		One booster dose of 0.3ml (30 µg), intramuscular administration. N=252 individuals ≥18 years old
	PHH-1V		One booster dose of 0.5ml (40 µg), intramuscular administration N=513 individuals ≥18 years old
Endpoints and definitions	Primary endpoint	*GMT ratio between Comirnaty and PHH-1V vaccines against D614G strain*	To determine and compare the neutralising antibody titres against D614G strain at Baseline and Day 14 after booster vaccination with Comirnaty (tozinameran) or PHH-1V. *This clinical trial started in November 2021 when D614G strain was still the relevant primary endpoint to be studied. However, due to the pandemic's evolution the response against the new strains of the virus became highly relevant (see below under the secondary endpoints).*
Endpoints and definitions	Secondary endpoints	*GMT ratio between Comirnaty and PHH-1V vaccines against Omicron BA.1, Beta, and Delta strains.*	To determine and compare the neutralising antibody titres against Omicron BA.1, Beta and Delta strains at Baseline and at Days 14, 28, 98 (for a subset of 20%) and 182 after booster with Comirnaty or PHH-1V.

	Secondary endpoints	*GMFR of Comirnaty and PHH-1V and GMRF ratio for Omicron BA.1, Beta, and Delta strains.*	To determine and compare the fold rise in neutralising antibody titres against Omicron D614G strain, BA.1, Beta and Delta strains at Days 14, 28, 98 (for a subset of 20%) and 182 after booster vaccination in the groups receiving Comirnaty or PHH-1V.
		Binding antibodies to the SARS-CoV-2 spike glycoprotein, and seroresponse rate after the booster dose with PHH-1V or Comirnaty.	Analysis of the fold change in binding antibodies and percentage of subjects that, after a booster dose, have a ≥4-fold change in binding antibodies titre from Baseline at Days 14, 28, 98 (for a subset of 20%) and 182 after the booster dose in both groups.
		T-cell mediated responses against the SARS-CoV-2 S glycoprotein	To evaluate the T-cell mediated responses against SARS-CoV-2 S glycoprotein at Baseline and Day 14 (subset of individuals) after the booster dose with PHH-1V or Comirnaty. To evaluate Th1/Th2 T-cell mediated responses against SARS-CoV-2 S glycoprotein at Baseline and Day 14 (subset of individuals) after the booster dose with PHH-1V or Comirnaty.
	Exploratory	Number of subjects with SARS-CoV-2 infections ≥14 days after booster dose with PHH-1V or Comirnaty	To determine the number of subjects with SARS-CoV-2 infection ≥14 days after booster dose with PHH-1V or Comirnaty.
		Number of severe infections of SARS-CoV-2	To determine the number of severe SARS-CoV-2 infection ≥14 days after booster dose with PHH-1V or Comirnaty
Database lock	18th July 2022 (Interim)		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	The following subject populations are used for the presentation and analysis of the data: - Modified ITT (mITT): All subjects who were randomly assigned to treatment who met the inclusion/exclusion criteria and received a dose of study drug. Subjects who tested positive for COVID-19 within 14 days of receiving study drug were excluded. Subjects were grouped as treated. - mITT3 (excluding confirmed COVID-19 cases): All subjects in the mITT without COVID-19 infections recorded prior to their 6 months visit date. Blood extractions to assess the immune response in the individuals receiving the booster with PHH-1V or Comirnaty were conducted at Baseline, and Days 14, 28, 98 (for a subset of approximately a 20% of the individuals), and 182.
Descriptive statistics and estimate variability	Post-booster GMT and GMT ratio between COVID-19 mRNA vaccine (tozinameran) and PHH-1V of neutralising antibody titres (PBNA) against D614G strain, Beta, Delta and Omicron BA.1 at days 14, 28, 98, and 182 post-booster dose.

	PHH-1V N=504		**COVID-19 mRNA vaccine (tozinameran) N=247**		**COVID-19 mRNA vaccine (tozinameran) / PHH-1V**
	GMT	95% CI	GMT	95% CI	GMT Ratio; (95% CI)
Day 14 post-booster					
D614G strain	1953.89	1667.17; 2289.93	3336.54	2778.56; 4006.57	1.71 (1.45; 2.02)
Beta	4278.92	3673.99; 4983.46	2659.02	2213.05; 3194.86	0.62 (0.52; 0.75)
Delta	1466.65	1250.52; 1720.14	1490.42	1238.77; 1793.19	1.02 (0.86; 1.21)
Omicron BA.1	2042.36	1775.91; 2348.79	1217.90	1023.84; 1448.75	0.60 (0.50; 0.72)
Day 28 post-booster					
D614G strain	2230.95	1903.29; 2615.01	2958.40	2465.00; 3550.55	1.33 (1.12; 1.56)
Beta	3774.87	3240.63; 4397.18	2467.06	2054.58; 2962.35	0.65 (0.54; 0.79)
Delta	1711.24	1458.85; 2007.29	1515.79	1260.56; 1822.71	0.89 (0.75; 1.05)
Omicron BA.1	1515.40	1317.43; 1743.13	996.73	838.49; 1184.83	0.66 (0.55; 0.79)
Day 98 post-booster (N: PHH-1V: 78; N: tozinameran: 42 as per protocol subset)					
D614G strain	1193.35	921.24; 1545.85	1048.32	750.90; 1463.54	0.88 (0.60; 1.29)
Beta	2051.21	1571.51; 2677.34	1179.68	831.77; 1673.11	0.58 (0.38; 087)
Delta	2089.64	1609.52; 2712.99	1093.64	780.28; 1532.87	0.52 (0.35; 0.77)
Omicron BA.1	658.87	506.16; 857.66	395.69	279.04; 561.10	0.60 (0.40; 0.91)

Day 182 post-booster					
D614G strain	1205.49	1028.22; 1413.33	751.64	626.02; 902.46	0.62 (0.53; 0.74)
Beta	2569.17	2204.98; 2993.52	1786.38	1487.00; 2146.03	0.70 (0.58; 0.84)
Delta	2303.74	1963.44; 2703.03	1257.77	1045.54; 1513.07	0.55 (0.46; 0.65)
Omicron BA.1	882.92	767.34; 1015.91	668.32	561.92; 794.85	0.76 (0.63; 0.91)

N: number of participants in the population per-protocol.
Abbreviations: GMT = Geometric Mean Titre; CI: Confidence intervals; PBNA = pseudovirion-based neutralisation assay
Non-inferiority between COVID-19 mRNA vaccine (tozinameran) and PHH-1V is concluded if the upper limit of the 2-sided 95% Confidence Interval (CI) of the GMT ratio COVID-19 mRNA vaccine (tozinameran)/PHH-1V is < 1.4.
Superiority between COVID-19 mRNA vaccine (tozinameran) and PHH-1V is concluded if the upper limit of the 2-sided 95% Confidence Interval of the GMT ratio COVID-19 mRNA vaccine (tozinameran)/PHH-1V is < 1.0.

Effect estimate per comparison	For D614G strain, the GMT ratio on Days 14 and 28 was 1.71 and 1.33 respectively, which does not meet the non-inferiority criteria. On Day 98, the GMT ratio was 0.88 which meets the non-inferiority criteria and the GMT ratio on Day 182 was 0.62 which meets the superiority criteria. For Beta variant, the GMT ratio on Day 14 of 0.62, on Day 28 of 0.65, on Day 98 of 0.58 and on Day 182 of 0.70 meet in all timepoint the superiority criteria. For the Delta variant the GMT ratio on Day 14 of 1.02, and on Day 28 of 0.89 meet the non-inferiority criteria. The GMT ratio on Day 98 of 0.52 and on Day 182 of 0.55 meet the superiority criteria. For Omicron BA.1, the GMT ratio on Day 14 of 0.60, on Day 28 of 0.66, on Day 98 of 0.60 and on Day 182 of 0.76 meet superiority criteria of the PHH-1V vaccine versus Comirnaty vaccine. Furthermore, at Day 182 the analysis was performed with the mITT3 (excluding the population with confirmed COVID-19 infections). For D614G strain the GMT ratio was 0.54. For Beta, the GMT ratio was 0.54. For Delta the GMT ratio was 0.43 and for Omicron BA.1, the GMT ratio was 0.56 which meet superiority criteria of the PHH-1V vaccine versus Comirnaty vaccine for all tested strains. It is confirmed a sustained immune response after PHH-1V booster dose.

Analysis description	Secondary analysis:
	The neutralising antibody levels observed after the booster with the PHH-1V at D182 were higher than those observed with Comirnaty vaccine, demonstrating a more sustained immune response for all tested strains. This fact was shown in individuals below 65 years old and in individuals 65 years old and older. The fold rise in neutralising antibody titres against all strains was tested and GMFR ratio calculated. For D614G strain, the GMFR ratio on Days 14 and 28 was 1.83 and 1.43 respectively, which does not meet the non-inferiority criteria. On Day 98, the GMFR ratio was 0.90 which meets the non-inferiority criteria and the GMFR ratio on Day 182 was 0.66 which meets the superiority criteria. For Beta variant, the GMFR ratio on Day 14 of 0.70, on Day 28 of 0.74, on Day 98 of 0.65 and on Day 182 of 0.78 meet in all timepoint the superiority criteria. For the Delta variant the GMFR ratio on Day 14 of 1.12, and on Day 28 of 0.98 meet the non-inferiority criteria. The GMFR ratio on Day 98 of 0.59 and on Day 182 of 0.60 meet the superiority criteria. For Omicron BA.1, the GMFR ratio on Day 14 of 0.69, on Day 28 of 0.76 meet superiority criteria. The GMFR ratio on Day 98 of 0.71 and on Day 182 of 0.87 meet non-inferiority criteria of the PHH-1V vaccine versus Comirnaty vaccine. A high seroresponse with a ≥4-fold change in binding antibodies titre from Baseline at Days 14, 28, 98 (for a subset of 20%), and 182 after the booster dose was observed after a booster dose of PHH-1V (Day 14: 98.4%, Day 28: 97.6%, Day 98: 94.9%, Day 182: 94.9%). The heterologous boost with PHH-1V, after a primary immunization with Comirnaty, elicited a Th1-$CD4^+$ T cell response, more potent than the response induced by the homologous boost with Comirnaty, and a $CD8^+$ T cell response specific against RBD. A total of 31.2% and 32.4% of non-severe Covid-cases were reported in PHH-1V and Comirnaty arms, respectively. There were no cases of severe COVID-19 infection and there were no immune-mediated adverse events in the study.

2.5.5.3. Clinical studies in special populations

No data in elderly (≥ 65 years), an important population with increased risk of morbidity and mortality (Liu et al., 2020; Mori et al., 2021), was initially provided. Upon request the Applicant provided data from Study HIPRA-HH-2.

Table 34 Qualitative analysis of % of responders (Day 14):

Variant	Statistic	PHH-1V	Comirnaty
D614G strain	Number of responders (%) [1]	25 (65.8 %)	18 (100%)
	95% CI (%) [2]	48.65 , 80.37	81.47 , 100
Beta	Number of responders (%) [1]	36 (94.7 %)	16 (88.9 %)
	95% CI [2]	82.25 , 99.36	65.29 , 98.62
Delta	Number of responders (%) [1]	34 (89.5%)	17 (94.4 %)

	95% CI [2]	75.20 , 97.06	72.71 , 99.86
Omicron	Number of responders (%) [1]	34 (89.5%)	16 (88.9%)
	95% CI [2]	75.20 , 97.06	65.29 98.62

Abbreviations: CI = confidence interval, mITT = modified intention-to-treat population.
1-A responder is defined as those subjects with a fold change in the neutralising antibody titre of 4 or greatger
2-Exact CI for the proportion of responders has been calculated using the Clopper-Pearson method.

Table 35 Geometric mean (geometric SD) for individuals below 65 years old and 65 years old and older for Wuham, Beta, Delta and Omicron variants (mITT; HIPRA-HH-2)

	Treatment	Baseline <65yoa	Baseline ≥65 yrs	Day 14 <65 yrs	Day 14 ≥65 yrs	Day 28 <65 yrs	Day 28 ≥65 yrs	Day 182 <65 yrs	Day 182 ≥65 yrs
Wuhan	PHH-1V	87.26 (2.73)	96.64 (2.70)	2116.45 (2.89)	1025.39 (3.34)	2326.46 (3.05)	1795.71 (3.93)	1228.65 (3.61)	1302.22 (5.25)
	Comirnaty	86.72 (2.62)	68.31 (2.34)	3454.85 (2.50)	2496.16 (2.29)	2970.63 (2.72)	3162.80 (2.30)	782.33 (3.29)	559.86 (3.77)
Beta	PHH-1V	64.79 (3.33)	55.71 (3.96)	4731.99 (3.51)	1482.45 (3.22)	3932 (3.39)	2563.65 (3.89)	2667.87 (3.52)	1912.83 (4.25)
	Comirnaty	62.40 <82.72<9	47.07 (2.25)	2753.32 (2.29)	1769.44 (3.65)	2537.15 (2.62)	1799.13 (4.27)	1898.10 (4.35)	895.78 (6.33)
Delta	PHH-1V	45.05 (2.81)	38.13 (3.24)	1562.56 (2.94)	611.91 (2.99)	1722.61 (3.21)	1372.67 (4.06)	2326.13 (3.58)	1864.24 (4.02)
	Comirnaty	41.87 (2.42)	33.05 (1.77)	1493.08 (2.28)	1259.41 (3.49)	1485.33 (2.47)	1610.31 (3.18)	1279.37 (4.39)	896.66 (4.69)
Omicron BA.1	PHH-1V	33.40 (2.75)	27.13 (2.24)	2245.75 (3.51)	715.09 (3.93)	1641.03 (3.68)	637.78 (4.33)	914.55 (3.76)	645.95 (5.48)
	Comirnaty	29.89 (2.22)	21.12 (1.14)	1269.26 (2.31)	723.91 (3.41)	1029.93 (2.46)	676.30 (3.41)	701.50 (4.75)	381.14 (5.66)

Source: Wuhan: HIPRA-HH-2 - Listing 16.2.6.1; Summary data: HIPRA-HH-2 -Table 14.2.1.1.1.2
Beta HIPRA-HH-5 - Interim Study Report, Version 3.0, 30th May 2022 - Table 14.2.1.2.
Delta: HIPRA-HH-2 - Listing 16.2.6.1; Summary data: HIPRA-HH-2 -Table 14.2.2.1.1.2
Omicron BA.1: HIPRA-HH-2 - Listing 16.2.6.1; Summary data: HIPRA-HH-2 -Table 14.2.2.1.1.2

Table 36 Geometric mean (Geometric SD) at baseline and at Day 182 for the individuals below 65 years old and 65 years old and older for Wuham, Beta, Delta and Omicron variants (mITT3; HIPRA-HH-1)

	Treatment	Baseline <65yrs	Baseline ≥65 yrs	Day 182 <65 yrs	Day 182 ≥65 yrs
Wuhan	PHH-1V	94.05 (2.90)	102.55 (2.74)	1160.79 (3.76)	990.92 (5.15)
	Comirnaty	88.40 (2.73)	84.86 (2.22)	647.92 (3.32)	412.89 (3.84)
Beta	PHH-1V	77.00 (3.53)	62.34 (4.24)	2336.17 (3.81)	1638.65 (4.48)
	Comirnaty	65.92 (2.93)	47.74 (2.41)	1309.85 (4.54)	491.32 (5.01)
Delta	PHH-1V	50.26 (3.17)	41.88 (3.51)	2100.53 (3.85)	1662.47 (4.20)
	Comirnaty	42.39 (2.51)	37.47 (1.80)	897.22 (4.73)	653.18 (5.03)
Omicron BA.1	PHH-1V	36.66 (3.10)	27.80 (2.37)	759.57 (3.99)	506.40 (5.53)
	Comirnaty	30.84 (2.36)	21.25 (1.16)	427.75 (4.61)	221.43 (5.20)

Source: Wuhan: HIPRA-HH-2 - Listing 16.2.6.1; Summary data: HIPRA-HH-2 -Table 14.2.1.1.7.2 (Version 4.0, 30th September 2022).
Beta: HIPRA-HH-2 - Listing 16.2.6.1; Summary data: HIPRA-HH-2 -Table 14.2.2.1.7.2 (Version 4.0, 30th September 2022).
Delta: HIPRA-HH-2 - Listing 16.2.6.1; Summary data: HIPRA-HH-2 -Table 14.2.2.1.7.2 (Version 4.0, 30th September 2022).
Omicron BA.1: HIPRA-HH-2 - Listing 16.2.6.1; Summary data: HIPRA-HH-2 -Table 14.2.2.1.7.2 (Version 4.0, 30th September 2022).

Only very limited data is available for 16-17 year old subjects in study HH-5. Please refer to supportive studies.

No data in special populations including hepatic impairment, renal impairment, pregnant or lactating women or in immunocompromised individuals is currently available. Of note, classical hepatically and renally impaired participants are not expected to have different pharmacokinetic (PK) exposure to the product due to the type of active substance (protein antigen) and its expected PK profile (lack of systemic exposure or metabolism by cytochromes, for example).

2.5.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

Analysis to support an indication for subjects previously vaccinated with mRNA Covid-19 vaccines

In the pivotal study, data was obtained only with the comparator Comirnaty. In order to support the broader indication for subjects previously vaccinated with mRNA vaccines, the Applicant provided the immunogenicity data for individuals previously vaccinated with two doses of Spikevax from study HIPRA-HH-5 and concluded that the neutralising antibody levels observed at Day 14 after the booster with PHH-1V clearly show a strong booster effect. It is agreed that an immune response can be observed with an increase in GMTs of 6-20 fold. Although, this increase is much lower compared to the data derived in study HIPRA-HH-2, it has to be considered that the baseline titres were also about 10 fold higher in Spikevax-vaccinated subjects. However, it has to be mentioned that the sample size is limited with 171 subjects and that the presented results could also be driven by a few strong responders. The higher baseline titres could also indicate previous unconfirmed Covid-19 infection in the respective subjects. Since the study was performed during the Omicron wave (first patient enrolled 03 February 2022), this cannot be ruled out. Nevertheless, the observed increase at D14 still indicates a considerable immune response to PHH-1V.

The following table integrates data from studies HIPRAHH-5 and HIPRA-HH-2 (subjects previously vaccinated with two doses of Comirnaty). In study HIPRA-HH-2 one arm received a booster dose of Comirnaty. It can be assumed that the titre achieved with the Comirnaty dose represents a protective level of neutralizing antibodies. It appears that subjects previously vaccinated with two doses of Spikevax achieved higher titres compared to the subject with three doses of Comirnaty for all tested variants. Of note, this is an informal across study comparison. Nevertheless, there is no concern that PHH-1V elicits protective titres also in subjects who were vaccinated with two doses of Spikevax.

	Spikevax/Spikevax +PHH-1V (HH-5)		**Cormirnaty/Comirnaty + PHH-1V (HH-2)**		**Cormirnaty/Comirnaty +Comirnaty (HH-2)**	
	GM (SD)	**GMT for adjusted treatment mean**	**GM (SD)**	**GMT for adjusted treatment mean**	**GM (SD)**	**GMT for adjusted treatment mean**
D614G strain						
Baseline	653.98 (2.88)	657.49	87.93 (2.73)	87.56	85.80 (2.62)	84.81
D14	4413.52 (2.71)	4437.27	2003.03 (2.97)	1998.95	3387.16 (2.50)	3357.50
Beta						
Baseline	490.57 (4.48)	497.77	66.79 (3.38)	66.55	61.13 (2.69)	60.60
D14	6758.78 (2.47)	6857.95	4332.46 (3.62)	4328.93	2671.59 (2.41)	2658.04
Delta						
Baseline	954.12 (3.63)	914.68	44.49 (2.87)	44.87	41.14 (2.38)	41.17
D14	6062.06 (2.41)	5811.47	1455.10 (3.03)	1471.60	1480.70 (2.36)	1487.13
Omicron						
Baseline	230.20 (6.40)	221.62	32.88 (2.71)	32.70	29.14 (2.16)	28.99
D14	4549.43 (2.67)	4379.81	2058.68 (3.67)	2053.73	1220.18 (2.42)	1219.08

The Applicant further presented an overview of safety data collected in study HH-5 in the respective subjects: 561 individuals vaccinated with two doses and 118 subjects vaccinated with one dose of Spikevax and having covid-19 infection or having received another dose of another vaccine (Comirnaty, Vaxzevria). It appears that more subjects that followed the primary vaccination with Spikevax/Spikevax tended to report solicited local and systemic events compared to the general population or subjects primary vaccinated with Comirnaty/Comirnaty, but numbers do not give rise to concern and the overall pattern of safety results are comparable to the overall population and to subjects previously vaccinated with Comirnaty. No concerns regarding a different safety profile arise from this data. However, the dataset is too small for any conclusions regarding uncommon adverse reactions.

The presented data supports an indication for subjects previously vaccinated with mRNA Covid-19 vaccines.

2.5.5.5. Supportive study(ies)

Study HH-5

This study is an ongoing, Phase III, open label, single arm, multi-centre, trial to assess the safety and immunogenicity of a booster vaccination with PHH-1V in adults vaccinated against COVID-19 with several primary vaccine schedules.

Objectives

The primary objective of this study was to assess safety and tolerability of PHH-1V as a booster dose in healthy adults vaccinated against COVID-19 with several primary vaccination schedules. Immunogenicity data was only collected in a subset of subjects.

Secondary objectives are:

- to determine and compare the changes of the immunogenicity measured by pseudovirus neutralisation against D614G strain strain and against Omicron, and any other relevant VoC in the epidemiologic moment, at Baseline and at Days 14, 91, 182 and 365, after booster of HIPRA's vaccine (PHH-1V) in a subset of participants; and
- to evaluate the immunogenicity measured by means of total antibody against Receptor Binding Domain of the Spike protein of SARS-CoV-2 quantification, measured by an electrochemiluminescence immunoassay (ECLIA) at Baseline and at Days 14, 91, 182 and 365 after booster of HIPRA's vaccine (PHH-1V) in a subset of participants.

