CLINICAL STUDY PROTOCOL

HIPRA-HH-5

A PHASE III, OPEN LABEL, SINGLE ARM, MULTI-CENTER, 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.

Sponsor:	HIPRA SCIENTIFIC, S.L.U. Avda. La Selva, 135 17170 Amer (Girona), Spain
EudraCT:	2022-000074-25
Investigational Product:	PHH-1V
Date of Issue:	28th January 2022
Version No.:	2.0
Supersedes Edition No. (Date)	V1.0 (11st January 2022)

SIGNATURE PAGE

Protocol Title: A Phase III, Open Label, Single Arm, Multi-centre 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

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INVESTIGATOR STATEMENT

I understand that all documentation provided to me by HIPRA SCIENTIFIC S.L.U. or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Independent Ethics Committee. No changes will be made to the study protocol without the prior written approval of HIPRA SCIENTIFIC S.L.U. and the Independent Ethics Committee, except when necessary to eliminate an immediate hazard to the patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Name	Investigator Signature	Date

Investigational site or name of institution and location (printed)

CLINICAL STUDY SYNOPSIS

Protocol code	HIPRA-HH-5	
Title of the Study	A phase III, open label, single arm, multi-centre, 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.	
EudraCT No.	2022-000074-25	
Clinical Phase	III	
Sites / countries	Phase III: This Phase of the clinical study will be conducted at approximately 20 sites located in Spain, Italy and Portugal, with a competitive enrolment.	
Study period	For safety assessment each subject will be followed for 26 weeks (182 days) after the administration of the booster vaccination on Day 0. For immunogenicity assessment each subject will be followed for 52 weeks (365 days) after the administration of the booster vaccination on Day 0	
Phase III: Primary objectives and endpoints	**Objective/s**	**Endpoint/s**
	1. To 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 vaccines.	Safety: 1.1. Number, percentage, and characteristics of solicited local and systemic reactions through Day 7 after vaccination. 1.2. Number, percentage, and characteristics of unsolicited local and systemic adverse events (AEs) through Day 28 after vaccination. 1.3. Number and percentage of serious adverse events (SAEs) through the end of the study. 1.4. Number and percentage of adverse event of special interest (AESI) through the end of the study. 1.5. Number and percentage of medically attended adverse events (MAAE) related to study vaccine through the end of the study. 1.6. Grade 3 and 4 changes from baseline in safety laboratory parameters at Days 14, 91 and 182 after vaccination.

Phase III: Secondary objectives and endpoints	1. To determine and compare the changes of the immunogenicity measured by pseudovirus neutralisation against Wuhan strain (also known as L strain) and against Omicron, and any other relevant Variants of Concern (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.	1.1 Neutralisation titre against Wuhan and Omicron strains, and any other relevant VOC in the epidemiologic moment, measured as inhibitory concentration 50 (IC_{50}) 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. 1.2 The geometric mean fold rise (GMFR) in neutralising antibody titre from baseline to Day 14.
	2. 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.	2.1 Binding antibodies titre measured for each individual sample and GMT for descriptive statistics analysis at Baseline and Days 14, 91, 182 and 365. 2.2 The geometric mean fold rise (GMFR) in binding antibody titre from baseline to Day 14. 2.3 The percentage of subjects that after the booster dose have a ≥4-fold change in binding antibodies titre from Baseline to Day 14.
Phase III: Exploratory objectives and endpoints	1. To assess number of subjects with SARS-CoV-2 infections ≥14 days after PHH-1V booster.	1.1. 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.
	2. To assess number of COVID-19 severe infections ≥14 days after receiving PHH-1V.	2.1 Number and percentage of COVID-19 severe infections ≥14 days after PHH-1V booster and through the end of the study. 2.2 Number and percentage of hospital admissions associated with COVID-19 ≥14 days after PHH-1V booster and through the end of the study.

		2.3 Number and percentage of intensive care unit (ICU) admissions associated with COVID-19 ≥14 days after PHH-1V booster and through the end of the study. 2.4 Number and percentage of non-invasive ventilation administration associated with COVID-19 ≥14 days after PHH-1V booster and through the end of the study. 2.5 Number and percentage of deaths associated with COVID-19 ≥14 days after PHH-1V booster and through the end of the study.
	3. To evaluate 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. T-cell mediated response will be performed in a subset of 30 subjects.	3.1 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 will be performed in 30 subjects.
	4. To assess 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. Th-1/Th2 T-cell mediated response will be performed in a subset of 30 subjects.	3.2 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 30 subjects.