Exploratory objectives include:

- the assessment of the number of subjects with SARS-CoV-2 infections ≥14 days after PHH-1V booster;
- the number of COVID-19 severe infections ≥14 days after receiving PHH-1V;
- the evaluation of T cell mediated responses against the SARS-CoV-2 S glycoprotein at Baseline and Day 14 in subjects who have received two doses of Vaxzevria vaccine and PHH-1V as a booster;
- the assessment of Th-1/Th-2 T cell mediated responses against the SARS-CoV-2 S glycoprotein at Baseline and Day 14 in subjects who have received two doses of Vaxzevria vaccine and PHH-1V as a booster

Outcomes/endpoints

The following secondary endpoints are related to efficacy:

- Neutralisation titre against D614G strain and Omicron strains, and any other relevant VoC in the epidemiologic moment, measured as inhibitory concentration 50 (IC50) by a pseudovirion-based neutralisation assay (PBNA) and reported as reciprocal concentration for each individual sample and geometric mean titre (GMT) for descriptive statistics analysis at Baseline and at Days 14, 91, 182, and 365.
- The geometric mean fold rise (GMFR) in neutralising antibody titre from Baseline to Day 14.
- Binding antibodies titre measured for each individual sample and GMT for descriptive statistics analysis at Baseline and Days 14, 91, 182, and 365.
- The GMFR in binding antibody titre from baseline to Day 14.
- The percentage of subjects that after the booster dose have a ≥4-fold change in binding antibodies titre from Baseline to Day 14.

The following exploratory endpoints are related to efficacy:

- T cell-mediated response to the SARS-CoV-2 S protein as measured by whole peripheral blood mononuclear cell (PBMC) stimulation by enzyme-linked immune absorbent spot (ELISpot) at Baseline and at Day 14. This analysis was performed in a subset of 27 subjects.
- CD4+/CD8+ T cell response to the SARS-CoV-2 S protein as measured by in vitro PBMC stimulation by cytokine staining assays at Baseline and at Day 14. This analysis was performed in a subset of 27 subjects.

Sample size

No formal sample size calculation was performed for this Phase III study.
The study is planned to be performed in approx. 3000 subjects ≥16 years old, mainly in Spain with few centres in Italy and Portugal and is still ongoing (*Date of the report: 30 May 2022 (version 2.0)*; Date first subject enrolled: 03 February 2022; Date last subject completed: Pending).

Subjects were eligible to enrolled when they had received: (1) two homologous doses of Comirnaty, Spikevax or Vaxzevria, (2) one dose of Janssen, (3) two heterologous doses of Comirnaty + Spikevax (or vice-versa), Vaxzevria + Comirnaty/Spikevax, or (4) one dose of vaccine (Comirnaty, Spikevax, Vaxzevria or Janssen) and had a confirmed COVID-19 infection before or after the vaccination.

Statistical methods

Descriptive analysis was performed for variables overall by time-point. Categorical variables were presented by means of number of cases and frequencies (%) and continuous variables were presented by number of non-missing observations, mean, standard deviation (SD), median, min and max. For the immunogenicity variables the geometric mean titre, geometric mean concentration, GMFR, and standard deviations will be presented, as appropriate. Dichotomised measures for immunogenicity were presented as frequencies and percentages. 95% confidence intervals (CI) were also provided, as appropriate. In general, missing data was not imputed. For exploratory endpoints related to the immunogenicity endpoints and T-cell, zero values were imputed to half of the lower limit of quantification (LLOQ). If other parameters were deemed appropriate for imputation, information was detailed in the Statistical Analysis Plan (SAP).

Geometric mean titre (GMT), geometric mean concentration (GMC), GMFR and standard deviations were calculated based on the log-transformed titres. Calculation of 95% CI was based on the t

distribution of the log-transformed titres or the difference in the log-transformed titres for GMT and GMFR, respectively, then back transformed to the original scale.

Results

This interim analysis (version 3.0) presents results from the first 2646 enrolled subjects who have completed Day 14 safety assessments in Spain. There were 2593 subjects in the modified intent-to-treat population and 230 subjects in the immunogenicity population.

The immunogenicity subset should include about 8% of the enrolled subjects with no history of SARS-CoV-2 infection (approx. 250 subjects: 100 subjects with two doses of Vaxzevria, 100 subjects with heterologous priming (Vaxzevria vaccine combined with messenger RNA vaccine) and 50 subjects with two doses of Spikevax. 16- or 17-year old subjects were to be vaccinated with two doses of Comirnaty.

Defined populations:

- Modified Intent-to-treat (mITT): All subjects in the ITT (enrolled, regardless of the subject's treatment status in the study) who met the inclusion/exclusion criteria, received a dose of study drug and had not tested positive for COVID-19 within 14 days of receiving study drug.
- Immunogenicity population (IGP): All subjects in the mITT who had a valid immunogenicity test result before receiving study drug and at least one valid result after dosing. Subjects were grouped following primary vaccination schemes. For the immunogenicity assessment, subjects who have a recorded case of COVID-19 were excluded.

At day 0, each subject will receive one dose of COVID-19 HIPRA's vaccine (PHH-1V; 0.5 mL (40 µg), single intramuscular administration; Batch number: 75N11). For immunogenicity assessment, each subject will be followed for 52 weeks (365 days) after the administration of the booster vaccination on Day 0. Evaluations of immunogenicity parameter will be performed at baseline and at Days 14, 91, 182 and 365.

Immunogenicity Results (secondary endpoints):

Neutralising antibody results demonstrate that PHH-1V vaccine was able to elicit high levels of neutralising antibodies for the D614G strain SARS-CoV-2 strain as well as the VOCs Beta, Delta and Omicron.

Neutralising antibody results for D614G strain

Table 37 Overview results HH-5 (D614G strain)

	Comirnaty/ Comirnaty 16-17 years old	Vaxzevria/ Vaxzevria	Vaxzevria/ Another Brand	Spikevax/ Spikevax	Overall
n	11	40	8	171	230
Neutralising antibody levels *[Geometric Mean (SD)];* See Table 7 in CSR					
Baseline	664.301 (1.8976)	268.428 (6.6954)	80.890 (3.2284)	653.975 (2.8833)	521.264 (3.7507)
D14	4385.316 (2.2425)	2138.295 (3.6655)	528.413 (3.4673)	4413.521 (2.7111)	3612.897 (3.1416)
Neutralising antibody GMT *[*GMT for adjusted treatment mean [1] (95% CI)]; See Table 8 in CSR					

Baseline	720.10 (356.963, 1452.643)	288.58 (194.563, 428.023)	76.32 (33.936, 171.644)	657.49 (499.523, 865.425)	
D14	4753.65 (356.453, 9589.482)	2298.81 (1549.886, 3409.627)	498.57 (221.688, 1121.263)	4437.27 (3371.158, 5840.545)	
Mean fold rise in neutralising antibodies titres *(SD)*; See Table 15 in CSR					
D0-D14	11.515 (14.2289)	50.891 (120.8642)	7.441 (3.8611)	15.373 (24.6924)	
GMFR adjusted treatment mean for neutralising antibody titres (95% CI); See Table 16 in CSR					
D0-D14	8.31 (3.249, 21.267)	7.77 (4.244, 14.207)	8.21 (2.836, 23.783)	7.58 (4.468, 12.869)	

[1] 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.

Neutralising antibody results for Beta

Table 38 Overview results HH-5 (Beta)

	Comirnaty/ Comirnaty 16-17 years old	Vaxzevria/ Vaxzevria	Vaxzevria/ Another Brand	Spikevax/ Spikevax	Overall
n	11	40	8	171	230
Neutralising antibody levels *[Geometric Mean (SD)];* See Table 9 in CSR					
Baseline	415.806 (4.4388)	508.468 (9.0251)	44.987 (1.8166)	490.570 (4.4803)	450.695 (5.3227)
D14	7775.798 (2.5255)	4721.410 (3.9729)	1099.743 (2.4612)	6758.781 (2.4694)	6001.448 (2.8780)
Neutralising antibody GMT *[*GMT for adjusted treatment mean [1] (95% CI)]; See Table 10 in CSR					
Baseline	471.68 (208.398, 1067.602)	539.49 (345.971, 841.257)	43.49 (16.906, 111.892)	497.77 (376.977, 657.263)	
D14	8820.74 (3897.144, 19964.718)	5009.47 (3212.533, 7811.540)	1063.22 (413.279, 2735.281)	6857.95 (5193.761, 9055.380)	
Mean fold rise in neutralising antibodies titres *(SD)*; See Table 17 in CSR					
D0-D14	47.227 (73.9457)	64.991 (170.2984)	29.790 (18.9059)	33.613 (53.0400)	
GMFR adjusted treatment mean for neutralising antibody titres (95% CI); See Table 18 in CSR					
D0-D14	17.58 (6.808, 45.390)	8.92 (5.165, 15.393)	27.03 (9.114, 80.135)	13.89 (9.244, 20.884)	

[1] 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.

Neutralising antibody results for Delta

Table 39 Overview results HH-5 (Delta)

	Comirnaty/ Comirnaty 16-17 years old	Vaxzevria/ Vaxzevria	Vaxzevria/ Another Brand	Spikevax/ Spikevax	Overall
n	11	40	8	171	230
Neutralising antibody levels *[Geometric Mean (SD)];* See Table 11 in CSR					
Baseline	741.184 (3.1767)	257.299 (7.9997)	101.920 (3.0495)	954.116 (3.6275)	694.361 (4.7712)
D14	6975.141 (2.2766)	2357.931 (4.1345)	986.606 (2.3153)	6062.056 (2.4131)	4861.710 (2.9812)
Neutralising antibody GMT *[*GMT for adjusted treatment mean [1] (95% CI)]; See Table 12 in CSR					
Baseline	803.84 (376.274, 1717.256)	283.75 (182.426, 441.345)	92.99 (38.829, 222.694)	914.68 (657.966, 1271.546)	
D14	7564.79 (3541.046, 16160.764)	2600.31 (1671.780, 4044.560)	900.15 (375.872, 2155.717)	5811.47 (4180.440, 8078.872)	
Mean fold rise in neutralising antibodies titres *(SD)*; See Table 19 in CSR					
D0-D14	19.821 (25.5334)	69.762 (162.2229)	11.366 (6.4578)	14.229 (23.3729)	
GMFR adjusted treatment mean for neutralising antibody titres (95% CI); See Table 20 in CSR					
D0-D14	10.09 (3.952, 25.744)	9.14 (5.283, 15.798)	11.20 (3.837, 32.723)	6.69 (4.345, 10.311)	

[1] 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.

Neutralising antibody results for Omicron

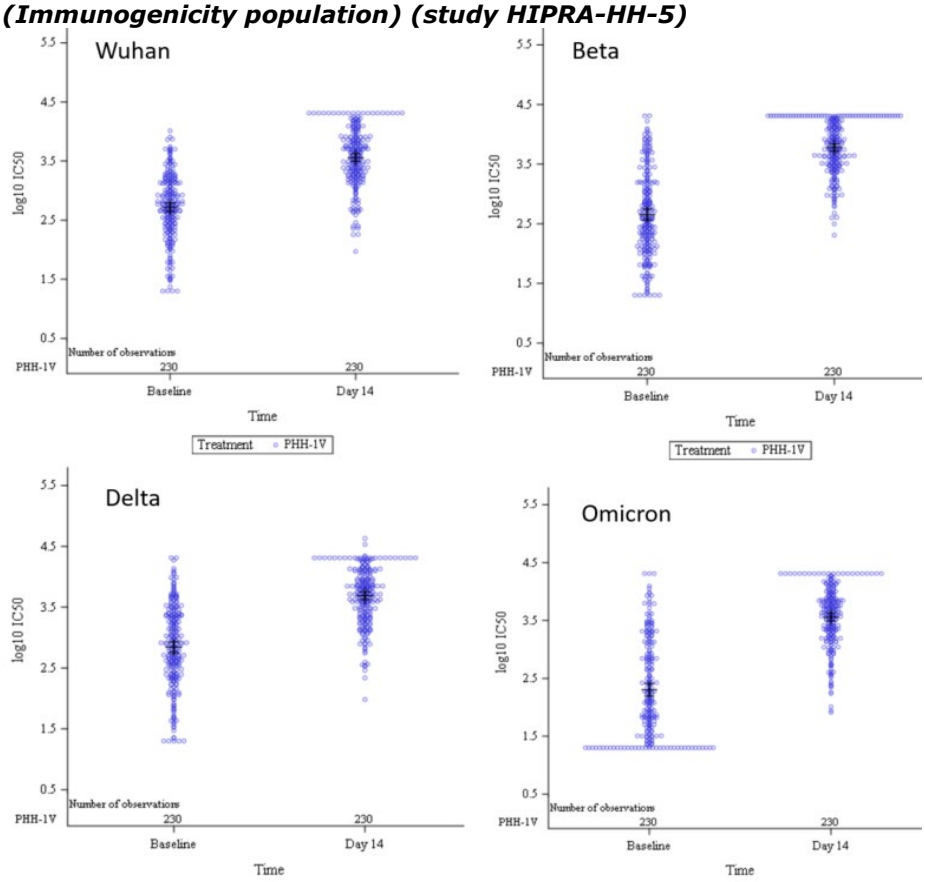
Table 40 Overview results HH-5 (Omicron)

	Comirnaty/ Comirnaty 16-17 years old	Vaxzevria/ Vaxzevria	Vaxzevria/ Another Brand	Spikevax/ Spikevax	Overall
n	11	40	8	171	230
Neutralising antibody levels *[Geometric Mean (SD)];* See Table 13 in CSR					
Baseline	259.739 (5.6669)	148.800 (9.1381)	37.402 (3.0694)	230.203 (6.4047)	201.469 (6.8363)
D14	5796.439 (2.7824)	1725.216 (5.0113)	658.891 (4.0537)	4549.430 (2.6740)	3635.497 (3.4215)
Neutralising antibody GMT [GMT for adjusted treatment mean [1] (95% CI)]; See Table 14 in CSR					
Baseline	257.99	159.34	37.71	221.62	

	(99.983, 665.708)	(94.017, 270.049)	(12.612, 112.741)	(155.507, 315.840)	
D14	5757.43 (2231.254, 14856.192)	1847.41 (1090.045, 3131.000)	664.28 (222.173, 1986.123)	4379.81 (3073.241, 6241.854)	
Mean fold rise in neutralising antibodies titres *(SD)*; See Table 21 in CSR					
D0-D14	47.138 (62.3867)	98.859 (211.7663)	22.940 (17.1138)	62.156 (101.6325)	
GMFR adjusted treatment mean for neutralising antibody titres (95% CI); See Table 22 in CSR					
D0-D14	23.32 (7.296, 74.530)	11.49 (6.135, 21.516)	18.16 (4.773, 69.105)	20.22 (13.473, 30.351)	

[1] 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.

Figure 8. Log$_{10}$ IC$_{50}$ against D614G strain, Beta, Delta and Omicron over time (Immunogenicity population) (study HIPRA-HH-5)



Percentage of subjects with ≥4-fold change in binding antibody

Percentage of subjects with ≥4-fold change in binding antibody titres from Baseline to Day 14 after a booster were high in all arms, ranging from 78% to 100% and demonstrating that a response in antibody titres was observed in most vaccinated subjects.

Table 41: Analysis of Fold Change in Binding Antibodies Titres (Immunogenicity Population)

	Comirnaty/ Comirnaty (N=11) 16-17 years old	**Vaxzevria/ Vaxzevria (N=40)**	**Vaxzevria/ Another Brand (N=8)**	**Spikevax/ Spikevax (N=171)**
Day 14				
Number of subjects included in the analysis n (%)	11 (100.0)	40 (100.0)	8 (100.0)	171 (100.0)
Number of responders n (%) [1]	9 (81.8)	33 (82.5)	8 (100.0)	134 (78.4)
Responders 95% CI [2]	(0.482, 0.977)	(0.672, 0.927)	(0.631, 1.000)	(0.714, 0.843)

Abbreviations: CI = Confidence interval, COVID-19 = Coronavirus Disease 2019; LS mean = least square mean, N = the number of subjects in the population, n = the number of subjects meeting the criterion, NC = not calculable.

[1] % = n / number of subjects in the analysis. A responder is defined as those subjects with a fold change in binding antibodies of 4 or greater. Fold rise is calculated as post-baseline titre/baseline titre.
[2] Exact CI for the proportion of responders has been calculated using the Clopper-Pearson method.

Exploratory endpoints

SARS-CoV-2/Covid-19 related endpoints ≥14 days after PHH-1V booster:

14 subjects were reported with a SARS-CoV-2 infection ≥14 days after PHH-1V booster.

No subjects experienced severe COVID-19 infections, were hospitalised due to COVID-19, or were admitted to the ICU due to COVID-19 ≥14 days after PHH-1V booster during the time of this report.

There have been no deaths associated with COVID-19 during the time of this report.

T-cell mediated response

• The RBD/Spike-specific IFN-γ+ T-cell response was analysed in a subset of 14 subjects immunised with PHH-1V after a primary vaccination with Vaxzevria. Data show that the heterologous booster with PHH-1V, after a primary vaccination with Vaxzevria elicits a significant IFN-γ+ T-cell response. (This report includes ELISpot data from day 0 (visit 2) and day 14 (visit 3). ICS is currently being performed and results will be included in the next Interim Report.)

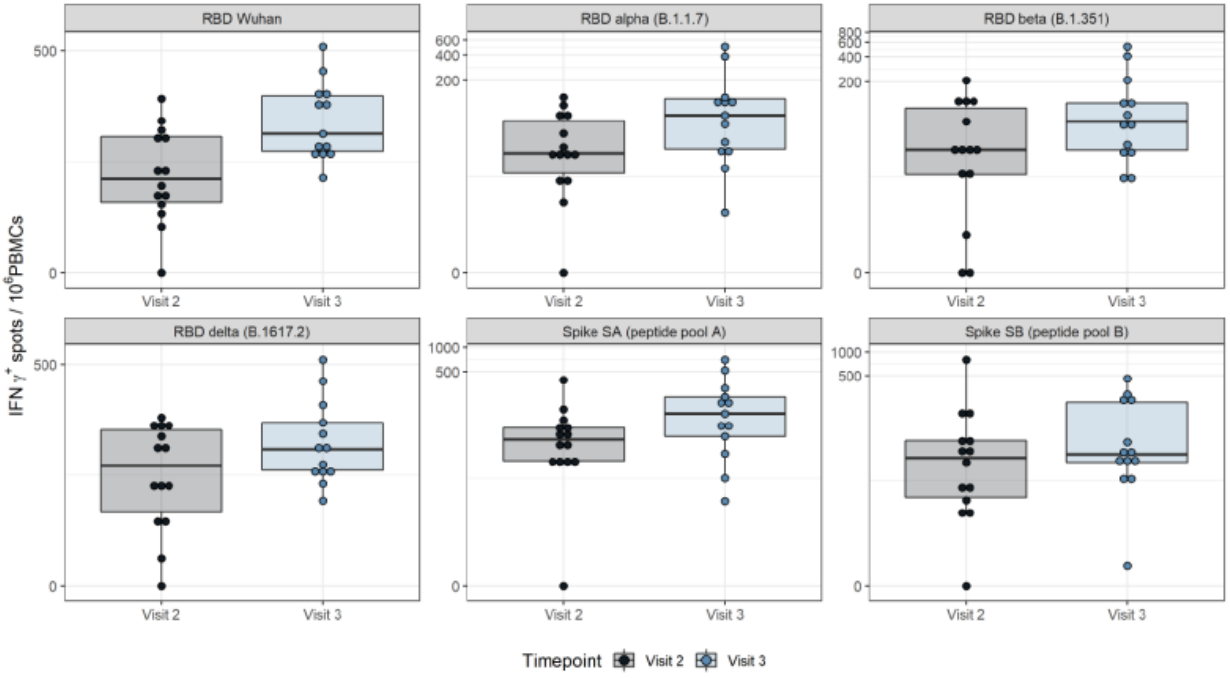
Table 42:IFN-γ responses determined by ELISpot assay in PBMC from subjects immunised with PHH-1V after a primary vaccination with Vaxzevria.

	PHH-1V	
	Visit 2 (n = 14)	Visit 3 (n = 13)
RBD Wuhan	13 (92.9%)	13 (100%)
RBD alpha (B.1.1.7)	13 (92.9%)	13 (100%)
RBD beta (B.1.351)	12 (85.7%)	13 (100%)
RBD delta (B.1617.2)	13 (92.9%)	13 (100%)
Spike SA (peptide pool A)	13 (92.9%)	13 (100%)
Spike SB (peptide pool B)	13 (92.9%)	13 (100%)
Responders*	13 (92.9%)	13 (100%)
Non-responders	1 (7.1%)	0 (0%)

Abbreviations: ELISpot = Enzyme-Linked Immune Absorbent Spot; IFN-γ = interferon gamma; PBMC = Peripheral Blood Mononuclear Cell; RBD = receptor binding domain.

Visit 2: D0; Visit 3: D14

Figure 9 . Frequencies of IFN-γ responses determined by ELISpot assay in PBMC from subjects immunized with PHH-1V after a primary vaccination with Vaxzevria. PBMC were isolated before the boost immunization (visit 2) and two weeks after boost with PHH-1V (visit 3), stimulated with RBD (D614G strain, RBD alpha, RBD beta and RBD delta) and Spike (SA, SB) peptide pools, and analysed by IFN-γ-specific ELISpot assay. A logarithmic scale has been used for plotting purposes.



Conclusion:

• The plan to include groups who received one or two doses of any of the four approved vaccines with or without having had natural infection is intended to mimic as much as possible the current EU scenario. Individuals are being vaccinated regardless of their infection history and regardless of the previous vaccination scheme. Thus, several primary vaccine combinations, and previously infected subjects were enrolled in this study. Local and systemic reactogenicity have been assessed separately in these sub-groups and also considering the time elapsed since completion of the primary vaccination sequence or previous COVID-19 infection.

• There were no cases of severe COVID-19 infection. The cases of COVID-19 infection reported were non-severe cases. Such findings indicate that PHH-1V provides protection to moderate, severe, life-threatening, and fatal forms of SARS-CoV-2 infections.

• Immunogenicity was assessed at Baseline and Day 14 in a subset of 230 subjects vaccinated with two doses of Comirnaty/Comirnaty (individuals 16-17 years old), Spikevax/Spikevax, Vaxzevria/Vaxzevria, or a combination of Vaxzevria and another brand of vaccine. In general, results showed a steep increase in immune response after PHH-1V vaccination, regardless of the brand of vaccine. The subsets previously vaccinated with Comirnaty/Comirnaty, Spikevax/Spikevax and Vaxzevria/Vaxzevria showed a high increase in the immune response after the PHH-1V booster dose.

The percentage of responders (subjects with ≥4-fold change in binding antibody titres from Baseline to Day 14 after a booster) demonstrated that a response in antibody titres was observed in most vaccinated subjects.

Study HAN-01

A phase IIb, multicenter, observed-blind, randomized, active controlled study to evaluate safety and immunogenicity of a recombinant protein RBD fusion dimer candidate vaccine against SARS-CoV-2 in adult healthy volunteers in Vietnam

The study was conducted in Vietnam in 256 healthy adults aged 18-60 (*Date of the interim report:* 6 April 2022 *(version 2.0)*; cut-off date: 28 December 2021; Date first subject enrolled: 11 November 2021; Date last subject completed: 11 January 2022). Subjects were eligible to enrolled when they had not received any Covid-19 vaccine and had no history of received COVID-19 infection.

Subjects are randomized (1:1) to receive either COVID-19 Vaccine HIPRA or Pfizer–BioNTech (Comirnaty). Finally, 121 participants received 2 doses of PHH-1V and 124 participants received 2 doses of Comirnaty vaccine. The study consists of a screening visit, vaccination, and revaccination 21 days later, and follow up visits according to the Schedule of visits. Each subject is followed for 24 weeks after the first dose. The study duration is approximately 30 weeks.

The primary objectives are to assess safety and tolerability and to evaluate the immunogenicity at baseline and 3-weeks after the first dose and 2-weeks after the second dose of COVID-19 HIPRA vaccine (control: Pfizer (D614G strain, non-inferiority)).

Secondary endpoints include the evaluation of different time points (e.g. 21 weeks) and different variant strains (Beta, Delta).

Exploratory endpoints include SARS-CoV-2/Covid-19 related endpoints (e.g. (severe) infections, ICU admission, death). Data on COVID-19 cases is not included in this Interim Report. Some Covid-19 cases were reported and all cases were asymptomatic, or mild cases in both groups. This parameter will be evaluated again in the next visit of this study and data included in next Interim Report.

Results

Table 43. Overview results HAN- 01

	PHH-1V			**Comirnaty**		
	Baseline	D21	D35	Baseline	D21	D35
N	126	126	120	126	126	123
Neutralising antibody levels (IC50)*; [Geometric Mean (SD)]*						
Omicron	20.40 (1.13)	26.58 (1.93)	107.90 (3.28)	20.26 (1.10)	26.72 (1.69)	114.00 (2.54)
Beta	20.24 (1.06)	309.81 (4.40)	2017.79 (3.32)	20.01 (1.01)	79.97 (3.37)	762.79 (2.73)
Delta	20.11 (1.05)	125.70 (5.30)	740.47 (3.87)	20.39 (1.20)	132.57 (2.99)	1290.72 (2.92)
Neutralising antibody GMT *[*GMT for adjusted treatment mean [1] (95% CI)];						
Omicron	20.395 (19.97, 20.83)	26.581 (23.67, 29.85)	107.896 (87.04, 133.74)	20.257 (19.93, 20.59)	26.717 (24.35, 29.31)	114.005 (96.53, 134.65)
Beta	20.235 (20.02, 20.46)	309.806 (238.56, 402.33)	2017.789 (1624.18, 2506.78)	20.014 (19.99, 20.041)	79.970 (64.55, 99.08)	762.788 (637.75, 912.34)
Delta	20.106 (19.93, 20.28)	125.698 (93.68, 168.65)	740.466 (579.862, 945.55)	20.385 (19.75, 21.05)	132.566 (109.27, 160.83)	1290.715 (1066.03, 1562.76)
GMFR (95% CI);						
Omicron	-	1.303 (1.158, 1.465)	5.283 (4.254, 6.562)	-	1.319 (1.200, 1.449)	5.625 (4.757, 6.652)
Beta	-	15.352	99.946	-	3.996	38.112

		(11.819, 19.942)	(80.325, 124.360)		(3.225, 4.950)	(31.858, 45.594)
Delta	-	6.251 (4.658, 8.389)	36.816 (28.838, 47.000)	-	6.513 (5.395, 7.834)	63.268 (52.459, 76.303)

Figure 10. PBNA titre distributions for Beta, Delta and Omicron variants in participants administered with Comirnaty or PHH-1V vaccines. Boxplots depicting the log10-PBNA titres in participants vaccinated with either Comirnaty or PHH-1V for the three tested variants.

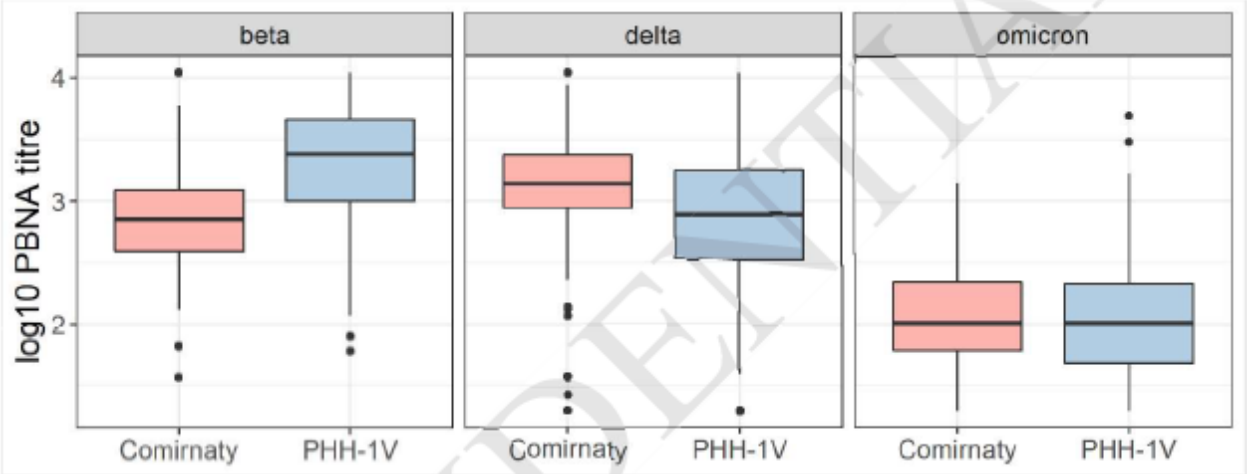


Table 44. Results of the comparisons between vaccines for each variant at D35.

	Mean PHH-1V	Mean Comirnaty	GMT ratio	95 % CI GMT ratio	Conclusion considering NI_m 1.50
Beta	3.30	2.88	0.378	[0.286, 0.500]	NON INFERIORITY and SUPERIORITY
Delta	2.87	3.11	1.742	[1.282, 2.371]	Inconclusive
Omicron	2.03	2.06	1.057	[0.807, 1.384]	NON INFERIORITY

The presented results show an increase in neutralising antibody titre for all variants. Superiority could be shown for the Beta variant, non-inferiority for Omicron and inconclusive results have been obtained for Delta (numerically lower). Immunogenicity results of this study are not considered relevant for the current application.

Study HH-10

A Phase IIb, double-blind, randomised, active-controlled, multi-centre, non-inferiority trial to assess immunogenicity and safety of a booster vaccination with a recombinant protein RBD fusion dimer candidate (PHH-1V) against SARS-CoV-2, in adults fully vaccinated with adenovirus vaccine against COVID-19

The study is planned to be performed in Spain in approx. 273 subjects ≥18 years old and is still ongoing (*Date of the report: 13 May 2022 (version 2.0)*; Date first subject enrolled: 25 March 2022; Date last subject completed: Pending). Subjects were eligible to enrolled when they had received two doses of Vaxzevria and had no history of Covid-19 infection. Subjects were randomly assigned (2:1) to receive either COVID-19 HIPRA's vaccine (PHH-1V; 0.5 mL (40 µg), single intramuscular administration. Batch number: 75N1116) or COVID-19 Pfizer–BioNTech's vaccine (Comirnaty; 0.3 mL (30 µg), single intramuscular administration; several commercial batches).

Subjects received a single booster dose, according to treatment assignment, on Day 0 and were observed for 15 minutes after vaccination. Subjects returned to the site on Days 14, 98, and 182 (final visit) for blood sample collection and safety follow-up. Each subject will be followed for 182 days after the administration of the booster vaccination on Day 0. The total clinical study duration for each subject will be up to 7 months.

The primary objectives of this study were to compare the change in immunogenicity against the Omicron strain at day 14 following the booster dose with the respective vaccines and to assess the safety and tolerability of PHH-1V as a booster dose in healthy adult subjects fully vaccinated against COVID-19 with Vaxzevria vaccine.

Secondary objectives included determining the immunogenicity of other VOCs (Beta, Delta) and of different timepoints also for the Omicron strain (Baseline, Days 14, 98, and 182).

Exploratory endpoints include SARS-CoV-2/Covid-19 related endpoints (e.g. number of (severe) infections) (not included in this report, updates expected in next cycle).

This interim analysis presents immunogenicity results from all enrolled subjects who have completed Day 14 assessments. At the date of data cut off (02 May 2022), 25 subjects were vaccinated, 17 subjects received the PHH-1V vaccine, and 8 subjects received the Comirnaty vaccine.

Results:

For all variants neutralising antibody levels sharply increased in both vaccine arms 14 days after receiving the booster.

Table 45. Overview preliminary D14 results study HH-10

	PHH-1V		**Comirnaty**	
	D0	***D14***	***D0***	***D14***
Omicron	n=11		n=5	
neutralising antibodies	33.634 (4.23)	846.95 (7.57)	20.000 (1.00)	395.36 (4.21)
GMT for adjusted treatment mean	37.89 (4.945, 290.418)	954.25 (124.514, 7313.155)	21.73 (3.226, 146.434)	429.66 (63.773, 2894.736)
Beta	N=16		N=8	
neutralising antibodies	53.886 (4.89)	2866.90 (4.48)	20.146 (1.02)	1274.90 (3.27)
GMT for adjusted treatment mean	63.27 (8.109, 493.622)	3365.94 (431.400, 26262.317)	23.07 (3.754, 141.771)	1459.87 (237.547, 8971.788)
Delta	N=16		N=8	
neutralising antibodies (SD)	51.966 (3.57)	1554.10 (2.90)	20.438 (1.05)	1839.99 (3.79)
GMT for adjusted treatment mean (95% CI)	56.41 (14.873, 213.912)	1686.85 (444.796, 6397.205)	21.88 (6.070, 78.879)	1969.94 (546.480, 7101.232)

• There were no statistically significant differences in GMFR against omicron, beta or delta variants with the PHH-1V vaccine compared to the Comirnaty vaccine.

• There is no statistically significant difference in fold change in binding antibodies between the vaccine arms on Day 14 (GMFR ratio of 2.89 [95% CI: 0.89, 9.41; p 0.0738]).

Overall, the results indicate that the PHH-1V vaccine is showing high levels of neutralising antibodies for the last and currently predominant VOCs. Data indicate that the booster with PHH-1V elicits an immune response similar to that of Comirnaty, although the sample size is small to be able to conduct statistics on noninferiority.

The main reason for this low sample size is the difficulty to recruit more subjects and the exclusion of numerous subjects due to exclusion criteria (e.g. SARS COV-2 positivity, inability to provide valid blood samples). Further, most of the subjects who have received two doses of Vaxzevria vaccine have already received their booster (third dose of mRNA vaccine) and/or they have been diagnosed with SARS-CoV-2 infection. Furthermore, there is a high number of subjects who received a heterologous primary vaccination scheme.

The study is ongoing and every effort to improve recruitment is being executed along the way. All study centres have been supported by the Sponsor in the implementation of several different recruitment strategies. Currently, there has been an active search for new potential centres to be added to this program once they confirm they have access to the target population.

2.5.6. 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 mRNA vaccine Comirnaty with established efficacy to the vaccine candidate PHH-1V. This approach is considered acceptable and was agreed to in the previous EMA-SA procedure (EMADOC-1700519818-742601, Case No.: EMA/SA/0000066056).

This MAA is based on the interim reports of several clinical studies, Study HH-1, HH-2, HH-5, HAN-01 and HH-10. Studies HH-2, HH-5 and HH-10 are currently still ongoing, Study HH-1 reached the 1 year follow-up in August 2022, HAN-01 is completed. The submission of the final CSRs is documented as commitments and is included in the RMP.

Study HH-2 is currently considered as the pivotal study for this application. It is a double-blind, randomized (2:1), active controlled (comparator Comirnaty 30 µg), multi-centre (10 sites in Spain), non-inferiority trial to evaluate immunogenicity and safety of a single PHH-1V dose (40 µg) as a booster vaccination (3rd dose) in adults (≥18, at least 10% >65 years) who previously received primary vaccination with Comirnaty.

All other studies are considered supportive:

- Study HH-5 is a phase III open label study to assess a booster vaccination in approx. 3000 subjects with different vaccination/Covid-19 infection history. The study is mainly focussed on safety but also includes an immunogenicity assessment in currently 230 subjects (approx. 250 planned)

- Study HH-1 is a Phase 1/2a, FIH dose-finding study for a two-dose primary immunization in 30 healthy adults aged 18-39. Study HH-1 is not considered suitable to support a claim for a booster (3rd) dose since a primary immunization schedule was evaluated and further the number of included subjects is limited.

- Study HAN-01 is a completed phase IIb study, for primary immunization (two doses) in adult healthy volunteers in Vietnam. Similar to study HH-1, this study is not considered suitable to support a claim for a booster (3rd) dose since a primary immunization schedule was evaluated.

- Study HH-10 is a Phase IIb study to assess immunogenicity and safety of a booster vaccination with PHH-1V in adults fully vaccinated with adenovirus vaccine. While this study could be important to

extend the indication also to subjects who have been received adenovirus vaccines, the data is currently too limited (25 subjects vaccinated) to support any such claim.

Pivotal Study HH-2

Study HH-2 is currently considered as the pivotal trial as it currently delivers the main immunogenicity data (751 subjects) for this application and immune responses pertaining to the Applicant's intended application as booster vaccination were investigated. Overall, the study design of Study HH-2 appears acceptable, selection criteria are considered appropriate and sampling time points (Day 14, Day 28, Day 98, Day 182, and Day 364 (final visit)) are considered adequate to capture immune response kinetics. Currently only immunogenicity data for Day 14, Day 28, and Day 182 assessments, as well as Day 98 assessments of a subset (~20%) of subjects are presented (interim study report version 5.0, dated 10 March 2023).

Stratification by age group (18-64 yoa, ≥65 yoa) with approximately 10% of the sample enrolled in the ≥65 yoa group is in principle endorsed.

The choice for Comirnaty as active comparator is considered adequate as this vaccine is authorized for booster vaccination and efficacy has been established.

Booster vaccination with either PHH-1V or Comirnaty was administered at least 182 days after the second dose of the primary series.

Approximately 602 subjects were planned for Study HH-2. However, 862 subjects were screened and 765 subjects vaccinated (513 PHH-1V; 252 Comirnaty). While in general a larger sample size could be preferable, this significant overrun had to be justified. Further, it had to be excluded that this overrun may have been driven by preliminary immunogenicity results. The Applicant argued that for logistics issues in the face of the dynamic epidemiologic situation a substantially larger number of subjects was included in the study compared to preplanned sample size targets. Moreover, the Applicant provided a re-analysis of the primary endpoints limited to the first 602 subjects (corresponding to the original sample size target) as requested. Since corresponding results are in line with results obtained from the mITT population (i.e. the primary analysis population) and support the main conclusions from Study HH2, this issue was resolved.

Overall, the chosen objectives and endpoints are appropriate to investigate immune responses for a booster application and were also accepted in the EMA-SA (EMADOC-1700519818-742601, Case No.: EMA/SA/0000066056).

Statistical methods are overall acceptable. However, the definition of the primary analysis population (mITT) differs between protocol and study report where subjects with COVID-19 infection <14 days after vaccination were excluded. This is also not in line with the estimand specified in the SAP. Respective sensitivity analyses, including analyses performed with a population in line with the estimand including subjects regardless of infection (mITT-2), were provided upon request which could address the raised concerns. In addition, a new analysis population 'mITT3' was introduced, defined as individuals included in the mITT but without COVID-19 infections confirmed by PCR or rapid antigen test between Day 0 and Day 182. Some ambiguities concerning the analysis model estimating GMT differences for VOCs noted in the results tables were addressed by the Applicant and it was clarified that while the table captions listed several visits, estimates were based on immunogenicity data up to Day 14 only. Technically, the multiple type I error rate is not controlled for conclusions on immunogenicity differences for VOCs. Nevertheless, the results are supportive of comparable or even better immunogenicity against Beta, Delta and Omicron.

Efficacy data and additional analyses

As this application is based on immunobridging, a proven surrogacy of PBNA for VNA for all different variants is a prerequisite for using PBNA as primary immunogenicity assay. This had also been emphasized during the scientific advice procedure ("The correlation with VNA as determined against whole virion needs to be demonstrated for the different strains", EMADOC-360526170-955736, Case No.: EMA/SA/0000078033). Initially several issues and lack of relevant data were identified regarding the used immunogenicity assays that questioned the validity of the presented data. The Applicant could mitigate the raised concerns and provided additional data to support the agreement between PBNA and VNA measurements. Consequently, the suitability of the PBNA as primary immunogenicity data source is accepted.

The currently available neutralizing antibody response was measured using PBNA. Only preliminary VNA data are available.

Only data for D614G strain and the Beta, Delta and Omicron BA.1 VOC were presented so far. Since PHH-1V's active substance consists of a RBD fusion heterodimer based on SARS-CoV-2 variants B.1.351 (Beta) and B.1.1.7 (Alpha), the lack of data regarding the Alpha VOC appeared counterintuitive. D614G strain was selected as it was the ancestral strain for which efficacy was demonstrated in most of the first clinical trials of already registered vaccines. Although currently not considered as VOC, Beta was selected as it is a variant that contains some of the most relevant mutations that have been sustained along the evolution of the virus. Delta and Omicron BA.1 were selected because these are the variants that are still of most concern at time of study conduct and considered as VOC. Although data on Alpha would have been expected due to the composition of the vaccine, lack thereof is not considered prohibitive of potential approval of this vaccine as it is not specifically developed as variant vaccine against Alpha. To date, there are no reliable data on the immunogenicity for the Omicron BA.4 and BA.5 sublineages. Albeit the Applicant developed a PBNA assay for BA.4/5 but could not provide documentation of a validated/qualified bridging.

Pivotal Study HH-2

In the pivotal HH2 study, PHH-1V failed to demonstrate non-inferiority against the active comparator Comirnaty in the primary efficacy endpoint (neutralizing antibody responses against the D614G strain at Day 14, PBNA). Thus, the multiple type I error rate was not controlled for conclusions on immunogenicity differences for VOCs. While PHH-1V failed to demonstrate non-inferiority against the active comparator Comirnaty in the primary efficacy endpoint (neutralizing antibody responses against the D614G strain strain at Day 14, PBNA), it was superior with regard to the Beta and Omicron VOC and non-inferior with regards to the Delta VOC (secondary endpoints, also neutralizing antibody responses at Day 14, PBNA). Notwithstanding that the primary endpoint was not met, the application can still be approvable, since the D614G strain strain has been superseded by the emerging VOCs in particular the recent Omicron VOC, rendering the secondary endpoints clinically more relevant than the primary endpoint.

The presented immunogenicity data is based on the modified ITT population (mITT) defined as all subjects who received a dose of study drug minus subjects that tested positive for COVID-19 within 14 days of receiving study drug. The exclusion of subjects with a positive test was however not prespecified and does not correspond to the initially defined estimand, which refers to vaccinated subjects regardless of infection. In addition, no consistent screening strategy for infections during the study and especially for these initial 14 days has been implemented. Since the study was performed during the Omicron wave with very high incidences also of asymptomatic cases, it cannot be assumed that all infections have been identified. While it can be assumed that both study arms were affected equally by potential infections, an overall influence cannot be ruled out. Consequently, respective analyses using a population according to the estimand (mITT-2) were requested together with reverse cumulative distribution curves of titres

for the primary endpoint and VOCs. According to the provided responses, there seem to be no or only slight differences between the mITT and mITT-2 results. In addition, the requested reverse cumulative probability plots (mITT baseline and Day 14) supported the finding of PHH-1V's failed non-inferiority vs Comirnaty for D614G strain, non-inferior immune response of PHH-1V to Comirnaty for Delta and superior immune response of PHH-1V over Comirnaty for Beta and Omicron, all with regard to neutralizing antibody titres.