Study population	Phase III: Approximately 3000 adults aged above 16 years old will receive HIPRA's boosting vaccine (PHH-1V).
Study Design	This is a phase III, open label, single arm, multi-centre clinical trial that aims to determine safety, reactogenicity, tolerability and immunogenicity of a booster vaccination with a recombinant protein receptor binding domain (RBD) fusion heterodimer candidate against SARS-CoV-2 developed by HIPRA (PHH-1V). In this phase III study, approximately 3000 eligible subjects who have received: • One dose of: Comirnaty + COVID-19 infection (before or after the vaccination) or, • One dose of: Spikevax + COVID-19 infection (before or after the vaccination) or, • One dose of: Vaxzevria + COVID-19 infection (before or after the vaccination) or, • One dose of: Janssen + COVID-19 infection (before or after the vaccination) or, • One dose of: Janssen or, • Two homologous doses of: Comirnaty + Comirnaty (with or without COVID-19 infection, before, in between or after the two doses) or, • Two homologous doses of: Spikevax + Spikevax (with or without COVID-19 infection, before, in between or after the two doses) or, • Two homologous doses of: Vaxzevria + Vaxzevria (with or without COVID-19 infection, before, in between or after the two doses) or, • Two homologous doses of: Janssen + Janssen (with or without COVID-19 infection, before, in between or after the two doses) or, • Two heterologous doses of: Comirnaty + Spikevax (or vice-versa) (with or without COVID-19 infection, before, in between or after the two doses) or, • Two heterologous doses of: Vaxzevria + Comirnaty (with or without COVID-19 infection, before, in between or after the two doses) or, • Two heterologous doses of: Vaxzevria + Spikevax (with or without COVID-19 infection, before, in between or after the two doses) 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, will be vaccinated with a single booster dose of PHH-1V on Day 0. For the safety assessment, subjects who have had a COVID-19 infection before, after or in between the two doses of the vaccines can be enrolled.

	Immunogenicity will be evaluated in a subset of about 8% of the enrolled subjects (250 subjects) in Spain with no history of SARS-CoV-2 infection. The immunogenicity subset will be conformed of subjects vaccinated with: • Approximately 100 subjects with two doses of Vaxzevria at least 91 days before PHH-1V booster administration (Adenoviral vector vaccine platform). o Approximately in 30 of these 100 subjects, cellular immunogenicity response will be evaluated as an exploratory objective. • Approximately 100 participants who have received heterologous priming with two doses of different authorised vaccines (Vaxzevria vaccine combined with mRNA vaccine) at least 91 days before PHH-1V booster administration. • Approximately 50 subjects with two doses of Spikevax at least 91 days before PHH-1V booster administration (mRNA vaccine platform) Immunogenicity will be evaluated in all the participants of 16 or 17 years old in Spain, that have never been infected with COVID-19 and vaccinated with: • Two doses of Pfizer vaccine at least 91 days before PHH-1V booster administration. For the immunogenicity assessment, subjects who have passed a COVID-19 will be excluded. All subjects will be provided with a paper diary on Day 0 to record solicited local and systemic reactions after vaccination through Day 7. Unsolicited adverse events will be reported through Day 28. SAEs, AESI and MAAE will be reported during all the duration of the study. Subjects will return to the site on Days 14, 91, 182 (final visit for 92% of participants) and 365 (final visit for 8% of participants in the immunogenicity assessment) for blood sample collection and safety follow-up. Subjects will receive a single booster dose, on Day 0 and will be observed for 15 minutes after vaccination. A DSMB will be available and may review safety data at any time point during the study as necessary and/or if requested by any of the involved PIs in case of observation of serious adverse events (SAEs). Once the first 1000 enrolled subjects have completed Day 14 safety assessments, a first interim analysis will be performed to assess the safety of PHH-1V. Once the first 2500 enrolled subjects have completed Day 14 safety assessments, a second interim analysis will be performed to assess the safety of PHH-1V.