Data for Day 98 was provided only for a subset of subjects (~20% of total subjects). An overall decrease of neutralizing antibody titres was observed compared to the Day 14 results. Notably, the results indicated that neutralizing antibodies may wane to a lesser degree in the PHH-1V arm than in the Comirnaty arm. Neutralizing antibody responses against D614G strain, Beta, Delta and Omicron BA.1 strain at Day 14, Day 28, Day 98 (subset of 20% of total subjects), and Day 182 were provided. Day 28 results are fairly similar to those measured on Day 14 with regard to the fact that PHH-1V's failed non-inferiority vs Comirnaty for D614G strain, non-inferior immune response of PHH-1V to Comirnaty for Delta, and superior immune response of PHH-1V over Comirnaty for Beta and Omicron. In contrast, the Day 182 results, as suggested by Day 98 data, show superior neutralizing immune responses of PHH-1V over Comirnaty for D614G strain, Beta, Delta and Omicron BA.1, indicative for less waning of PHH-1V-elicited immune responses compared to Comirnaty-elicited immune responses. Still, the clinical relevance in terms of protections remains unknown.

The Applicant introduced a new analysis population 'mITT3', defined as all subjects in the mITT without confirmed COVID-19 infection/s between study treatment and Day 182 visit. Subjects with asymptomatic infections are not included in this population due to lack of regular routine testing. Day 182 data shows that across all tested strains (D614G strain, Beta, Delta, Omicron BA.1) nAb GMTs and nAbs GMFRs are in both treatment arms higher in the mITT than in the mITT3, highly likely due to increased immune responses upon COVID-19 infections.

Of the overall 751 subjects (mITT/PP baseline numbers), 56 included subjects were ≥65 yoa. This is below the targeted 10% of the overall population. The presented immune responses of the mITT-2 population for each tested variant are lower in these 56 subjects compared to the overall mITT-2 analyses. Although an overall lower immune response is expected in older subjects compared to younger subjects, the data also revealed differences between treatment arms. The age-related effect on nAb GMTs seemed to be more pronounced for PHH-1V compared to Comirnaty. At Day 14, for D614G strain, Beta and Delta, the nAb GMTs were considerably lower compared to the Comirnaty arm, while the results for all subjects indicated comparable or higher nAb GMTs for the PHH-1V arm (except for D614G strain). For Omicron, nAb GMTs in both arms are similar, while in the overall population the GMT was higher in the PHH-1V arm. On the other hand, responder analysis of neutralizing immune responses of elderly subjects indicates largely similar percentages (except for D614G strain) of subjects achieving an at least 4-fold rise in neutralizing antibodies, which is considered reassuring to some extent as it is indicative for a sufficient protection after the booster dose. In contrast to the above mentioned Day 14 results (i.e. lower nAb GMTs for D614G strain, Beta and Delta in the PHH-1V arm compared to the Comirnaty arm for subjects ≥65 years of age (yoa) while the results for all subjects indicated comparable or higher nAb GMTs for the PHH-1V arm (except for D614G strain) and similar nAb GMTs for Omicron in both arms for subjects ≥65 yoa while in the overall population the GMT was higher in the PHH-1V arm), the Day 182 results showed higher nAb GMTs in the PHH-1V arm than in the Comirnaty arm for all tested strain (D614G strain, Beta, Delta, Omicron BA.1) in subjects ≥65 yoa. Therefore, it seems that the reduced waning of immune responses observed in the PHH-1V arm compared to the Comirnaty arm for both age cohorts (<65 yoa, ≥65 yoa) overcomes the initially observed lower neutralizing immune responses in subjects ≥65 yoa who received PHH-1V compared to Comirnaty.

Taken together, the results indicate that neutralizing antibody responses wane to a lesser degree in the PHH-1V arm than in the Comirnaty arm across all analysed data sets (mITT, mITT2, mITT3), age cohorts (above or below 65 yoa) and strains (D614G strain, Beta, Delta, Omicron BA.1).

Day 14 and Day 28 data of subjects who achieved an at least 4-fold rise in nAbs for each variant (D614G strain, Beta, Delta, Omicron BA.1 strains) for study HIPRA-HH-2 shows that the percentages of subjects with an at least 4-fold rise in nAbs are fairly similar between the PHH-1V and Comirnaty treatment, in particular with regard to Omicron BA.1.

In addition, very limited data regarding cellular immunogenicity including T-cell-mediated response and $CD4^+$ and $CD8^+$ T-cell response were provided (8 PHH-1V and 7 Comirnaty subjects). Both treatment groups showed a significant activation of IFN-γ producing lymphocytes after the in vitro re-stimulation with peptides pool of RBD (D614G strain, Alpha, Beta and Delta variants) at 2 weeks post-boost. No significant differences were observed between PHH-1V and Comirnaty groups when PBMC were stimulated in vitro with RBD antigens. However, the Comirnaty group showed a higher activation of IFN-γ producing cells after the in vitro stimulation with the Spike (SA and SB) antigens at 2 weeks post-boost while in the PHH-1V group only showed some activation of IFN-γ producing lymphocytes after the in vitro stimulation with the Spike SA antigen and practically no activation with the Spike SB antigen. Hence, the characterization of the antigen-specific T cell responses demonstrated that the boost immunization with the PHH-1V vaccine induced the activation of CD4+ T cells expressing IFN-γ after re-stimulation with RBD peptides (from D614G strain sequence and Alpha and Beta variants), even with a more potent response compared to the Comirnaty boost. CD4+ IFN-γ+ T cell response was also observed after the re-stimulation with Spike SA peptides in the group vaccinated with PHH-1V, although no activation was elicited by the Spike SB peptides. All these ICS results should be handled with caution, since they were studied in a very restricted patient subpopulation.

Covid-19 infections were reported for 4.1% after booster vaccination with PHH-1V whereas 4.8% of subjects had a Covid-19 infection after booster vaccination with Comirnaty. Further no severe Covid-19 infections, ICU admissions, ventilation events or deaths related to Covid-19 were reported.

Supportive Dose-finding Study HH-1

This FIH dose-finding study evaluated a two-dose primary immunization. The Applicant provided results based on PBNA data for the Alpha, Beta, Gamma and Delta variant and based on VNA data for Alpha. Based on these results, all applied doses (10, 20, and 40 µg) of PHH-1V were immunogenic in the studied population aged 18-39, which is indicated by the elicitation of both neutralizing and binding antibodies and is further supported by analyses of the cellular immune response.

The highest dose of 40 µg dose yielded the highest mean values at D35 (i.e. 14 days after second dose) across all currently available neutralizing antibody analyses (Alpha, Beta, Gamma, and Delta PBNA and Alpha VNA). Hence, the decision to apply the 40 µg in further studies (e.g. HH-2) appears plausible. However, it is important to note that no clear dose-dependent effect on immunogenicity can be concluded. Furthermore, the dose-finding was not specifically designed for booster vaccination but only for primary vaccination. Therefore, there remains some uncertainty whether the chosen dose is indeed the most optimal dose for booster vaccination.

Other supportive studies

Studies HAN-01 and HH-10 do not provide informative data for the current indication (primary immunization scheme, subjects that received other primary vaccination than mRNA vaccines).

Study HH-5 was mainly intended to assess safety aspects in a population with broader immunization history (Covid-19 vaccination and infections; approx. 3000 subjects). Immunogenicity was assessed in a subset of 230 subjects without prior (symptomatic/detected) Covid-19 infection. This subset mainly included subjects with a primary immunization with two doses of Spikevax. The results are overall comparable to the pivotal study and the data in Spikevax primed subjects was used to justify the indication.

2.5.7. Conclusions on the clinical efficacy

In summary, the provided results are indicative of a superior neutralizing immune responses of PHH-1V over the active comparator Comirnaty against Omicron BA.1 and Beta, as well as non-inferior neutralizing immune response against Delta, 14 days after booster administration. Additionally, long-term data indicates that antibodies may wane to a lesser degree after PHH-1V administration than after Comirnaty administration for subjects above or below 65 years of age and irrespective of the virus strain.

2.5.8. Clinical safety

The applicant has provided interim safety data from the clinical studies HIPRA HH-1, HIPRA HH-2, HIPRA HH-5, HIPRA HH-10 and HAN-01.

- **Study HIPRA HH-2** evaluated one vaccination as booster dose (3rd vaccination) of Bimervax in comparison to Comirnaty (n=513 for Bimervax and n=252 for Comirnaty). Primary safety objective: To assess the safety and tolerability of Bimervax as a booster dose in healthy adult subjects fully vaccinated against COVID-19 with the Comirnaty vaccine. Data cut-off date of available interim study report: 17th of February 2022.
- **Study HIPRA HH-5** evaluated the booster vaccination with Bimervax in subjects with a variety of possible primary vaccinations, but primarily included subjects with prior homologous Comirnaty (C/C; n=1535) or Spikevax vaccination (S/S; n=561; subject numbers based on exposure data from data cut-off on 31st of March 2022, as per data cut-off on 18th of July n=2661 subjects were exposed to Bimervax in study HH-5). Primary safety objective: To assess the safety and tolerability of Bimervax as a booster dose in healthy adult subjects vaccinated against COVID-19 with the Comirnaty, Spikevax, Vaxzevria or JCOVDEN vaccines. Data cut-off date of available interim study report: 31st of March 2022.
- **Study HIPRA HH-10** is designed to investigate the booster vaccination with Bimervax in subjects that had received two doses of Vaxzevria as primary vaccination, but the currently available interim study report for study HH-10 comprises data for n=25 subjects (n=17 for Bimervax and n=8 for Comirnaty). Primary safety objective: To assess the safety and tolerability of Bimervax as a booster dose in healthy adult subjects fully vaccinated against COVID-19 with the Vaxzevria vaccine. Data cut-off date of available interim study report: 2nd of May 2022. Note that no safety data were provided in the interim study report. However, safety data for study HH-10 were only provided as part of pooled safety data with comparable clinical studies HH-2 and HH-5 (data extraction time 18th of July 2022). More details regarding study specific safety results are to be submitted with the final study report.

Subjects were provided with a paper diary to record local and systemic reactions after vaccination from Day 0 through Day 7. Unsolicited adverse events (local and systemic) were reported through Day 28. Serious adverse events (SAEs), adverse events of special interest (AESIs), and medically attended adverse events (MAAEs) were reported throughout the duration of the studies. Adverse events were assessed at each visit based on careful clinical observation of the subject, laboratory tests or spontaneous reports by the subject discovered as a result of general questioning by the study staff. All AEs were to be recorded in the eCRF. It has to be noted that safety data for studies HH-1 and HAN-01 were also submitted, but these studies followed a primary vaccination scheme for Bimervax (i.e., first and second dose of COVID-19 vaccine), which is not the vaccination scheme licensed with this procedure. Data of these two studies do not essentially contribute to the evaluation of safety for the licensed single booster vaccination after primary vaccination scheme with mRNA vaccines but are considered supportive. Thus, the discussion of provided data is focused on studies HH-2, HH-5 and HH-10 with in total more than 3000 subjects exposed to Bimervax.

- **Study HIPRA HH-1** evaluated two vaccinations as primary immunization (5 subjects for 10µg of Bimervax or 10 subjects each arm for 20µg and 40µg of Bimervax compared to Comirnaty). Primary safety objective: To assess safety and tolerability of Bimervax in adult healthy volunteers. Safety was measured by solicited and unsolicited reactions (local and systemic) following each dose vaccination. Data cut-off date of available interim study report: 12th of May 2022.
- **Study HAN-01** was a Phase IIb, randomized, controlled, observer-blinded clinical trial to evaluate safety and immunogenicity of Bimervax in a total of 256 healthy adults not vaccinated previously with any Covid-19 vaccine and without a prior Covid-19 infection. Treatment groups received either 2 doses of Bimervax or 2 doses of Comirnaty. Doses were separated 21 days for each of the vaccines. Comparative data from active control arms receiving Comirnaty is available from Phase I and II studies (HH-1: n=5; HH-2: n=252). Primary safety objective: To assess safety and tolerability of Bimervax in healthy adult volunteers. Safety was measured by solicited and unsolicited reactions (local and systemic) following each dose vaccination. Data cut-off date of available interim study report: 28th of December 2021. Currently limited data are provided for this study.

2.5.8.1. Patient exposure

The safety population was defined as the number of subjects that received at least one dose of study vaccine.

The overall available dataset for **study HIPRA HH-1** (25 subjects exposed to PHH-1V (+5 Comirnaty); Two doses of PHH-1V were administered in 5 subjects (10µg + Comirnaty) or 10 subjects each in the 20µg and 40µg study arms) and **study HAN-01** (n=128 subjects exposed to two doses of Bimervax) is limited. The submitted data from these studies are not considered sufficient for any conclusion on safety of PHH-1V used as primary vaccination.

Extent of exposure:

In general, the provided extent of exposure is currently restricted to number of subjects that received one (booster in studies **HH-2, HH-5, HH-10**) and or two vaccinations (**HH-1 and HAN-01**). Please, refer to Table 46 for additional details. Note that study HH-4 is planned with 400 included subjects to be exposed to PHH-1V, but currently no data are available for this study.

Table 46 Overall extent of exposure in the PHH-1V clinical development plan (adults)

Product and Dose level	# of doses	HIPRA-HH-1 Phase I/IIa	HIPRA-HH-2 Phase IIb	HIPRA-HH-5 Phase III	HIPRA-HH-10 Phase IIb	HAN-01 Phase IIb	HIPRA-HH-4 Phase III	TOTAL
PHH-1V 10 µg	Two[1]	5	-	-	-	-	-	5
PHH-1V 20 µg	Two[1]	10	-	-	-	-	-	10
PHH-1V 40 µg	One (booster)	-	513	2646	182	-	400[2]	3741
	Two[1]	10	-	-	-	128	-	138
Comirnaty 30 µg mRNA	One (booster)	-	252	-	91	-	-	343
	Two[1]	5	-	-	-	128	-	133

[1] Two doses administered as a homologous prime-boost sequence in naïve participants.
[2] Estimated maximum number. Study is ongoing and final numbers are not available.

Duration of follow up

The Applicant provided information regarding the follow up time in studies HH-2 (cut-off date: 17th of February 2022, overall mean 78 days, range 70-92 days) and study HH-5 (data cut-off date: 18th of July 2022, a mean of 5.015 months have elapsed since the last participant received the booster dose of PHH-1V). Currently no information on safety follow up is available for study HH-10 (data cut-off date: 2nd of May 2022). A dedicated safety discussion for study HH-10 will be provided in the final study report.

Subject disposition

Subject disposition for studies with PHH-1V as booster vaccination (HIPRA HH-2, HIPRA HH-5, HIPRA HH-10) is presented in the tables below.

Study HIPRA HH-2

Subject enrolment and disposition for study HH-2 (as per data cut-off date on 15th of November 2021)

Table 47 Subject Enrolment and Disposition

	Statistics	PHH-1V	Comirnaty	Overall
Enrolled population	n			862
Intention-to-treat (ITT)	n	522	260	782
Modified Intention-to-treat (mITT)	n (%)	504 (100.0)	247 (100.0)	751 (100.0)
mITT excluding all subjects with COVID-19 infections (mITT3 (excluding confirmed COVID-19 cases)	n (%)	347 (68.8)	167 (67.6)	514 (68.4)
Per-protocol set (PP)	n (%)	504 (100.0)	247 (100.0)	751 (100.0)
Immunogenicity population	n (%)	503 (99.8)	246 (99.6)	749 (99.7)
Safety population (SP) set	n (%)	513 (101.8)	252 (102.0)	765 (101.9)
Subjects who completed the study	n (%)	0	0	0
Subjects who prematurely discontinued study	n (%)	3 (0.6)	1 (0.4)	4 (0.5)
Reason for study withdrawal	n (%)			
Lost to follow-up		2 (0.4)	0	2 (0.3)
Withdrew consent to participate in study		0	1 (0.4)	1 (0.1)
Withdrawal by subject		1 (0.2)	0	1 (0.1)

Abbreviations: n = the number of subjects meeting the criterion.

Study HIPRA HH-5

Subject enrolment and disposition for study HH-5 (as per data cut-off date on 31st of March 2022)

Table 48 Subject Enrolment and Disposition

	Statistics	PHH-1V
Enrolled population	n	2646
Intention-to-treat (ITT)	n	2646
Modified Intention-to-treat (mITT)	n (%)	2593 (100.0)
Immunogenicity population (IGP)	n (%)	230 (8.87)
Safety population	n (%)	2646 (102.04)
Subjects who completed the study	n (%)	0
Subjects who prematurely discontinued study	n (%)	4 (0.15)
Reason for study withdrawal	n (%)	
Did not attend the visit 3		1 (0.04)
Refused to continue		1 (0.04)
Traffic accident		1 (0.04)
Withdrawal		1 (0.04)

Abbreviations: n = the number of subjects meeting the criterion.

Study HIPRA HH-10

Subject enrolment and disposition for study HH-10 (as per data cut-off date on 2nd of May 2022)

Table 49 Subject Enrolment and Disposition

	Statistics	PHH-1V	Comirnaty	Overall
Enrolled population	n			25
Intention-to-treat (ITT)	n	17	8	25
Modified Intention-to-treat (mITT)	n (%)	16 (100.0)	8 (100.0)	24 (100.0)
Per-protocol set (PP)	n (%)	16 (100.0)	8 (100.0)	24 (100.0)
Immunogenicity population	n (%)	11 (68.8)	5 (62.5)	16 (66.7)
Safety population (SP) set	n (%)	17 (106.3)	8 (100.0)	25 (104.2)
Subjects who completed the study	n (%)	0	0	0
Subjects who prematurely discontinued study	n (%)	0	0	0

Abbreviations: n = the number of subjects meeting the criterion.

Demographics

A summary of the demographics of the evaluated safety population in studies HIPRA-HH-2, HIPRA-HH-5 and HIPRA-HH-10 is provided in Table 50. Table 51. Table 56

Table 50 Demographics and Baseline characteristics of Study HIPRA HH-2 (Safety Population)

	Statistics	PHH-1V (N=513)	Comirnaty (N=252)	Overall (N=765)
Age (years)	n	513	252	765
	Mean	42.1	41.6	41.9
	SD	14.55	14.97	14.68
	Minimum	19	20	19
	Median	42.0	40.0	42.0
	Interquartile Range	26.0	25.0	26.0
	Maximum	76	74	76
Age group n (%)	18 to 64 years old	475 (92.6)	234 (92.9)	709 (92.7)
	65 years old and over	38 (7.4)	18 (7.1)	56 (7.3)
Sex n (%)	Male	188 (36.6)	93 (36.9)	281 (36.7)
	Female	325 (63.4)	159 (63.1)	484 (63.3)
Race n (%)	Black or African American	0	0	0
	American Indian or Alaska Native	2 (0.4)	0	2 (0.3)
	Asian	4 (0.8)	1 (0.4)	5 (0.7)
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	505 (98.4)	250 (99.2)	755 (98.7)
	Other	2 (0.4)	1 (0.4)	3 (0.4)
Ethnicity n (%)	Hispanic or Latino	170 (33.1)	77 (30.6)	247 (32.3)
	Not Hispanic or Latino	343 (66.9)	175 (69.4)	518 (67.7)
Body mass index (kg/m^2) at Screening	n	513	252	765
	Mean	24.803	24.641	24.750
	SD	4.2534	3.9617	4.1577

	Statistics	PHH-1V (N=513)	Comirnaty (N=252)	Overall (N=765)
	Minimum	16.98	17.90	16.98
	Median	24.030	23.730	23.920
	Interquartile Range	4.950	4.650	4.790
	Maximum	39.78	39.86	39.86

Abbreviations: n = the number of subjects meeting the criterion.

Table 51 Demographics and Baseline Characteristics for study HIPRA HH-5 (Safety Population)

	Statistics	PHH-1V (N=2646)
Age (years)	n	2646
	Mean	34.4
	SD	12.74
	Minimum	16
	Median	33.0
	Interquartile Range	22.0

	Statistics	PHH-1V (N=2646)
	Maximum	85
Age group, n (%)	≥ 16 to < 18 years	36 (1.36)
	≥ 18 to < 65 years	2589 (97.85)
	≥ 65 years	21 (0.79)
Sex, n (%)	Male	1389 (52.49)
	Female	1256 (47.47)
	Unknown	0
	Undifferentiated	1 (0.04)
Race, n (%)	Black or African American	8 (0.30)
	American Indian or Alaska Native	7 (0.26)
	Asian	2 (0.08)
	Native Hawaiian or Other Pacific Islander	0
	White	2618 (98.94)
	Other	11 (0.42)
Ethnicity, n (%)	Hispanic or Latino	408 (15.42)
	Not Hispanic or Latino	2227 (84.16)
	Not Reported	9 (0.34)
	Unknown	2 (0.08)
Body mass index (kg/m^2) at Screening	n	2025
	Mean	24.68
	SD	4.69
	Minimum	14.82
	Median	23.81
	Interquartile Range	5.46
	Maximum	51.9
Previous COVID-19 infection status after primary COVID-19 vaccination, n (%)	Yes	1152 (43.54)
	≤ 3 months	693 (26.19)
	> 3 months	58 (2.19)
	Prior to the last primary vaccination	384 (14.51)
	Missing vaccination date	6 (0.23)
	Other missing	11 (0.42)

	Statistics	PHH-1V (N=2646)
	No	1494 (56.46)
Primary COVID-19 vaccination group, n (%)	Comirnaty*	198 (7.48)
	Comirnaty/Comirnaty	1535 (58.01)
	Comirnaty/Spikevax	13 (0.49)
	Janssen*	48 (1.81)
	Janssen/Comirnaty	19 (0.72)
	Janssen/Janssen	7 (0.26)
	Janssen/Spikevax	12 (0.45)
	Spikevax*	90 (3.40)
	Spikevax/Spikevax	561 (21.20)
	Spikevax/Vaxzevria	2 (0.08)
	Vaxzevria*	5 (0.19)
	Vaxzevria/Comirnaty	35 (1.32)
	Vaxzevria/Spikevax	1 (0.04)
	Vaxzevria/Vaxzevria	112 (4.23)
Time elapsed since last primary COVID-19 vaccination dose or COVID-19 infection, n (%)	≤ 3 months	33 (1.25)
	> 3 to ≤ 6 months	706 (26.68)
	> 6 to ≤ 12 months	1842 (69.61)
	> 12 months	45 (1.70)
	Missing 2nd vaccine date	10 (0.38)
	Other missing	10 (0.38)
Test type of prior COVID-19 infections, n (%)	RAT	675 (25.51)
	PCR	466 (17.61)
Severity of prior COVID-19 infections, n (%)	Severe	6 (0.23)**
	Non-severe	1146 (43.31)

Abbreviations: COVID-19 = corona virus disease 2019; N = the number of subjects in the population; n = the number of subjects meeting the criterion; PCR = polymerase chain reaction; RAT = rapid antigen test; SD = standard deviation.

*Subjects with one dose of COVID-19 vaccination and COVID-19 infection (before or after the vaccination)

** Five cases were wrongly categorised as severe and one case has been confirmed as incorrectly recorded, this has since been corrected in the study database

Table 52 Demographics and Baseline Characteristics for study HIPRA HH-10 (Safety Population)

	Statistics	PHH-1V (N=17)	Comirnaty (N=8)	Overall (N=25)
Age (years)	n	17	8	25
	Mean	45.5	47.6	46.2
	SD	13.19	11.92	12.59
	Minimum	21	30	21
	Median	44.0	45.5	45.0
	Maximum	65	68	68
Sex, n (%)	Male	13 (76.5)	5 (62.5)	18 (72.0)
	Female	4 (23.5)	3 (37.5)	7 (28.0)
	Unknown	0	0	0
	Undifferentiated	0	0	0
Race, n (%)	Black or African American	0	0	0
	American Indian or Alaska Native	0	0	0
	Asian	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	17 (100.0)	8 (100.0)	25 (100.0)
	Other	0	0	0
Ethnicity, n (%)	Hispanic or Latino	1 (5.9)	0	1 (4.0)
	Not Hispanic or Latino	16 (94.1)	8 (100.0)	24 (96.0)
	Not Reported	0	0	0
	Unknown	0	0	0
Body mass index (kg/m^2) at Screening	n	14	7	21
	Mean	25.806	26.984	26.199
	SD	3.3697	5.6716	4.1659
	Minimum	20.31	22.27	20.31
	Median	25.855	25.220	25.260
	Maximum	33.21	36.89	36.89

Abbreviations: n = the number of subjects meeting the criterion; SD = standard deviation.
Source: Table 14.1.2

2.5.8.2. Adverse events

Data for the dose finding study **HIPRA-HH-01** is provided separately as different doses and a distinct vaccination scheme were followed (primary vaccination scheme with two doses), in order to provide insight in aspects relevant for dose finding.

Treatment-emergent adverse events (TEAEs), solicited local and systemic adverse events as well as unsolicited adverse events from studies **HIPRA-HH-2, HIPRA-HH-5** and **HIPRA-HH-10** are presented as pooled safety data with data extraction time 18th of July 2022. Pooled safety data were requested as vaccination schemes and applied doses were the same in all three studies. Data from individual studies are discussed where considered essential.

Safety data from study **HAN-01** are not presented in detail in this report, due to differences in the applied vaccination scheme (two primary vaccinations rather than a booster vaccination) and limited data provided. However, safety data relevant for the MA are discussed where needed.

Study HIPRA-HH-1

Most of the subjects in all study cohorts reported solicited adverse events within 7 days after each dose. The majority of adverse event were local. There was no grade 3 solicited adverse events reported. The most frequently reported local AE were pain at the injection site or local sensitivity and the most frequently reported general AE were headache end fatigue. (Table 53)

Table 53 Overall number (%) of subjects with solicited AEs by kind of AE and their maximum grade during 7 days following either first or second vaccination in the safety population (HIPRA-HH-1)

	Maximum grade by subject	PHH-1V 10 µg (n = 5)	PHH-1V 20 µg (n = 10)	PHH-1V 40 µg (n = 10)	Comirnaty 30 µg (n = 5)	TOTAL (n=30) n (%)
Pain at the injection site	1	2 (100.0%)	6 (100.0%)	7 (100.0%)	4 (80.0%)	19 (95.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (5.0%)
	TOTAL	2 (100.0%)	6 (100.0%)	7 (100.0%)	5 (100.0%)	20 (100.0%)
Local sensitivity	1	1 (33.3%)	4 (50.0%)	6 (75.0%)	2 (50.0%)	13 (56.5%)
	2	2 (66.7%)	4 (50.0%)	2 (25.0%)	2 (50.0%)	10 (43.5%)
	TOTAL	3 (100.0%)	8 (100.0%)	8 (100.0%)	4 (100.0%)	23 (100.0%)
Erythema / Redness	1	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
	TOTAL	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
Induration / Swelling	1	1 (100.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	2 (100.0%)
	TOTAL	1 (100.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	2 (100.0%)
Fever	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)
	TOTAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)	2 (100.0%)
Vomiting / Nausea	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	2 (100.0%)
	TOTAL	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	2 (100.0%)
Diarrhoea	1	0 (0.0%)	2 (100.0%)	1 (100.0%)	0 (0.0%)	3 (100.0%)
	TOTAL	0 (0.0%)	2 (100.0%)	1 (100.0%)	0 (0.0%)	3 (100.0%)
Headache	1	0 (0.0%)	3 (100.0%)	4 (80.0%)	1 (33.3%)	8 (72.7%)
	2	0 (0.0%)	0 (0.0%)	1 (20.0%)	2 (66.7%)	3 (27.3%)
	TOTAL	0 (0.0%)	3 (100.0%)	5 (100.0%)	3 (100.0%)	11 (100.0%)
Fatigue / Tiredness	1	1 (100.0%)	3 (75.0%)	4 (100.0%)	1 (50.0%)	9 (81.8%)
	2	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (50.0%)	2 (18.2%)
	TOTAL	1 (100.0%)	4 (100.0%)	4 (100.0%)	2 (100.0%)	11 (100.0%)
Myalgia / Muscle pain	1	0 (0.0%)	1 (100.0%)	1 (100.0%)	1 (50.0%)	3 (75.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (25.0%)
	TOTAL	0 (0.0%)	1 (100.0%)	1 (100.0%)	2 (100.0%)	4 (100.0%)

Frequencies reported in this table are expressed as percentage of subjects with a given AE in relation to all the subjects that presented at least one AE
Source: HIPRA-HH-1 - Short Term Interim Analysis Report, 12th May 2022 **-** Summary Table 3.3 (including kind and maximum grade of AE after the first and second vaccinations).

The number of percentage of subjects reporting at least one unsolicited AE throughout the study are provided in Table 54.

Table 54 ***Number of subjects with at least one kind of unsolicited AE and occurrences classified by severity (HIPRA-HH-1)***

Type of AE	Cat.	HIPRA (10 µg) (n=5) Occurrences / Subjects (%) [95%CI]	HIPRA (20 µg) (n=10) Occurrences / Subjects (%)[95%CI]	HIPRA (40 µg) (n=10) Occurrences / Subjects (%)[95%CI]	Pfizer (n=5) Occurrences / Subjects (%) (%)[95%CI]	TOTAL (n=30) Occurrences / Subjects (%) (%)[95%CI]
AE	No	1 (20.0%) [0.5%, 71.6%]	2 (20.0%) [2.5%, 55.6%]	2 (20.0%) [2.5%, 55.6%]	2 (40.0%) [5.3%, 85.3%]	7 (23.3%) [9.9%, 42.3%]
	Yes	12/4 [80.0%) [28.4%, 99.5%]	27/8 (80.0%) [44.4%, 97.5%]	17/8 (80.0%) [44.4%, 97.5%]	4/3 (60.0%) [14.7%, 94.7%]	60/23 [76.7%) [57.7%, 90.1%]
SAE	No	5 (100.0%) [54.9%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	5 (100.0%) [54.9%, 100.0%]	30 (100.0%) [90.5%, 100.0%]
Related AE	No	3 (60.0%) [14.7%, 94.7%]	6 (60.0%) [26.2%, 87.8%]	4 (40.0%) [12.2%, 73.8%]	3 (60.0%) [14.7%, 94.7%]	16 (53.3%) [34.3%, 71.7%]
	Yes	7/2 [40.0%) [5.3%, 85.3%]	13/4 (40.0%) [12.2%, 73.8%]	12/6 (60.0%) [26.2%, 87.8%]	2/2 [40.0%) [5.3%, 85.3%]	34/14 [46.7%) [28.3%, 65.7%]
Related SAE	No	5 (100.0%) [54.9%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	5 (100.0%) [54.9%, 100.0%]	30 (100.0%) [90.5%, 100.0%]
DLT	No	5 (100.0%) [54.9%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	5 (100.0%) [54.9%, 100.0%]	30 (100.0%) [90.5%, 100.0%]
Related DLT	No	5 (100.0%) [54.9%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	5 (100.0%) [54.9%, 100.0%]	30 (100.0%) [90.5%, 100.0%]
AESI	No	5 (100.0%) [54.9%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	5 (100.0%) [54.9%, 100.0%]	30 (100.0%) [90.5%, 100.0%]
Related AESI	No	5 (100.0%) [54.9%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	10 (100.0%) [74.1%, 100.0%]	5 (100.0%) [54.9%, 100.0%]	30 (100.0%) [90.5%, 100.0%]
MAAE*	No	5 (100.0%) [54.9%, 100.0%]	8 (80.0%) [44.4%, 97.5%]	9 (90.0%) [55.5%, 99.7%]	5 (100.0%) [54.9%, 100.0%]	27 (90.0%) [73.5%, 97.9%]
	Yes	0 (0.0%) [0.0%, 45.1%]	3/2 (20.0%) [2.5%, 55.6%]	1/1 (10.0%) [0.3%, 44.5%]	0 (0.0%) [0.0%, 45.1%]	4/3 (10.0%) [2.1%, 26.5%]
Related MAAE	No	5 (100.0%) [54.9%, 100.0%]	9 (90.0%) [55.5%, 99.7%]	9 (90.0%) [55.5%, 99.7%]	5 (100.0%) [54.9%, 100.0%]	28 (93.3%) [77.9%, 99.2%]
	Yes	0 (0.0%) [0.0%, 45.1%]	1/1 (10.0%) [0.3%, 44.5%]	1/1 (10.0%) [0.3%, 44.5%]	0 (0.0%) [0.0%, 45.1%]	2/2 [6.7%) [0.8%, 22.1%]

AE: adverse event; AESI: AE of special interest; DLT: Dose limiting toxicity; MAAE: medically attended adverse events; SAE: severe adverse event.

Pooled safety data for the booster vaccination with PHH-1V from studies HIPRA-HH-2, HIPRA-HH-5 and HIPRA-HH-10

A total of 9279 TEAEs were reported in 2818 (88.29%) subjects in Studies HH-2, HH-5, and HH-10. The most frequently reported events by System Order Class (SOC) (reported by ≥10% subjects) were General disorders and administration site conditions (6352 TEAEs reported in 2721 (85.24%) subjects), Nervous system disorders (1114 TEAEs in 1034 (32.39%) subjects), Musculoskeletal and connective disorders (740 TEAEs in 691 (21.65%) subjects) and Gastrointestinal disorders (531 TEAEs in 404 (12.66%) subjects).

The most frequently reported preferred terms (reported by ≥1% subjects) were injection site pain (82.46%), headache (31.39%), fatigue (31.14%), myalgia (20.71%), injection site swelling (7.96%), diarrhoea (7.71%), injection site erythema (7.14%), vomiting (5.29%), injection site induration (2.32%), pyrexia (1.97%), COVID-19 (1.50%), nausea (1.47%), lymphadenopathy (1.32%) and axillary pain (1.28%).

Solicited local reactions (day 0 through day 7)

Overall, the majority of solicited local reactions occurred on Day 0 with 4267 events in 2324 (71.81%) subjects in Studies HH-2, HH-5, and HH-10. This frequency decreased each day through to Day 7 (Day 1: 68.08%; Day 2: 33.36%; Day 3: 13.60%; Day 4: 5.80%; Day 5: 2.91%; Day 6: 2.19%; Day 7: 1.85%). The most frequently reported solicited local reactions from Day 0 to Day 7 were pain and tenderness on the vaccine administration site, with 65.48% of subjects experiencing pain and 58.30% of subjects experiencing tenderness on Day 0 and decreasing to 1.22% and 1.38%, respectively, on Day 7. Please, refer to Table 55 for additional details.

Table 55 ***Summary of solicited local reactions from day 0 through day 7 (Pooled safety data from HIPRA-HH-2, HIPRA-HH-5 and HIPRA-HH-10*****)**

		PHH-1V (N=3192)	
Timepoint	Events	Events	Subjects (%)
Day 0	Total number of events	4267	2324 (72.81)
	Erythema/Redness	118	118 (3.70)
	Induration/Swelling	197	197 (6.17)
	Pain	2091	2090 (65.48)
	Tenderness	1861	1861 (58.30)
Day 1	Total number of events	3927	2173 (68.08)
	Erythema/Redness	155	155 (4.86)
	Induration/Swelling	218	218 (6.83)
	Pain	1850	1849 (57.93)
	Tenderness	1704	1704 (53.38)
Day 2	Total number of events	1883	1065 (33.36)
	Erythema/Redness	116	116 (3.63)
	Induration/Swelling	133	133 (4.17)
	Pain	792	792 (24.81)
	Tenderness	842	842 (26.38)
Day 3	Total number of events	761	434 (13.60)
	Erythema/Redness	73	73 (2.29)
	Induration/Swelling	74	74 (2.32)
	Pain	288	288 (9.02)
	Tenderness	326	326 (10.21)

Day 4	Total number of events	329	185 (5.80)
	Erythema/Redness	43	43 (1.35)
	Induration/Swelling	43	42 (1.32)
	Pain	113	113 (3.54)
	Tenderness	130	130 (4.07)
Day 5	Total number of events	164	93 (2.91)
	Erythema/Redness	27	27 (0.85)
	Induration/Swelling	18	18 (0.56)
	Pain	53	53 (1.66)
	Tenderness	66	66 (2.07)
Day 6	Total number of events	118	70 (2.19)
	Erythema/Redness	15	15 (0.47)
	Induration/Swelling	8	8 (0.25)
	Pain	44	44 (1.38)
	Tenderness	51	51 (1.60)
Day 7	Total number of events	103	59 (1.85)
	Erythema/Redness	13	13 (0.41)
	Induration/Swelling	7	7 (0.22)
	Pain	39	39 (1.22)
	Tenderness	44	44 (1.38)

If a subject experienced more than one event, the subject is counted once for each type of event.
N = the number of subjects in the population. (%) = Subjects/N*100.
Source: Listing 16.2.7.2

PROGRAM NAME: t-14-3-1-5-ae DATE OF RUN: 11AUG2022 TIME OF RUN: 5:44:02 DATE OF EXTRACTION: 18JUL2022

Solicited systemic events (day 0 through day 7)

On Day 0, the overall number of solicited systemic events was 1528 in 890 (27.88%) subjects in Studies HH-2, HH-5, and HH-10. The percentage of subjects with solicited systemic adverse events on Day 1 was 31.64%, 18.11 % on Day 2 and 5.51% on Day 7. The most frequently reported solicited systemic event from Day 0 through to Day 7 was fatigue. Overall, the percentage of subjects who reported fatigue was 17.26% on Day 0, 19.24% on Day 1, 10.43% on Day 2, 6.23% on Day 3, 4.73% on Day 4, 4.51% on Day 5, 3.67% on Day 6, and 2.76% on Day 7.

Table 56 Summary of solicited systemic reactions from day 0 through day 7 (Pooled safety data from HIPRA-HH-2, HIPRA-HH-5 and HIPRA-HH-10)

HIPRA: Pooled Safety (HIPRA-HH-2, HIPRA-HH-5 and HIPRA-HH-10)

Table 14.3.1.6

Summary of Solicited Systemic Events from Day 0 through Day 7
(Safety Population)

		PHH-1V (N=3192)	
Timepoint	Events	Events	Subjects (%)
Day 0	Total number of events	1528	890 (27.88)
	Chills	1	1 (0.03)
	Diarrhoea	77	77 (2.41)
	Fatigue	551	551 (17.26)
	Fever	13	13 (0.41)
	Headache	455	455 (14.25)
	Joint Pain	3	3 (0.09)
	Malaise	3	3 (0.09)
	Myalgia/Muscle Pain	357	357 (11.18)
	Nausea/Vomiting	68	66 (2.07)
Day 1	Total number of events	1799	1010 (31.64)
	Chills	4	4 (0.13)
	Diarrhoea	109	108 (3.38)
	Fatigue	614	614 (19.24)
	Fever	20	20 (0.63)
	Headache	543	543 (17.01)
	Joint Pain	2	2 (0.06)
	Malaise	4	4 (0.13)
	Myalgia/Muscle Pain	420	420 (13.16)
	Nausea/Vomiting	83	83 (2.60)
Day 2	Total number of events	983	578 (18.11)
	Chills	1	1 (0.03)
	Diarrhoea	74	74 (2.32)
	Fatigue	333	333 (10.43)
	Fever	13	13 (0.41)
	Headache	282	282 (8.83)
	Joint Pain	3	2 (0.06)
	Malaise	3	3 (0.09)
	Myalgia/Muscle Pain	224	224 (7.02)
	Nausea/Vomiting	50	49 (1.54)
Day 3	Total number of events	616	376 (11.78)
	Chills	1	1 (0.03)
	Diarrhoea	65	65 (2.04)
	Fatigue	199	199 (6.23)
	Fever	10	10 (0.31)
	Headache	185	185 (5.80)
	Joint Pain	1	1 (0.03)
	Malaise	2	2 (0.06)
	Myalgia/Muscle Pain	119	119 (3.73)
	Nausea/Vomiting	34	34 (1.07)
Day 4	Total number of events	499	286 (8.96)
	Chills	2	2 (0.06)
	Diarrhoea	54	54 (1.69)
	Fatigue	151	151 (4.73)
	Fever	13	13 (0.41)
	Headache	145	145 (4.54)
	Joint Pain	1	1 (0.03)
	Malaise	2	2 (0.06)
	Myalgia/Muscle Pain	99	99 (3.10)
	Nausea/Vomiting	32	30 (0.94)
Day 5	Total number of events	455	265 (8.30)
	Chills	1	1 (0.03)
	Diarrhoea	50	50 (1.57)
	Fatigue	144	144 (4.51)
	Fever	13	13 (0.41)
	Headache	136	136 (4.26)
	Joint Pain	2	2 (0.06)
	Malaise	2	2 (0.06)
	Myalgia/Muscle Pain	82	81 (2.54)
	Nausea/Vomiting	25	24 (0.75)

Day 6	Total number of events	385	226 (7.08)
	Chills	1	1 (0.03)
	Diarrhoea	48	48 (1.50)
	Fatigue	117	117 (3.67)
	Fever	10	10 (0.31)
	Headache	121	121 (3.79)
	Joint Pain	1	1 (0.03)
	Malaise	1	1 (0.03)
	Myalgia/Muscle Pain	67	67 (2.10)
	Nausea/Vomiting	19	19 (0.60)
Day 7	Total number of events	314	176 (5.51)
	Chills	1	1 (0.03)
	Diarrhoea	36	36 (1.13)
	Fatigue	89	89 (2.79)
	Fever	9	9 (0.28)
	Headache	99	99 (3.10)
	Joint Pain	1	1 (0.03)
	Malaise	1	1 (0.03)
	Myalgia/Muscle Pain	60	60 (1.88)
	Nausea/Vomiting	18	18 (0.56)

If a subject experienced more than one event, the subject is counted once for each type of event.
N = the number of subjects in the population. (%) = Subjects/N*100.
Source: Listing 16.2.7.2

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Unsolicited events (day 0 through day 28)

Overall, 1019 unsolicited local and systemic adverse events were reported in 711 (22.27%) subjects in Studies HH-2, HH-5, and HH-10. The most frequently reported unsolicited local and systemic adverse event was COVID-19 with 48 events in 48 (1.50%) subjects. Other frequently reported unsolicited local and systemic adverse events reported in ≥1% of subjects included lymphadenopathy (42 events in 42 [1.32%] subjects), headache (48 events in 41 [1.28%] subjects) and axillary pain (45 events in 41 [1.28%] subjects).

AESIs

The list of defined Adverse Events of Special Interest to be collected as per study protocol in studies HH-2, HH-5 and HH-10 is provided in Table 57

Table 57 List of AESI collected in studies HH-2, HH-5 and HH-10

Categories	Diagnoses (as MedDRA Preferred Terms)
Neuroinflammatory Disorders	Acute disseminated encephalomyelitis (including site specific variants: e.g., non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralyses/paresis (e.g., Bell's palsy), generalised convulsion, Guillain-Barre syndrome (including Miller Fisher syndrome and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, uveitis
COVID-19 cases happening ≥14 days post-booster	Confirmed COVID-19 case through RT-PCR or RAT.

Musculoskeletal and Connective Tissue Disorders	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome
Vasculidities	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotising vasculitis and anti-neutrophil cytoplasmic antibody [ANCA] positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis)
Gastrointestinal Disorders	Crohn's disease, celiac disease, ulcerative colitis, ulcerative proctitis Hepatic Disorders: Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, primary biliary cirrhosis
Renal Disorders	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis membranoproliferative glomerulonephritis, and mesangio proliferative glomerulonephritis
Cardiac Disorders	Autoimmune myocarditis/cardiomyopathy

Categories	Diagnoses (as MedDRA Preferred Terms)
Skin Disorders	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens- Johnson syndrome, Sweet's syndrome
Hematologic Disorders	Autoimmune haemolytic anaemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia
Metabolic Disorders	Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis*, diabetes mellitus type 1, Addison's disease
Other Disorders	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anaemia, sarcoidosis, hypersensitivity.