	Also, once data of Day 14 of all enrolled subjects in the immunogenicity subset will be available, a third interim analysis will be performed to assess the observed immunogenicity response of the PHH-1V booster dose.
Study blind	This study is unblinded since it is a single arm clinical trial
Selection criteria	The inclusion and exclusion criteria for enrolling are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. **Inclusion Criteria** Subjects must meet all the following criteria to be considered eligible for the study: 1. Male or female, ≥ 16 years old at Day 0. 2. Participant must provide consent indicating that she or he understands the purpose and potential risks and is willing and able to participate in the study and comply with all the study requirements and procedures (scheduled visits, laboratory tests, complete diaries, etc). In subjects of 16 and 17 years old, apart from their assent, participation in the study must be approved by their legal tutors though informed consent form. 3. Participant who has a SARS-CoV-2 vaccination scheme recognized by the authorities of the country with any of the following vaccines: Comirnaty, Spikevax, Vaxzevria or Janssen vaccine at least 91 days and preferably a maximum of 240 days before Day 0. Homologous and heterologous prime vaccinations are allowed. Individuals with a history of non-severe COVID-19 infection can be included. Following local authorities recognized vaccination scheme, subjects can participate in the following cases: <u>For safety assessment:</u> – two doses of any of the vaccines mentioned above (homologous or heterologous) – two doses of any of the vaccines mentioned above (homologous or heterologous) + non-severe COVID-19 infection (before, in between or after the second dose). – one dose of any of the vaccines mentioned above + non-severe COVID-19 infection (before or after the dose). – one dose of Janssen vaccine NOTE: Non-severe COVID-19 infections after ≥14 days of the second dose are permitted if passed at least 30 days before Day 0 (30 days from the day of COVID-19 infection confirmation via RT-PCR or RAT).

	For immunogenicity assessment: - Two doses of Vaxzevria with no previous COVID-19 infection - Two doses of Spikevax with no previous COVID-19 infection - Two heterologous doses of different authorised vaccines (Vaxzevria combined with mRNA vaccine) with no previous COVID-19 infection. - In subjects of 16 or 17 years old in Spain, two doses of Comirnaty with no previous COVID-19 infection 4. Participants may have underlying illnesses if are stable and well-controlled according to the investigator judgment. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months prior to screening and for which neither a significant change in treatment or hospitalization for worsening is expected in the near future. 5. Participant agrees not to donate blood, blood products and bone marrow at least 3 months before and after vaccination. 6. Contraceptive use should be consistent with local regulation for participants in clinical trials. a. Female participants of childbearing potential [defined as any female who has experienced menarche and until becoming postmenopausal* (defined as having ≥ 12 months amenorrhea prior to screening without an alternative cause) unless is surgically sterile]: i. Have a negative pregnancy test on the day of vaccination. ii. Use of any acceptable contraceptive method that should be started on day 0 and until 8 weeks after vaccination. Acceptable contraceptive methods are: 1. Hormonal contraception (progestogen-only or combined): oral, injectable or transdermal (patch). 2. Intrauterine device. 3. Vasectomized partner (the vasectomized partner should be the sole partner for that participant). 4. Sexual abstinence **, as a form of contraception, is acceptable if in line with the participant's lifestyle. 5. Condom b. Male participants: i. Vasectomized participants. ii. Refrain from donating sperm for at least 28 days after day 0. iii. Agree to use a male condom may be considered in women of childbearing potential partners, from screening and for at least 28 days after day 0.

iv. Sexual abstinence**, as a form of contraception, is acceptable if in line with the participant's lifestyle.

* A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

** Sexual abstinence is considered an effective method only if defined as refraining from heterosexual intercourse from screening until 8 weeks after receiving the vaccine for female participants and from screening until 4 weeks for male participants. Periodic abstinence (e.g., calendar, ovulation) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

7. History of anaphylaxis to any prior vaccine.

8. Previous severe SARS-CoV-2 infections are not permitted.
   Note: Severity explained as any episode of COVID-19 requiring ≥ 24hrs of hospitalization.