* For Hashimoto thyroiditis: new onset only

There were 341 AESIs in 340 (10.65%) subjects in Studies HH-2, HH-5, and HH-10. The most frequently reported AESI was COVID-19 and SARS-CoV-2 test positive: 227 cases in 7.11% and 95 cases in 2.98% of subjects. Only COVID-19 cases occurring ≥ 14 days post vaccination and throughout the duration of the study were considered as AESIs. There were no severe COVID-19 cases. Furthermore, two cases of urticaria were reported as well as one case of asymptomatic Covid-19, pericarditis and thrombocytopenia each. No AESI was reported for study HH-1 and one AESI (appendicitis) was reported for study HAN-01. Note that definitions of AESI might deviate from above mentioned pooled studies. However, no details are currently provided for study HAN-01.

MAAEs

Overall, there were 295 MAAEs in 226 (7.08%) subjects in Studies HH-2, HH-5, and HH-10. The most frequently reported MAAE was infections and infestations (123 events in 111 [3.48%] subjects). Other frequently reported MAAEs with reported frequencies ≥0,5% included Musculoskeletal and connective tissue disorders (30 events in 23 [0.72%] subjects) and Injury, poisoning and procedural complications (20 events in 20 [0.63%] subjects).

2.5.8.3. Serious adverse event/deaths/other significant events

Study HH-1:

No SAEs (including death) have been reported in this study.

Study HH-2:

A total of four subjects have reported SAEs in this study, from which 3 were in the PHH-1V group. No death has been reported in this study.

Details on the SAEs are provided as follows:

- A 60-69 year-old subject experienced myocardial infarction around 6 weeks after vaccination with PHH-1V. The subject had a history of arterial hypertension and dyslipidaemia, as well as pulmonary bullae, and gastric ulcer. The event resolved after treatment (stent implantation) and was rated without reasonable possibility of relatedness to the vaccine.

- One SAE of acute pyelonephritis (moderate intensity) was reported in a 20-29-year-old subject more than 2 months after vaccination with PHH-1V. The event resolved 10 days after start of the event. No reasonable possibility of relatedness to the vaccine was concluded.

- One SAE of transient ischemic attack was reported on the Comirnaty vaccine arm in a 70-79-year-old subject around 3 months after booster vaccination with PHH-1V. The event was considered mild in intensity and resolved 1 week after start of the event. No reasonable possibility of relatedness to the vaccine was concluded.

- A 50-59-year-old subject was involved in an accident (>5 months from vaccination with PHH-V1) resulting in multiple rib fractures and clavicular left fracture, a pulmonary contusion left upper lobe and simple left renal cyst rupture. The event was considered potentially life threatening but is reported as resolving/recovering. No reasonable possibility of relatedness to the vaccine was concluded.

Study HH-5:

A total of ten subjects reported SAEs (including one death) in study HH-5.

- A 20-29-year-old subject died 2 days after vaccination with PHH-1V due to a road traffic accident. The death was considered unrelated to the administration of PHH 1V.

- A 30-39-year-old subject experienced a grade 2 pericarditis 14 days after vaccination with PHH-1V. The event was of moderate intensity and was considered not resolved at the data cut off of the interim report. The event was considered as possible related to vaccination by the investigator assessment.

- A 20-29-year-old subject had a serious event of food allergy one week after receiving PHH-1V. The event was considered potentially life threatening, without reasonable possibility to be related to the vaccination and was resolved one day after start of the event.

- A 20-29-year-old female had an acute abdomen ovarian endometrioma with symptoms starting 5 days after vaccination with PHH-1V. The event was considered severe in intensity, without reasonable possibility to be related to the vaccine. The event was resolved around 2 months after start of the event.

- A 30-39-year-old subject had a vestibular syndrome 21 days after vaccination The event was considered severe in intensity, without reasonable possibility to be related to the vaccine and the event outcome was resolved around 3 months after start of the event.

- A 50-59-year-old subject had a right ankle ligament injury around 2 months after receiving PHH-1V. The event was reported as mild in intensity, without reasonable possibility to be related to the vaccine and was considered recovered/resolved 2 days after the event has started

- A 20-29-year-old subject had a recurrent shoulder dislocations 80 days after vaccination. The event was reported as mild in intensity, without reasonable possibility to be related to the vaccine and the outcome was recovered 8 days after start of the event.

- A 40-49-year-old subject had a dilated cardiomyopathy with severe ventricular dysfunction starting more than 3 months after vaccination. The event was reported as potentially life-threatening and without reasonable possibility to be related to the vaccine. The subject has been discharged from the hospital and the event is ongoing at the cut-off date of the latest report

- A 30-39-year-old subject had gonococcal urethritis starting 2 months after vaccination. The event was reported as mild in intensity, without reasonable possibility to be related to the vaccine and recovered/resolved 2 days after the event has started.

- A 30-39-year-old subject had an anaphylaxis approximately 3 months after vaccination. The event was reported as life-threatening and without reasonable possibility to be related to the vaccine and resolved the same day it started.

Study HH-10

No SAEs (including death) have been reported in this study.

HAN-01

Two subjects reported SAEs after exposure to PHH-1V, one subject with vestibular disorder and one subject with appendicitis. None of the cases was considered product related. No death was reported in the study.

2.5.8.4. Laboratory findings

No laboratory data following vaccination with PHH-1V was provided from study HIPRA HH-1. Only pre-randomization data was provided.

Regarding study HIPRA HH-2, the Applicant stated that no clinically significant findings in Haematology and Vital signs were observed. Three events were observed regarding Biochemistry parameters: 1 in the PHH-1V group (hypoglycaemia) and 2 in the Comirnaty group (transaminase increase).

In Study HIPRA HH-5, the Applicant states that no noteworthy changes or trends occurred in haematology or biochemistry laboratory evaluations. Furthermore, it is stated that no clinically significant vital sign measurement (with data cut-off date on 31st of March) was observed among the subjects during the period of the current study report

For study HIPRA HH-10 no listing of abnormal laboratory values was provided. The respective listing is expected with the final study report.

No pattern of concern was identified from currently reported data (data cut-off date of interim study report 28th of December 2021) for study HAN-01 regarding subjects with clinically significant changes in laboratory parameters.

2.5.8.5. Safety in special populations

No data in special populations including hepatic impairment, renal impairment, pregnant or lactating women or in immunocompromised individuals is currently available. Of note, classical hepatically and renally impaired participants are not expected to have different pharmacokinetic (PK) exposure to the product due to the type of active substance (protein antigen) and its expected PK profile (lack of systemic exposure or metabolism by cytochromes, for example). Use in immunocompromised patients is considered missing information in the RMP and will be addressed via additional pharmacovigilance activities.

Elderly population

Safety data for the elderly population 65 years of age and older were provided for studies HH-2 and HH-5. Detailed safety data from study HH-10 are still awaited with the final study report, but it is noted that the reported maximum age in the study group treated with PHH-1V was 65 years. During study HH-2 in total 56 subjects ≥65 years were followed (n=38 received PHH-1V and n=18 received Comirnaty) and during study HH-5 in total 22 subjects ≥65 years were followed (all received PHH-1V). The Applicant provided safety findings for elderly subjects in studies HH-2 and HH-5 Table 58.

Table 58 Summary of treatment emergent adverse events (TEAEs) – elderly population ≥65 years (safety population; study HIPRA-HH-2 and HIPRA-HH-5)

	HIPRA-HH-2						HIPRA-HH-5	
	PHH-1V (N=38)		Comirnaty (N=18)		Overall (N=56)		PHH-1V (N=22)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Total number of TEAEs	58	28 (73.7)	36	15 (83.3)	94	43 (76.8)	40	15 (68.18)
Total number of serious TEAEs	0	0	0	0	0	0		
Total number of subjects with TEAEs leading to death	0		0		0			
TEAE intensity [1]								
Mild (Grade 1)	54	25 (65.8)	36	15 (83.3)	90	40 (71.4)	32	10 (45.45)
Moderate (Grade 2)	4	3 (7.9)	0	0	4	3 (5.4)	7	4 (18.18)
Severe (Grade 3)	0	0	0	0	0	0	1	1 (4.55)
Grade 4	0	0	0	0	0	0	0	0
Relationship to study treatment [1]								
Not related	10	3 (7.9)	2	0	12	3 (5.4)	4	1 (4.55)
Unlikely related	1	0	1	0	2	0	1	0
Possibly related	4	3 (7.9)	0	0	4	3 (5.4)	0	0
Probably related	10	6 (15.8)	1	0	11	6 (10.7)	0	0
Related	33	16 (42.1)	32	15 (83.3)	65	31 (55.4)	35	14 (63.64)
Unrelated [2]	11	3 (7.9)	3	0	14	3 (5.4)	5	1 (4.55)
Related [3]	47	25 (65.8)	33	15 (83.3)	80	40 (71.4)	35	14 (63.64)

A Treatment emergent adverse events (TEAE) is defined as an adverse event that started on or after the date of administration of study treatment until 28 days thereafter.
[1] If a subject experienced more than one TEAE, the subject is counted once at the most severe or most related event.
[2] Unrelated adverse events are those classified as not related and unlikely related.
[3] Related adverse events are those classified as possibly, probably and related. If a TEAE has a missing relationship it is assumed to be related to the study treatment for analysis purposes.
4 AEs with relationship to study drug as 'Not Applicable' have not been counted for this interim analysis until the relationship to study drug is clarified on a query.
N = the number of subjects in the population. (%) = Subjects/N*100.

The most common SOC in both studies was General disorders and administration site conditions with 68 TEAEs in 39 subjects (69.6%) in HIPRA-HH-2 and 30 events in 13 (59.09%) subjects in HIPRA-HH-5 (principally pain at the injection site), which was followed by Nervous system disorders in both studies (5 events in 5 subjects (13.2%) and 3 events in 3 subjects (13.64%) in study HH-2 and HH-5 respectively). The AEs were mild or moderate. No severe TEAEs were reported.

Safety pooled data by age subgroups (below 65 years, 65-74 years, 75-84 years and above 84) was provided as shown in the Table 59.

Overall, 88.63%, 71,70% and 83.33% of the participants aged below 65 years of age, 65-74 and 75-84 reported TEAEs. No TEAE was reported in 1 subject aged older than 84.

2760 TEAEs were reported in 43 subjects (76.8%), corresponding to 58 TEAEs in 28 (73.7%) subjects in the PHH-1V group and 36 events in 15 subjects (83.3%) in the Comirnaty group. In HIPRA-HH-5 40 events were reported in 15 (68.18%) elderly subjects. Majority of the TEAEs were non serious and none of them lead to drop out from the study (Table 59).

TEAEs considered related to vaccination by age group are described in Table 59.

Table 59. Number and percentage of participants with TEAEs by age group (safety population; related and non-related TEAEs) in studies HIPRA-HH-2 and HIPRA-HH-5 (cut-off date 18th July 2022)

	Age <65 (N=3114)		Age 65-74 (N=53)		Age 75-84 (N=6)		Age >84 (N=1)	
	N	%	N	%	N	%	N	%
Total number of TEAEs (related and non-related)	2760	88.63	38	71.70	5	83.33	0	0
Total number of serious TEAEs (related and non-related)	6	0.19	0	0	0	0	0	0
Fatal (car accident)	1	0.03	0	0	0	0	0	0
Hospitalization/prolong existing hospitalization	3	0.10	0	0	0	0	0	0
Life-threatening	1	0.03	0	0	0	0	0	0
Disability/incapacity	0	0	0	0	0	0	0	0
Other (medically significant)	2	0.06	0	0	0	0	0	0
TEAEs leading to drop-out	0	0	0	0	0	0	0	0

Source: HIPRA-HH-2 and HIPRA-HH-5
A Treatment emergent adverse event (TEAE) is defined as an adverse event that started on or after the date of administration of study treatment until 28 days thereafter.
No drop-outs due to adverse event have been reported in the EoS page on the EDC.
[1] Preferred Terms at least 1% more frequent in elderly versus general population and 2 or more events. N = the number of subjects in the population. (%) = Subjects/N*100.

Table 60. ***Number and percentage of participants with related-TEAEs by age group (safety population) in studies HIPRA-HH-2 and HIPRA-HH-5 (cut-off date 18th July 2022)***

	Age <65 (N=3114)		Age 65-74 (N=53)		Age 75-84 (N=6)		Age >84 (N=1)	
	N	%	N	%	N	%	N	%
Total number of TEAEs	2725	87.51	34	64.15	5	83.33	0	0
Total number of serious TEAEs	1	0.03	0	0	0	0	0	0
Fatal	0	0	0	0	0	0	0	0
Hospitalization/prolong existing hospitalization	1	0.03	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0	0
Disability/incapacity	0	0	0	0	0	0	0	0
Other (medically significant)	1	0.03	0	0	0	0	0	0
TEAEs leading to drop-out	0	0	0	0	0	0	0	0

Source: HIPRA-HH-2 and HIPRA-HH-5
A related treatment emergent adverse event (TEAE) is defined as an adverse event that started on or after the date of administration of study treatment until 28 days thereafter and that it is considered related to the product under investigation.
No drop-outs due to adverse event have been reported in the EoS page on the EDC.
[1] Preferred Terms at least 1% more frequent in elderly versus general population and 2 or more events. N = the number of subjects in the population. (%) = Subjects/N*100.

2.5.8.6. Use in Pregnancy and Lactation

Pregnant or lactating women or women intending to become pregnant or planning to breastfeed during the study have been excluded from participation in clinical studies. No cases of inadvertent exposure to Bimervax during pregnancy or breastfeeding have been reported in the clinical studies up to the cut-off dates submitted in this MAA. Use in pregnancy and lactation is listed as missing information in the RMP and will be addressed via additional pharmacovigilance activities. Administration of Bimervax during pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

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

No interaction studies have been performed and the concomitant administration of PHH-1V with other vaccines has not been studied. Interaction with other vaccines will be followed as part of the RMP.

2.5.8.8. Discontinuation due to adverse events

In study HIPRA HH-2 (cut-off date 18th July 2022), there were a total of 4 subjects who prematurely discontinued from the study, 3 of them after PHH-1V and 1 subject after Comirnaty. Reasons for discontinuation are currently unknown and are expected be provided with the final study report.

In study HIPRA HH-5 (cut-off 31st March 2022), a total of 4 subjects prematurely discontinued participation in the study, all of them in the PHH-1V study group. Reasons for subject premature discontinuation included no attendance on Day 14 visit, refusal to continue in the study, traffic accident and withdrawal of consent.

Overall, no concerns arise from the reported discontinuations in studies HIPRA HH-2 and HIPRA HH-5. A full list of discontinuations is expected in the final clinical study report of all clinical studies.

2.5.8.9. Post marketing experience

There's no post-marketing data for this vaccine.

2.5.9. Discussion on clinical safety

Interim safety data are available from a two-dose primary vaccination (i.e., first and second vaccination with PHH-1V) in studies HH-1 and HAN-01 as well as from booster vaccination (i.e., third vaccination) in studies HH-2, HH-5 and HH-10. Upon request the Applicant clarified that beyond the first week after vaccination, adverse events were collected at the investigational site during subject visits on days 14 and 28 via anamnesis that covered the periods from days 0-14 and days 14-28. No diary documentation was required for participants beyond day 7, but participants have been encouraged and reminded to report any AE at the time of their occurrence at any point during the study. Any reported AE was registered in the eCRF.

The MAA at hand addresses a booster dose in previously immunised subjects and thus this assessment is focused on clinical studies that followed a respective patient population (i.e., from studies HH-2, HH-5 and HH-10). Currently available interim data for study HH-10 comprise n=25 subjects (n=17 for PHH-1V and n=8 for Comirnaty), which is not considered sufficient for robust conclusions. Thus, data from this study are pooled with data from studies HH-2 and HH-5 to allow for robust conclusions from >3000 subjects exposed to PHH-1V as booster vaccination. The main data relevant for the assessment of safety are considered to derive from studies HH-2 (n=513 subjects exposed to PHH-1V) and HH-5 (n=2646 subjects exposed to PHH-1V, mostly subjects that received Comirnaty/Comirnaty with n=1535 or Spikevax/Spikevax with n=561 as primary vaccination; numbers refer to data cut-off from 31st of March 2022). Therefore, the assessment of data will concentrate to a large proportion on data reported for these two studies. Upon request the Applicant provided pooled safety data for subjects that were boosted with PHH-1V in studies HH-2, HH-5 and HH-10. Treatment related AEs for pooled safety data (i.e., pooled safety data for the booster vaccination with PHH-1V from clinical studies HH-2, HH-5 and HH-10) are also reported in the SmPC.

Provided interim information are to be complemented in future clinical study report submissions. In study HH-5, 2646 subjects received one dose of PHH-1V (as per data cut-off from 31st of March 2022; data cut-off from 18th of July reports 2661 subjects exposed to PHH-1V in study HH-5). The number of subjects older than 65 years of age (n=38 for PHH-1V and n=18 for Comirnaty in study HH-2 and n=22 for study HH-5) and ≥16 to <18 years (n=36 in study HH-5) is limited but considered acceptable. Applicant provided the requested AE data from the studies HH-2 and HH-5 specific for the elderly population. No trends of AE frequencies in favour of the population below or above 65 years can be drawn from the provided data. This also means that the safety of PHH-1V might not be worse in the elderly subgroup than in the subgroup below 65 years. However, the number and percentage of patients between 65 and 74 yoa are low and those of patients below 75 and 84 yoa is very low. Thus, the above-mentioned findings must be handled with caution. It is further recognized that more female subjects were included in study HH-2 (i.e., approximately 37% male and 63% female) and slightly more male subjects were included in study HH-5 (52.5% male and 47.5% female). The imbalance in gender is comparable for both treatment groups in study HH-2. This minimal imbalance in gender is not considered to affect the interpretation of study results. In total 4 subjects prematurely discontinued from study HH-2 after study drug exposure (3 subjects after PHH-1V and 1 subject after Comirnaty, referred to the available interim study report with data cut-off on 18th of July). Reasons for discontinuation are currently unclear, but low numbers do not raise a concern. Still, reasons are expected to be provided with the final study report. The Applicant clarified that other participants discontinued before drug exposure mainly because no valid vaccination certificate could be provided for study participation. Four (0.15%) subjects prematurely discontinued participation in study HH-5 (all

subjects in this study were vaccinated with PHH-1V). Reasons for subject premature discontinuation included no attendance on Day 14, refusal to continue in the study, traffic accident, and withdrawal of consent (referred to the available interim study report for HH-5 with data cut-off on 31st of March). No concerns arise from reported discontinuations.

Study HH-5 was a single-arm study (all subjects received PHH-1V) and thus, no direct comparison within study HH-5 is given. To facilitate contextualisation of the data, frequencies are being compared to study HH-2. Individual study results as well as provided pooled safety data across clinical studies HH-2, HH-5 and HH-10 are discussed in the following. TEAEs are defined as adverse events that started on or after the date of study treatment administration until 28 days thereafter. Participants were observed for at least 28 days, allowing an assessment of the data. According to the most actual study report for study HH-2 (i.e. v.4.0) with safety data cut-off date on 17th of February 2022 (as clarified by the Applicant this date is distinct from the depicted data cut-off date 18th of July, which only refers to an update of immunogenicity data;), a total of 2642 TEAEs were reported in 696 (91.0%) subjects, including 1581 TEAEs in 458 (89.3%) subjects that received the PHH-1V vaccine and 1061 TEAEs in 238 (94.4%) subjects that received the Comirnaty vaccine. No pattern of concern is identified from reported numbers in TEAEs when comparing events reported for PHH-1V to events reported for Comirnaty in study HH-2. In fact, events for PHH-1V appear to be generally milder compared to events in association with Comirnaty as booster vaccine (i.e., milder, but less moderate and severe TEAEs for the PHH-1V treatment group compared to the Comirnaty treatment group). In total 7552 TEAEs are reported in 2337 subjects (of n=2661 exposed subjects) that received a booster vaccination with PHH-1V during study HH-5 as per data cut-off on 18th of July. The frequency in total number of TEAEs is comparable in HH-5 (87.82%) and HH-2 (89.3%) and is slightly lower compared to Comirnaty in study HH-2 (94.4%; values refer to data-cut on 18th of July 2022). For pooled safety data overall 9279 TEAEs in 2818 subjects and 8639 related TEAEs in 2778 subjects were reported from 3192 subjects that received PHH-1V as a booster vaccine during studies HH-2, HH-5 and HH-10 (i.e., 88.3% and 87% for TEAEs and related TEAEs, respectively). Of those, 7651 TEAEs were reported as mild in intensity in 1909 (59.81%) subjects, 1540 TEAEs were reported as moderate in intensity in 847 (26.54%) subjects, 87 TEAEs were reported as severe in intensity in 61 (1.91%) subjects, and 1 TEAE was reported as missing in 1 (0.03%) subject.

Considering the classification of AEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) in study HH-2, gastrointestinal disorders (13.3% vs. 8.3% for PHH-1V and Comirnaty, respectively) as well as respiratory, thoracic and mediastinal disorders (3.3% vs. 1.6% for PHH-1V and Comirnaty, respectively) are the only two categories of system organ class with higher incidences in the PHH-1V group compared to subjects treated with Comirnaty. Most pronounced appear differences in PT diarrhoea (7.2% vs. 2.4% for PHH-1V and Comirnaty, respectively), cough (1% vs. 0% for PHH-1V and Comirnaty, respectively) and oropharyngeal pain (1% vs. 0% for PHH-1V and Comirnaty, respectively). Besides these SOCs, also asthenia (1.8% vs. 1.2% for PHH-1V and Comirnaty, respectively), upper respiratory tract infection (1% vs. 0.4% for PHH-1V and Comirnaty, respectively), nausea (5.8% vs. 5.2% for PHH-1V and Comirnaty, respectively) and vomiting (1.9% vs. 1.2% for PHH-1V and Comirnaty, respectively) are reported PTs with slightly higher incidences for booster with PHH-1V. Most outstanding differences in PT as reported in study HH-5 and compared to study HH-2 are evident for malaise (20.26% of subjects in study HH-5, but none reported in study HH-2 for PHH-1V or Comirnaty), injection site swelling (9.56% in study HH-5, 0.6% for PHH-1V in HH-2 and 2.8% for Comirnaty in HH-2), injection site induration (1.21% in HH-5, 8.6% for PHH-1V in HH-2 and 17.1% for Comirnaty in HH-2), nausea (none in HH-5, 5.8% for PHH-1V in HH-2 and 5.2% for Comirnaty in HH-2), vomiting (5.93% in HH-5, 1.9% for PHH-1V in HH-2 and 1.2% for Comirnaty in HH-2) and myalgia (1.81% in HH-5, 19.5% for PHH-1V in HH-2 and 34.1% for Comirnaty in HH-2; reported data refer to frequencies as reported in the currently provided interim study reports with data cut-off 18th of July for study HH-2 and 31st of March for study HH-5).

For the first two days of the 7-day observation period for solicited systemic events after booster vaccination in study HH-2 the total number of events is higher for the group vaccinated with Comirnaty. Only diarrhoea was reported with higher incidences for the PHH-1V treatment group throughout the observation period of 7 days. However, starting with day 3 post-vaccination the total number of events is higher for the group treated with PHH-1V and remains higher until day 7. Still, principally less subjects are affected by solicited systemic AEs after booster vaccination with PHH-1V compared to those vaccinated with Comirnaty (with diarrhoea as an exception with mildly higher incidences after PHH-1V). Upon request the Applicant confirmed that the mean duration of headache and fever was 0.2 days longer for both events in subjects after vaccination with PHH-1V compared to the mean duration after vaccination with Comirnaty. Importantly, the general proportion of subjects reporting headache or fever was higher after vaccination with Comirnaty compared to vaccination with PHH-1V. Generally, a lower rate of subjects was affected by solicited systemic AEs after booster vaccination with PHH-1V compared to those vaccinated with Comirnaty. The only exception appears to be diarrhoea with slightly higher incidences after PHH-1V. Potentially longer duration of events after PHH-1V compared to Comirnaty (e.g., 0.2 days for headache and fever) does not indicate a major safety concern. Similar conclusions regarding solicited local and solicited systemic event apply when considering primary vaccination (with a focus on Comirnaty/Comirnaty and Spikevax/Spikevax, due to low subject numbers for other subgroups) and time since last primary Covid-19 vaccination as assessed during study HH-5. Still, it appears that more subjects that followed the primary Spikevax/Spikevax vaccination tended to report solicited local and systemic events, but numbers do not give rise to concern. No major discrepancies were identified for subjects with >3 to ≤6 month or >6 to ≤12 months elapsed time since the last primary vaccination (data for ≤3 months and >12 months are limited).

The proportion of subjects taking pain medication and/or antipyretics during study HH-2 as well as the amount of such medication was proportionally higher for the Comirnaty group (44% and 25.14% of subjects after booster with Comirnaty and PHH-1V, respectively). A very comparable pattern in the use of concomitant medication is seen from provided information for study HH-5. No concerns arise from reported concomitant medication from studies HH-2 and HH-5.

Throughout the 7-day observation period for solicited local reactions after booster vaccination, no event (i.e., erythema/redness, induration/swelling, pain and tenderness) was reported with higher incidences for subjects treated with PHH-1V compared to subjects treated with Comirnaty during study HH-2. Similar as observed for solicited systemic events, also for solicited local reactions it appears that local reactions were more frequently reported in study HH-5 during the first days compared to study HH-2 (most striking in pain and tenderness). However, this difference is not present in following days of observation. Importantly, the general reporting of solicited local reactions is lower for PHH-1V in study HH-5 than for Comirnaty in HH-2 and does not indicate any major safety concern.

Data as reported in study HH-2 regarding unsolicited systemic and local adverse events indicate lower incidences for PHH-1V compared to Comirnaty and do not give reason of concern. However, a substantially lower frequency is reported in study HH-5 (18.59% and 28.8% for PHH-1V in study HH-5 and study HH-2, respectively). Upon request the Applicant clarified that the main cause for the overall higher frequency of unsolicited adverse events in study HH-2 is the higher rate of Covid-19 infections that occurred during the study time compared to study HH-5. Fluctuation in infection waves across the population of study HH-2 and HH5 can be agreed as reason for the discrepancy between both studies. It is noted that Covid-19 infection beyond 14 days after vaccination were considered an AESI and not as an unsolicited systemic event. Similar conclusions regarding unsolicited local and unsolicited systemic events apply when considering primary vaccination subgroups (with a focus on Comirnaty/Comirnaty and Spikevax/Spikevax, due to low subject numbers for other subgroups) and time since last primary Covid-19 vaccination as assessed during study HH-5.

With respect to pooled safety data Medically Attended Adverse Events were mostly reported for SOC Infections and infestations (in 3.48% of subjects across the three pooled studies). No other SOC was reported in more than 1% of subjects (next most frequent SOC was Musculoskeletal and connective tissue disorders in 0.72% of subjects) and the most frequently reported PTs were Covid-19 (0.53% of subjects), nasopharyngitis (in 0.38% of subjects) and urinary tract infection (in 0.31% of subjects). No concerns arise from reported MAAEs. Adverse events of special interest were reported in 10.65% of subjects across the three pooled studies and were mostly related to Covid-19 infections (7.11% with reported Covid-19, 2.09% with SARS-CoV-2 test positive and 0.03% with asymptomatic Covid-19). It is noted that Covid-19 infections happening before day 14 were considered as adverse events only and not as AESI. Covid-19 infections are also discussed further in the section regarding clinical efficacy. Urticaria was reported in 2 subjects and single events of pericarditis and thrombocytopenia were also reported. No concerns arise from reported AESIs (pooled safety data refer to data cut-off on 18th of July 2022).

No death was reported during study HH-2 and 1 death in study HH-5 was considered unrelated to the administration of PHH 1V (traffic accident). No concerns arise from reported fatal events. Serious adverse events were generally rare in clinical studies HH-2 (n=3 subjects that received PHH-1V reported with narrative from >500 subjects exposed to PHH-1V) and HH-5 (n=9 subjects with narratives and one subject reported dead during study from >2600 exposed subjects). Currently, occurred SAEs are too limited to robustly conclude on study vaccine related cases. However, since the casual relationship between the vaccination with Bimervax and pericarditis cannot be excluded, the Applicant agreed to include pericarditis in section 4.8. of the SmPC. Post-authorisation safety measures for close monitoring of the occurrence of pericarditis/myocarditis as proposed by the Applicant (defining them as AESIs, further characterization in the PASS and inclusion as important identified/potential risks in the safety concerns of the RMP) are agreed and endorsed.

No concerns arise from reported laboratory findings. Measurements that were detected as AEs (in total 38 events during study HH-5 from >2600 subjects that exposed to PHH-1V) do not give rise to conclude any pattern that might indicate a major risk upon booster vaccination with PHH-1V (3 grade 3 events, all of which considered unrelated and of distinct character, and no grade 4 event). Similarly, the lack of clinically significant findings regarding vital sign measures also supports this impression (as per data cut-off on 31st of March 2022).

A major objection had been raised during the procedure regarding high level of residual host cell proteins, which was also considered concerning from a safety perspective with respect to CHO HCP specific antibodies. For addressing the MO from a clinical perspective, the Applicant randomly selected study participants from trials HH-5 and HH-2 to test serum samples for immunogenicity against CHO HCP, i.e., IgG antibody detection with the ELISA VM-859-00 in serum samples. Provided data do not indicate any significant rise in IgG antibody titres against CHO HCP in serum samples of subjects vaccinated with PHH-1V during studies HH-2 and HH-5 (i.e., single booster vaccination). Importantly, the reliability of measures provided by the used VM-859-00 assay are questioned due to uncertainties regarding crucial aspects of the provided assay validation. Furthermore, it is also noted that it appears more appropriate to evaluate the presence and levels of IgG antibodies after repeated exposure to the vaccine (e.g., studies HAN-01 and/or the extension period of study HH-2 would appear more suitable for this approach). In summary, from a clinical perspective submitted data were not considered adequate to address the raised concern regarding potential immunogenicity of HCPs. This is mainly based on the issues raised regarding the assay used for determination of immune response against HCP. Based on theoretical considerations, an immune response against HCP would not be unexpected. The applicant was therefore asked to provide a risk assessment to estimate in how far a potential immune response against HCP contained in PHH-1V is of clinical relevance. For this risk assessment, the results of the characterisation of HCP content as requested in the quality section, should be

considered. The Applicant committed to perform the requested in-depth characterization of the qualitative HCP profile including a full risk evaluation of identified HCPs and to submit results within 2 months post-approval (REC7).

2.5.10. Conclusions on the clinical safety

Based on the currently available data PHH-1V appears to be less reactogenic compared to Comirnaty. Gastrointestinal disorders (especially diarrhoea) seem to occur more frequently in the PHH1V group. Headache and fever occur with longer duration in the PHH-1V group (i.e. 0.2 days longer compared to Comirnaty). Data from study HH-5 on a higher number of subjects generally confirm results from study HH-2. Pooled safety data are reported from studies HH-10, HH-2 and HH-5.

It is noted that the vaccine contains a high level of residual host cell proteins (HCP). Based on theoretical considerations, an immune response against HCP would not be unexpected. The applicant was therefore asked to provide a risk assessment to estimate in how far a potential immune response against HCP contained in PHH-1V is of clinical relevance. For this risk assessment, the results of the characterisation of HCP content as requested in the quality section, should be considered. The Applicant committed to submit results of an in-depth characterization of the qualitative HCP profile including a full risk evaluation of identified HCPs within 2 months post-approval.

2.6. Risk Management Plan

The applicant has submitted an RMP version 1.0 including the following summary of safety concerns:

2.6.1. Safety concerns

Summary of safety concerns	
Important identified risks	Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
	Myocarditis
Missing information	Use in pregnancy and while breastfeeding
	Use in immunocompromised patients
	Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety

2.6.2. Pharmacovigilance plan

The applicant intends to address the identified safety concerns through continuation of safety surveillance from the six ongoing interventional clinical trials and two planned category 3 non-interventional post authorisation safety studies. The applicant has proposed also one non-interventional effectiveness study. The studies are summarised in Table 61. The proposed additional pharmacovigilance activities are appropriate for further characterisation the safety profile of the product.

Table 61 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation.				
Not applicable.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances.				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
HIPRA-HH-1 *On-going*	Evaluate safety and immunogenicity of recombinant protein RBD fusion heterodimer candidate vaccine against SARS-CoV-2 in adult healthy volunteers	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis/Pericarditis Long-term safety	Protocol submission	20 June 2021
			Final CSR	31 March 2023
HIPRA-HH-2 *On-going*	Assess immunogenicity and safety of a booster vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults fully vaccinated against COVID-19 with the Comirnaty vaccine	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis/Pericarditis Long-term safety	Protocol submission	28 October 2021
			Final CSR	31 December 2023
HIPRA-HH-5 *On-going*	Assess the safety and tolerability of PHH-1V as a booster dose in healthy adult subjects vaccinated against COVID-19 with the Comirnaty, Spikevax, Vaxzevria or Janssen vaccine. The secondary objectives include immunogenicity evaluation.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis/Pericarditis Long-term safety	Protocol submission	24 January 2022
			Final CSR	31 August 2023
HIPRA-HH-10 *On-going*	Determine and compare the changes of the immunogenicity measured by pseudovirus neutralisation against Omicron strain at Baseline and Day 14, in subjects who have received two doses of Vaxzevria vaccine	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	Protocol submission	04 March 2022

	and PHH-1V as a booster, versus subjects who have received two doses of Vaxzevria and Comirnaty as a booster, at least 91 days and with a maximum of 240 days before day 0. Assess the safety and tolerability of PHH-1V as a booster dose in healthy adult subjects fully vaccinated against COVID-19 with the Vaxzevria vaccine.	Myocarditis/Pericarditis Long-term safety	Final CSR	30 June 2023

HAN-01 *On-going*	Evaluate safety and immunogenicity of recombinant protein RBD fusion heterodimer candidate vaccine against SARS-CoV-2 in adult healthy volunteers	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis/Pericarditis Long-term safety	Protocol submission	30 October 2021
			Final CSR	30 April 2023
HIPRA-HH-4 *On-going*	To determine and compare the changes of the immunogenicity measured by pseudovirus (or live virus for the HIV cohort*) neutralization against Omicron, Beta and Delta any other relevant Variants of Concern (VOC) in the epidemiologic moment, at Baseline and at Day 14 after administration of HIPRA's vaccine (PHH-1V). To determine and compare the changes of the immunogenicity measured by pseudovirus (or live virus for the HIV cohort) neutralization against Omicron, Beta and Delta and any other relevant Variants of Concern (VOC) in the epidemiologic moment at Days, 91, 182 and 365, after administration of HIPRA's vaccine (PHH-1V). To evaluate the immunogenicity measured by means of total antibody against Receptor Binding Domain of the Spike protein of SARS-CoV-2 quantification, measured by an electrochemiluminescence immunoassay (ECLIA) at Baseline and at Days 14, 91,	Use in immunocompromised patients Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis/Pericarditis Long-term safety	Protocol submission	24 March 2022
			Final CSR	31 January 2024

	182 and 365 after administration of HIPRA's vaccine (PHH-1V). To assess the safety and tolerability of PHH-1V as an additional dose in adult individuals with pre-existing immunosuppressive conditions			

Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU *Planned*	Vaccine utilisation study: To characterise recipients of the BIMERVAX in relation to demographics and clinical characteristics at the time of vaccination, including the following: pregnancy status, age of childbearing potential, immunocompromised status, comorbidities, presence of autoimmune and inflammatory disorders, and interactions with other vaccines (influenza). Comparative safety study: 1. Cohort design: To estimate the effect of BIMERVAX on adverse events of special interest (AESIs)—as described in a protocol for the vACCine covid-19 monitoring readinESS (ACCESS) compared with that of other COVID-19 vaccines authorised for the booster indication. 2. SCRI design: To estimate the effect of the BIMERVAX booster on selected AESIs (those that can be studied under a self-controlled design as specified in ACCESS) compared with no COVID-19 vaccine as a booster.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Myocarditis/Pericarditis Long-term safety	Protocol submission	31 July 2023
			Final study report	*31 July 2026
Post-authorisation safety study of the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) *Planned*	To evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with a COVID-19 vaccine.	Use in pregnancy and in breast feeding	Protocol submission	31 July 2023
			Final study report	31 July 2029

*36 months after rollout of BIMERVAX booster vaccination campaigns in the first participating country

Study Status	Summary of objectives	Effectiveness uncertainties addressed	Milestones	Due dates
Post-authorisation effectiveness study of BIMERVAX emulsion for injection in Europe in VAC4EU *Planned*	To estimate the effect of the BIMERVAX on COVID-19–related outcomes—i.e., COVID-19 infection, COVID-19–related hospitalisations or emergency department visits—compared with other COVID-19 vaccines authorised for the booster indication.	COVID-19 vaccine effectiveness in real-world setting	Protocol submission	31 August 2023
			Final study report	*31 August 2025/ 31 August 2026

* 24-36 months after rollout of BIMERVAX vaccine booster vaccination campaigns in the first participating country. Pending timelines and potential seasonality of booster campaigns. Once actual timelines are known, a second interim report may be needed

2.6.3. Risk minimisation measures

Routine risk minimisation activities only are proposed to manage the safety concerns of the medicinal product.

Table 62 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Pericarditis	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-1; protocol submission on 20 June 2021; final CSR estimated date 31 March 2023. • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 31 December 2023. • HIPRA-HH-5; protocol submission on 24 January 2022; final CSR estimated date 31 August 2023. • HIPRA-HH-10; protocol submission on 04 March 2022; final CSR estimated date 30 June 2023. • HAN-01; protocol submission on 30 October 2021; final CSR estimated date 30 April 2023. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 31 January 2024 **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Important potential risks		
Myocarditis	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-1; protocol submission on 20 June 2021; final CSR estimated date 31 March 2023.

Important potential risks		
		• HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 31 December 2023. • HIPRA-HH-5; protocol submission on 24 January 2022; final CSR estimated date 31 August 2023. • HIPRA-HH-10; protocol submission on 04 March 2022; final CSR estimated date 30 June 2023. • HAN-01; protocol submission on 30 October 2021; final CSR estimated date 30 April 2023. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 31 January 2024 **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-1; protocol submission on 20 June 2021; final CSR estimated date 31 March 2023. • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 31 December 2023. • HIPRA-HH-5; protocol submission on 24 January 2022; final CSR estimated date 31 August 2023. • HIPRA-HH-10; protocol submission on 04 March 2022; final CSR estimated date 30 June 2023. • HAN-01; protocol submission on 30 October 2021; final CSR estimated date 30 April 2023. • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 31 January 2024 **Post-authorisation safety study**

Important potential risks		
		Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Missing information		
Use in pregnancy and while breastfeeding	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026. Post-authorisation safety study of the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER); protocol submission on 31 July 2023; final study report 31 July 2029.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in immunocompromised patients	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 31 January 2024. **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	submission on 31 July 2023; final study report 31 July 2026.
Use in patients with autoimmune or inflammatory disorders	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Interaction with other vaccines	Routine risk communication: SmPC section 4.5 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.
Long-term safety	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection *None* Additional pharmacovigilance activities: **Ongoing clinical trials** • HIPRA-HH-1; protocol submission on 20 June 2021; final CSR estimated date 31 March 2023. • HIPRA-HH-2; protocol submission on 28 October 2021; final CSR estimated date 31 December 2023. • HIPRA-HH-5; protocol submission on 24 January 2022; final CSR estimated date 31 August 2023. • HIPRA-HH-10; protocol submission on 04 March 2022; final CSR estimated date 30 June 2023. • HAN-01; protocol submission on 30 October 2021; final CSR estimated date 30 April 2023.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		• HIPRA-HH-4; protocol submission on 24 March 2022; final CSR estimated date 31 January 2024 **Post-authorisation safety study** • Post-authorisation safety study of BIMERVAX emulsion for injection in Europe in VAC4EU; protocol submission on 31 July 2023; final study report 31 July 2026.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the labelling flexibilities described in the Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/689080/2020 rev.3) document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities.

EU packaging specific derogations

Outer and immediate packaging in EN only

Outer and immediate labelling will be provided in English only for all EU Member States (MSs), as well as Norway and Iceland. The labelling flexibility is granted until end of September 2023.

English only printed package leaflet

If required, EN printed package leaflet (PL) will be supplied to EU MSs, including Norway and Iceland. Except for those countries that require it in their national language as per labelling Q&A. The applicant plans to provide electronic and downloadable national translations of the Package Leaflet for other Member States/languages via a QR code. The labelling flexibility is granted until end of September 2023.

Omission of the Blue Box information on the outer carton

Due to the use of one unified EN packing across all the EU countries, the Blue Box will not be displayed on the outer carton. The labelling flexibility is granted until end of September 2023. The information,

normally provided in the market specific packaging Blue Box area of the carton, will be provided as an electronic version on the website (via the QR code/URL)

2.8.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals 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:

Statutory information

• Approved regulatory information, including the Package Leaflet (PL) and Summary of Product Characteristics (SmPC);

• Vaccination card;

• Blue Box information as required by each Member State.

2.8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004,) COVID-19 Vaccine (recombinant, adjuvanted) 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 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.

Additionally, there are 7 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), Vaxzevria

(EMEA/H/C/005675), Jcovden (EMEA/H/C/005737), Nuvaxovid (EMEA/H/C/005808), COVID-19 Vaccine (inactivated, adjuvanted) Valneva (EMEA/H/C/006019) and VidPrevtyn Beta (EMEA/H/C/005754). The mRNA vaccines include in their marketing authorisation adapted Omicron vaccines.

3.1.3. Main clinical studies

The clinical programme to develop PHH-1V consists of several trials from which interim reports of five studies have been submitted to support the use of this vaccine as a booster:

Study HH-1, Study HH-2, Study HH-5, Study HAN-01 and Study HH-10. Study HH-2, Study HH-5, and Study HH-10 are currently still ongoing, Study HH-1 reached the 1-year follow-up in August 2022, HAN-01 is completed.

Study HH-2 is currently considered as the pivotal study for this application. It is a double-blind, randomized (2:1), active controlled (comparator Comirnaty 30 µg), multi-centre (10 sites in Spain), non-inferiority trial to evaluate immunogenicity and safety of a single PHH-1V dose (40 µg) as a booster vaccination (3rd dose) in adults (18 yoa or older, at least 10% >65 years) who previously received primary vaccination with Comirnaty. 252 individuals 18 yoa or older received one dose of Comirnaty, 513 individuals 18 yoa or older old received one dose of Bimervax.

All other studies are considered supportive:

- Study HH-5 is a phase III open label study to assess a booster vaccination in approx. 3000 subjects with different vaccination/Covid-19 infection history. The study is mainly focussed on safety but also includes an immunogenicity assessment in currently 230 subjects (approx. 250 planned)
- Study HH-1 is a Phase 1/2a, FIH dose-finding study for a two-dose primary immunization in 30 healthy adults aged 18-39. Study HH-1 is not considered suitable to support a claim for a booster dose since a primary immunization schedule was evaluated and in addition, the number of subjects enrolled is limited.
- Study HAN-01 is a completed phase IIb study, for a two-dose primary immunization in adult healthy volunteers in Vietnam. Like study HH-1, this study is not considered suitable to support a claim for a booster dose since a primary immunization schedule was evaluated.
- Study HH-10 is a Phase IIb study to assess immunogenicity and safety of a booster vaccination with PHH-1V in adults fully vaccinated with adenovirus vaccine. Currently the data is too limited (25 subjects vaccinated) to support any such claim.