9. Participant received or plans to receive:
   a. Live attenuated vaccines (licensed) within 4 weeks before or after receiving any study vaccine.
   b. Other not live vaccines (licensed) within 14 days before and after receiving any study vaccine

10. Pregnancy or breast-feeding at screening or Day 0 (vaccination time-point) or willingness/intention to become pregnant during the study.

<u>Medical conditions</u>

11. Participant has a clinically significant acute illness (this does not include minor self-limited illness such as mild diarrhoea) or fever (temperature ≥38º C (100.4ºF) at screening or within 48 hours prior to the planned vaccination (Day 0).

12. Participant had a surgery requiring hospitalization (defined as inpatient stay for > 24 hours) before vaccination and he/she has not received the hospital discharge at day 0; or has a surgery requiring hospitalization planned within 12 weeks after study vaccine administration. Minor surgical procedures not requiring hospitalization are accepted.

13. Participant has any active malignancy even if under treatment except for (at the discretion of the investigator):

	a. Non-melanoma adequately treated skin cancer without evidence of disease b. Adequately treated uterine cervical carcinoma in situ without evidence of disease c. Adequately treated anal carcinoma in situ without evidence of disease d. Localized prostate cancer 14. Participant has ongoing severe and non-stable psychiatric condition likely to affect participation in the study (e.g., ongoing and non-stable severe depression, recent suicidal ideation, severe eating disorder, psychosis) 15. Participant has a problematic or risk use of substances including alcohol (except tobacco) that can compromise the study follow-up. Problematic or risk use of psychoactive substances is understood as the one that causes evident damage, whether it is dependence or any other physical, psychological, or social problem or that carries a high risk of suffering these damages. The negative consequences that consumption causes to third parties could be included. 16. Participant has a bleeding disorder (e.g., factor deficiency, platelet disorder), blood dyscrasia, or continuous use of anticoagulants or has any condition that in the opinion of the investigator contraindicates intramuscular injections or frequent phlebotomy. The use of ≤ 325mg of aspirin or ≤ 75mg of clopidogrel per day as prophylaxis is permitted but not combined. 17. Participant has abnormal function of the immune system as in autoimmune diseases, asplenia, recurrent infections or congenital/acquired immunodeficiency. Participants with stable clinical conditions (e.g., autoimmune thyroiditis, celiac disease, type 1- diabetes) under non-immune-modifying treatment (e.g., hydroxychloroquine , rituximab, cyclosporine) and participants living with HIV with CD4 T cell count ≥ 400 cells/mm3 under stable antiretroviral treatment with a fully suppressed viral load ≥ 1 year are permitted [one or two non-consecutives blips (HIV viral load ≤ 500 viral copies) are permitted]. 18. Participants have clinically significant and unstable cardiovascular, respiratory, hepatic, neurological, gastrointestinal, renal, or any other medical disorder as judged by the investigator and defined as disease requiring hospitalization or addition of new treatments or major dose adjustments within 3 months before screening. <u>Prior/Concomitant Therapy and Clinical Study Experience</u>. 19. Chronic or recurrent administration (during at least 14 days) of systemic immunosuppressant medication (defined as given by oral or parenteral routes) within 12 weeks preceding the planned administration of study vaccine (Day 0). The use of a prednisone dose < 10mg per day or equivalent,

	ocular, topical, inhaled and nasal corticoids are allowed. 20. Subject has received immunoglobulins and/or blood-derived products 12 weeks prior vaccination (Day 0) or expects to receive them during the study. 21. Participant received any immunotherapy (monoclonal antibodies, plasma) aimed to prevent or treat COVID-19 within 90 days preceding the planned administration of study vaccine. 22. Participation in any research involving an investigational product (drug, biologic, device) within 12 weeks prior to vaccination and during the study. 23. Participant has donated ≥ 450ml of blood products within 12 weeks before screening. 24. Participant has any medical condition and/or finding that in the investigator opinion might increase participant risks, interfere with the study or impair interpretation of study data.
Investigational Product	Single administration of COVID-19 HIPRA's vaccine (PHH-1V).
Reference product	Not applicable
Route of administration, pharmaceutical form and dosage	The investigational product is administered by the intramuscular route. It is presented in the following form: • COVID-19 HIPRA's vaccine (PHH-1V) multi-dose vial of 10ml ready to use. Each dose will consist in a volume of 0.5 ml of PHH-1V (40 µg of protein). Therefore, each vial will have 10 doses of PHH-1V vaccine.
Analyses populations	The following analyses populations are included in this study protocol: • Enrolled (EP): All subjects who have signed the Informed Consent Form (ICF). • Intent-to-treat (ITT): All subjects who are randomised, regardless of the subjects' treatment status in the study. • Modified Intent-to-treat (mITT): All subjects in the ITT who meet the inclusion/exclusion criteria, received a dose of study drug and did not tested positive for COVID-19 within 14 days of the receiving study drug. • Immunogenicity (IGP): All subjects in the immunogenicity subset of mITT who had a valid immunogenicity test result before receiving study drug and at least one valid result after dosing.