3.2. Favourable effects

Primary endpoint

For the D614G strain, the GMT ratio on Days 14 and 28 was 1.71 and 1.33 respectively, which does not meet the non-inferiority criteria. On Day 98, the GMT ratio was 0.88 which meets the non-inferiority criteria and the GMT ratio on Day 182 was 0.62 which meets the superiority criteria.

Secondary endpoints

For the Beta variant, the GMT ratios on Day 14 of 0.62, on Day 28 of 0.65, on Day 98 of 0.58 and on Day 182 of 0.70 all meet the superiority criteria.

For the Delta variant the GMT ratios on Day 14 of 1.02, and on Day 28 of 0.89 meet the non-inferiority criteria. The GMT ratios on Day 98 of 0.52 and on Day 182 of 0.55 meet the superiority criteria.

For Omicron BA.1, the GMT ratios on Day 14 of 0.60, on Day 28 of 0.66, on Day 98 of 0.60 and on Day 182 of 0.76 meet superiority criteria.

Furthermore, at Day 182 the analysis was performed with the mITT3 (excluding the population with confirmed COVID-19 infections). For the D614G strain the GMT ratio was 0.54. For Beta, the GMT ratio was 0.54. For Delta the GMT ratio was 0.43 and for Omicron BA.1 the GMT ratio was 0.56. Consequently, all tested strains meet 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 D614G strain, the GMFR ratios on Days 14 and 28 were 1.83 and 1.43 and did not meet the non-inferiority criteria. On Day 98, the GMFR ratio was 0.90 which meets the non-inferiority criteria and the GMFR ratio on Day 182 was 0.66 which meets the superiority criteria.

For the Beta variant, the GMFR ratio on Day 14 of 0.70, on Day 28 of 0.74, on Day 98 of 0.65 and on Day 182 of 0.78 all meet the superiority criteria.

For the Delta variant the GMFR ratio on Day 14 of 1.12, and on Day 28 of 0.98 meet the non-inferiority criteria. The GMFR ratio on Day 98 of 0.59 and on Day 182 of 0.60 meet the superiority criteria.

For Omicron BA.1, the GMFR ratio on Day 14 of 0.69, on Day 28 of 0.76 meet superiority criteria. The GMFR ratio on Day 98 of 0.71 and on Day 182 of 0.87 meet non-inferiority criteria

The heterologous boost with Bimervax, after a primary immunization with Comirnaty, elicited a Th1-CD4+ T cell response, more potent than the response induced by the homologous boost with Comirnaty, and a CD8+ T cell response specific against RBD.

Exploratory endpoints

A total of 31.2% and 32.4% of non-severe Covid-cases were reported in the Bimervax and Comirnaty arms, respectively. There were no cases of severe COVID-19 infection and there were no immune-mediated adverse events in the study.

Elderly subjects

At D14 the immune response for each tested variant are lower compared to the overall mITT-2 analyses. For D614G strain, Beta and Delta, the nAb GMTs were lower compared to the Comirnaty arm. For Omicron, nAb GMTs in both arms are similar. Responder analysis indicates largely similar percentages (except for D614G strain) of subjects achieving an at least 4-fold rise in neutralizing antibodies indicative for a sufficient protection.

The Day 182 results showed higher nAb GMTs with PHH-1V compared to Comirnaty for all tested strains.

3.3. Uncertainties and limitations about favourable effects

No correlate of protection against COVID-19 exists. The immunobridging approach of PHH-1V to Comirnaty with known efficacy is therefore essential for the interpretation of a potential protective effect of PHH-1V.

In the pivotal HH2 study, PHH-1V failed to demonstrate non-inferiority against the active comparator Comirnaty in the primary efficacy endpoint (neutralizing antibody responses against the D614G strain at Day 14, PBNA). Thus, the multiple type I error rate was not controlled for conclusions on immunogenicity differences for VOCs.

The modified ITT population (mITT) was defined as all subjects who received a dose of study drug minus subjects that tested positive for COVID-19 within 14 days of receiving study drug. The exclusion

of subjects with a positive test was however not prespecified and does not correspond to the initially defined estimand (vaccinated subjects regardless of infection). In addition, as the study was performed during the omicron wave with very high incidences also of asymptomatic cases, it cannot be assumed that all infections have been identified, since no consistent screening strategy for infections during the study has been implemented and an overall influence on study results cannot be ruled out.

Assays: The PBNAs (and the VNA) do not provide absolute determinations of the nAB content in patient's sera, as none of the PBNAs (and the VNA) has been calibrated to adequate reference standards (e.g., sera with known nAB level). Consequently, throughout the clinical studies, only relative nAB titres were and can be measured with the established PBNAs and the alpha-variant VNA. This means the efficacy evaluation of PHH-1V solely needs to rely on a relative comparison between nAB levels between different treatment arms. The obtained results can therefore not be directly compared to other data sources.

To date, there are no reliable data on the immunogenicity for the Omicron BA.4 and BA.5 sublineages. Albeit the Applicant developed a PBNA assay for BA.4/5 by using the same method as for the previous variants, the HEK-293 cell line used for the previous variants had to be replaced for the Vero E6 cell line without implementation of a validated/qualified bridging assay.

The dose finding Study HH-1 was not specifically designed for booster vaccination but only for primary vaccination and no clear dose-dependent effect on immunogenicity can be concluded. Therefore, there remains some uncertainty whether the chosen dose is indeed the most optimal dose for booster vaccination.

Only limited data is available for paediatric subjects: 36 subjects 16-17 yoa received primary immunisation with Comirnaty followed by one PHH-1V dose in study HH-5 of which only 11 are included in the immunogenicity subset

Vaccinations with Bimervax have been applied 182 days after the second dose of the primary series. Only very limited immunogenicity data is available for shorter time frames.

Of overall 751 subjects (mITT/PP baseline numbers), 56 included subjects were ≥65 yoa. This is below the targeted 10% of the overall population. The number and percentage of patients between 65 and 74 yoa are low and those of patients between 75 and 84 yoa is very low.

3.4. Unfavourable effects

The main data relevant for the assessment of safety are derived from studies HH-2 (n=513 subjects exposed to PHH-1V) and HH-5 (n=2646 subjects exposed to PHH-1V). Despite limited in sample size, also data from study HH-10 were considered relevant for the total safety pool.

Provided pooled safety data from studies HH-2, HH-5 and HH-10 (all with data extraction on 18th of July 2022 and analysis run on 11th of August 2022) concluded a total of 9279 TEAEs reported in 2818 subjects (8639 related TEAEs in 2778 subjects). Events for PHH-1V appear to be generally milder compared to events in association with Comirnaty as booster vaccine. The frequency of TEAEs following PHH-1V is comparable across studies in HH-5 (87.82%) and HH-2 (89.3%) and is slightly lower compared to Comirnaty in study HH-2 (94.4%).

By SOC and PT, in study HH-2, gastrointestinal disorders (13.3% vs. 8.3% for PHH-1V and Comirnaty, respectively) as well as respiratory, thoracic and mediastinal disorders (3.3% vs. 1.6% for PHH-1V and Comirnaty, respectively) are the two categories of system organ class with higher incidences in the PHH-1V group compared to subjects treated with Comirnaty. Most pronounced differences were found in PTs diarrhoea (7.2% vs. 2.4% for PHH-1V and Comirnaty, respectively), cough (1% vs. 0% for PHH-

1V and Comirnaty, respectively) and oropharyngeal pain (1% vs. 0% for PHH-1V and Comirnaty, respectively).

In study HH-2 the total number of as well as the overall rate of subjects with solicited systemic events after booster vaccination is higher for the group vaccinated with Comirnaty for the first two days of the 7-day observation period. However, starting with day 3 post-vaccination the total number of events is higher for the group treated with PHH-1V and remains higher until day 7. The mean duration of headache and fever was 0.2 days longer for both events in subjects after vaccination with PHH-1V compared to the mean duration after vaccination with Comirnaty. Importantly, the general proportion of subjects reporting headache or fever was higher after vaccination with Comirnaty compared to vaccination with PHH-1V. Only diarrhoea was reported with higher incidences for the PHH-1V group throughout the observation period of 7 days. Still, less subjects reported solicited systemic AEs after booster vaccination with PHH-1V compared to those vaccinated with Comirnaty (except for diarrhoea) in Study HH-2.

The proportion of subjects taking pain medication and/or antipyretics as well as the amount of such medication was proportionally higher for the Comirnaty group (44% and 25.14% of subjects after booster with Comirnaty and PHH-1V, respectively). These data do indicate a potentially better tolerability for the booster vaccination with PHH-1V.

Throughout the 7-day observation period for solicited local reactions after booster vaccination, no event (i.e., erythema/redness, induration/swelling, pain and tenderness) was reported with higher incidences for subjects vaccinated with PHH-1V compared to subjects vaccinated with Comirnaty during study HH-2.

Data as reported in study HH-2 regarding unsolicited systemic and local adverse events indicate lower incidences for PHH-1V compared to Comirnaty and do not give reason of concern.

With respect to pooled safety data, Medically Attended Adverse Events were mostly reported for SOC Infections and infestations (3.48% of subjects across the pooled studies HH-2, HH-5 and HH-10). No other SOC was reported in more than 1% of subjects.

Adverse events of special interest were reported in 10.65% of subjects across the pooled studies HH-2, HH-5 and HH-10 and were mostly related to Covid-19 infections. One SAE of pericarditis was reported with relation to the study vaccine, and it is listed as an adverse reaction.

3.5. Uncertainties and limitations about unfavourable effects

More female subjects were included in study HH-2 (i.e., approximately 37% male and 63% female), but slightly more male subjects were included in study HH-5 (52.5% male and 47.5% female). Reasons for the imbalance are not entirely evident, but the imbalance in gender in study HH-2 was comparable for both study groups and is not considered to affect the interpretation of study results.

The number of subjects older than 65 years of age (n=38 for PHH-1V and n=18 for Comirnaty in study HH-2 and n=22 for study HH-5) and ≥16 to <18 years (n=36 in study HH-5) is limited but considered acceptable. The Applicant provided the requested AE data from the studies HH-2 and HH-5 specific for the elderly population. However, the number and percentage of patients between 65 and 74 yoa are low and those of patients between 75 and 84 yoa is very low. Thus, the above-mentioned findings must be handled with caution.

Beyond the first week after vaccination, adverse events were collected at the investigational site during subject visits on days 14 and 28 via anamnesis that covered the periods from days 0-14 and days 14-28. No diary documentation was required for participants beyond day 7, but participants have been

encouraged and reminded to report any AE at the time of their occurrence at any point during the study. Any reported AE was registered in the eCRF.

Comparison of HH-2 and HH-5 showed a remarkable differences for malaise (20.26% of subjects in study HH-5, but none reported in study HH-2 for PHH-1V or Comirnaty), injection site swelling (9.56% in study HH-5, 0.6% for PHH-1V in HH-2 and 2.8% for Comirnaty in HH-2), injection site induration (1.21% in HH-5, 8.6% for PHH-1V in HH-2 and 17.1% for Comirnaty in HH-2), nausea (none in HH-5, 5.8% for PHH-1V in HH-2 and 5.2% for Comirnaty in HH-2), vomiting (5.93% in HH-5, 1.9% for PHH-1V in HH-2 and 1.2% for Comirnaty in HH-2) and myalgia (1.81% in HH-5, 19.5% for PHH-1V in HH-2 and 34.1% for Comirnaty in HH-2). Reasons for the distinct pattern per study could be related to individual interpretation regarding the reporting of AEs per patient diary, but these are not entirely clear.

A substantially lower frequency of unsolicited AEs reported in study HH-5 compared to study HH-2 (18.59% and 28.8% for PHH-1V in study HH-5 and study HH-2, respectively) was considered related to seasonal fluctuations in infection waves that affected both studies in a distinct manner.

Vaccination with PHH-1V following the primary Spikevax/Spikevax vaccination schedule, resulted in a higher frequency of solicited local and systemic events compared to other primary vaccination schemes. Reasons are currently unclear, but numbers do not give rise to concern.

All subjects were tested for SARS-CoV-2 at screening, symptomatic and asymptomatic subjects in close contact with a subject known with Covid-19 were assessed via the standard procedure in the health system. No dedicated screening system after vaccination was established for study participants. This strategy does not ensure that all COVID-19 cases have been observed in the study and in case studies are performed in different countries/regions the standard procedures might differ. However, it is acknowledged that severe cases would have most likely been detected.

A possible impact on clinical safety from high remaining HCP content is currently unclear. The Applicant committed to submit results of an in-depth characterization of the qualitative HCP profile including a full risk evaluation of identified HCPs within 2 months post-approval (REC7).

Studies are still ongoing and data for individual studies were provided at distinct data cut-offs. Further updates of data with the final study reports should be anticipated.

3.6. Effects Table

Table 63 ***Effects Table for Bimervax (indicated as a booster for active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA COVID-19 vaccine, data cut-off: 18th July 2022 for pooled safety data)***

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Immune response (primary endpoint)	Noninferiority SARS-CoV-2 Neutralisation against D614G strain at D14	nAb GMT (95% CI)	1953.89 (1667.17; 2289.93)	3336.54 (2778.56 ; 4006.57)	1.71 (1.45; 2.02) – NI not met	HIPRA-HH-2
Immune response (secondary endpoint	Noninferiority SARS-CoV-2 Neutralisation against Beta at D14	nAb GMT (95% CI)	4278.92 (3673.99; 4983.46)	2659.02 (2213.05 ; 3194.86)	0.62 (0.52; 0.75) – "superior" no multiplicity control	HIPRA-HH-2
Immune response (secondary endpoint	Noninferiority SARS-CoV-2 Neutralisation against Delta at D14	nAb GMT (95% CI)	1466.65 (1250.52; 1720.14)	1490.42 (1238.77 ; 1793.19)	1.02 (0.86; 1.21) – "noninferior", no multiplicity control	
Immune response (secondary endpoint)	Noninferiority SARS-CoV-2 Neutralisation against Omicron BA.1 at D14	nAb GMT (95% CI)	2042.36 (1775.91; 2348.79)	1217.90 (1023.84 ; 1448.75)	0.60 (0.50; 0.72) – "superior" no multiplicity control	
Immune response (secondary endpoint)	Noninferiority SARS-CoV-2 Neutralisation against D614G strain at D28	nAb GMT (95% CI)	2230.95 (1903.29; 2615.01)	2958.40 (2465.00 ; 3550.55)	1.33 (1.12; 1.56) "noninferior", no multiplicity control	
Immune response (secondary endpoint)	Noninferiority SARS-CoV-2 Neutralisation against Beta at D28	nAb GMT (95% CI)	3774.87 (3240.63; 4397.18)	2467.06 (2054.58 ; 2962.35)	0.65 (0.54; 0.79) "superior", no multiplicity control	
Immune response (secondary endpoint)	Noninferiority SARS-CoV-2 Neutralisation against Delta at D28	nAb GMT (95% CI)	1711.24 (1458.85; 2007.29)	1515.79 (1260.56 ; 1822.71)	0.89 (0.75; 1.05) "noninferior", no multiplicity control	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Immune response (secondary endpoint)	SARS-CoV-2 Neutralisation against Omicron BA.1 at D28	nAb GMT (95% CI)	1515.40 (1317.43; 1743.13)	996.73 (838.49; 1184.83)	0.66 (0.55; 0.79) "superior", no multiplicity control	
Immune response (secondary endpoint)	Noninferiority SARS-CoV-2 Neutralisation against D614G strain at D182	nAb GMT (95% CI)	1205.49 (1028.22; 1413.33)	751.64 (626.02; 902.46)	0.62 (0.53; 0.74) "superior", no multiplicity control	
Immune response (secondary endpoint)	Noninferiority SARS-CoV-2 Neutralisation against Beta at D182	nAb GMT (95% CI)	2569.17 (2204.98; 2993.52)	1786.38 (1487.00 ; 2146.03)	0.70 (0.58; 0.84) "superior", no multiplicity control	
Immune response (secondary endpoint)	Noninferiority SARS-CoV-2 Neutralisation against Delta at D182	nAb GMT (95% CI)	2303.74 (1963.44; 2703.03)	1257.77 (1045.54 ; 1513.07)	0.55 (0.46; 0.65) "superior", no multiplicity control	
Immune response (secondary endpoint)	SARS-CoV-2 Neutralisation against Omicron BA.1 at D182	nAb GMT (95% CI)	882.92 (767.34; 1015.91)	668.32 (561.92; 794.85)	0.76 (0.63; 0.91) "superior", no multiplicity control	
Unfavourable Effects						
Study HH-2						
Any TEAE	Incidence	%	89.3	94.4		HH-2, Module 2.7.4, eCTD 0006
Solicited systemic events, D0	Incidence	%	27.9	34.9		
Solicited systemic events, D7	Incidence	%	4.3	4.0		
Solicited local events, D0	Incidence	%	79.1	85.7		
Solicited local events, D7	Incidence	%	1.6	2.0		
Unsolicited events	Incidence	%	28.8	35.7		
TEAE by SOC and PT						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
General d. and admin site c.	Incidence	%	82.8	91.3		
Inj. site pain	Incidence	%	79.7	89.3		
Fatigue	Incidence	%	27.5	42.1		
Nervous system disord.	Incidence	%	32.7	42.1		
Headache	Incidence	%	31.2	40.1		
Musculoskeletal and connective t.d.	Incidence	%	21.6	37.4		
Myalgia	Incidence	%	19.5	34.4		
GI disorders	Incidence	%	13.3	8.3		
Diarrhoea	Incidence	%	7.2	2.4		
Nausea	Incidence	%	5.8	5.2		
Vomiting	Incidence	%	1.9	1.2		
Pooled safety data by SOC and PT						Pooled safety data from HH-2, HH-5 and HH-10, Mod. 2.5, eCTD 0006
General d. and admin site c.	Incidence	%	84.9	-		
Inj. site pain	Incidence	%	82.17			
Fatigue	Incidence	%	30.86			
Nervous system disord.	Incidence	%	30.73			
Headache	Incidence	%	30.23			
Dizziness	Incidence	%	0.41			
Musculoskeletal and connective t.d.	Incidence	%	20.55			

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
GI disorders	Incidence	%	11.31			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

While PHH-1V failed to demonstrate non-inferiority against the active comparator Comirnaty in the primary efficacy endpoint (neutralizing antibody responses against the D614G strain at Day 14, PBNA), it was superior with regard to the Beta and Omicron VOC and non-inferior with regards to the Delta VOC (secondary endpoints, also neutralizing antibody responses at Day 14, PBNA). Notwithstanding that the primary endpoint was not met, the application could still be approvable, since the D614G strain has been superseded by the emerging VOCs in particular the recent Omicron VOC, rendering the secondary endpoints clinically more relevant than the primary endpoint.

The submitted overall data was not considered suitable to support a claim for a booster dose for previously immunized subjects irrespective of the vaccine administered previously. Only an indication including subjects with primary immunization with mRNA vaccines is acceptable.

Booster vaccination with either PHH-1V or Comirnaty was administered at least 182 days after the second dose of the primary series for most study participants. Available data for booster vaccinations with PHH-1V below 6 months after the second dose of the primary series are currently limited. Thus, based on available data the interval between the last dose of previous COVID-19 vaccine and Bimervax should be at least 6 months.

Although limited data is available in individuals 16 yoa and older (36 subjects 16-17 yoa received primary immunisation with Comirnaty followed by one PHH-1V dose in study HH-5 of which only 11 are included in the immunogenicity subset), the respective results show a strong increase of neutralizing immune responses after PHH-1V administration. In addition, data on neutralizing GMTs do not suggest apparent differences to that obtained in adults and it is noted that higher GMTs were obtained. Thus, the data supports an indication in individuals 16 yoa or older.

Safety data are rather limited considering the total amount of subjects followed (around 3000) but provided results do not indicate major deviations from licensed Covid-19 vaccines (i.e., Comirnaty as tested in study HH-2) and the overall safety database is considered sufficient to conclude on the safety profile. Gastrointestinal disorders appear more pronounced (specifically PT diarrhoea), but PHH-1V appears to be less reactogenic compared to Comirnaty, based on the currently available data. A serious adverse event of pericarditis is noted with concern, as similar events were reported for other Covid-19 vaccines as well. Further observation appears crucial during post-marketing, but overall, the safety database is considered acceptable. A possible impact on clinical safety from high remaining HCP content is currently unclear, but the Applicant committed to submit results of an in-depth characterization of the qualitative HCP profile including a full risk evaluation of identified HCPs within 2 months post-approval (REC7).

3.7.2. Balance of benefits and risks

The immunobridging approach used for this application is considered acceptable and the provided data allow to assume efficacy for the booster vaccination with Bimervax in subjects who have previously

received a mRNA COVID 19 vaccine. The provided data further show an acceptable safety profile, overall comparable to other COVID-19 vaccines.

The benefit/risk balance of Bimervax for the sought indication "active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA COVID-19 vaccine" is positive.

Furthermore, in view of the development programme, the nature of the product and the data package provided, the dossier is considered comprehensive vis-à-vis the dossier requirements for a vaccine authorisation using an immuno-bridging approach.

3.8. Conclusions

The overall benefit/risk balance of Bimervax is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

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

'BIMERVAX is indicated as a booster for active immunisation to prevent COVID-19 in individuals 16 years of age and older who have previously received a mRNA COVID-19 vaccine.

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

The CHMP therefore recommends the granting of the marketing authorisation 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.

Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion heterodimer – B.1.351-B.1.1.7 strains is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.