	• Safety (SP): All enrolled subjects who received the study drug. This population will be used for all safety analyses.

Statistical Methods and Planned Analyses	**Sample size:** A sample size of 3000 participants is proposed. This sample size together with those participants enrolled in Phase IIb fulfil the requirements of the minimum safety population established in the (EMEA/CHMP/VWP/164653/05 Rev. 1, 2018; FDA CBER, 2020). **Interim analysis:** Once the first 1000 enrolled subjects have completed Day 14 safety assessments, a first interim analysis will be performed to assess the safety of PHH-1V. Once the first 2500 enrolled subjects have completed Day 14 safety assessments, a second interim analysis will be performed to assess the safety of PHH-1V. Also, once data of Day 14 of all enrolled subjects in the immunogenicity subset will be available, a third interim analysis will be performed to assess the observed immunogenicity response of the PHH-1V booster dose. **Statistical methods:** No formal statistical analysis will be performed on the primary and secondary endpoints. Descriptive analysis will be performed for variables overall by time-point. Categorical variables will be presented by means of number of cases and frequencies (%) and continuous variables will be 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 will be presented as frequencies and percentages. 95% confidence intervals (CI) will be also provided, as appropriate. In general, missing data will not be imputed. For exploratory endpoints related to the immunogenicity endpoints and T-cell, zero values will be imputed to half of the lower limit of quantification (LLOQ). If other parameters are deemed appropriate for imputation, information will be detailed in the Statistical Analysis Plan (SAP). Geometric mean titre (GMT), geometric mean concentration (GMC), GMFR and standard deviations will be calculated based on the log-transformed titres. Calculation of 95% CI will be 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. Further details on methodology for summary and statistical analyses of the data collected in this study will be detailed in the study SAP.

	Safety analysis Solicited local reactions and systemic events from Day 0 through Day 7 after boost vaccination will be presented by intensity and cumulatively across severity levels. Unsolicited local and systemic reactogenicity adverse events from Day 0 through Day 28 after boost vaccination will be presented by intensity and cumulatively across severity levels. Adverse Events and SAEs will be categorised according to Medical Dictionary for Regulatory Activities (MedDRA) terms and summarised by System Organ Class (SOC) and Preferred Term (PT). Summaries of local and systemic solicited AEs will be presented by SOC and PT for events occurring by Day 7. In addition, AEs will be summarised by maximum intensity and causal relationship to study drug. A separate summary of AESI, including potentially immune-mediated medical conditions (PIMMCs) and MAAE will be reported. Laboratory parameters will be summarised as actual values and change from baseline over time. Shift tables from baseline to worst on-study value and baseline to Days 14, 91 and 182 value will be reported. The safety analyses for the Phase III will be performed using the SP and for each primary vaccination scheme. **Immunogenicity analysis** For each subset of subjects included in the immunogenicity population, the following data will be presented: • The neutralizing antibody titre and the total binding antibodies measured for each individual sample and the GMT with its 95% confidence intervals at baseline and at Days 14, 91, 82 and 365 • The geometric mean fold rise (GMFR) in neutralizing antibody titre and in total binding antibodies from baseline to Day 14. • The percentage of subjects that after the booster dose have a ≥4-fold change in total binding antibodies titre from Baseline to Day 14
Post-Trial vaccination	Participants of this trial are eligible to receive a further vaccination of a commercial vaccine in order to qualify for international travel if needed, 3 months after receiving HIPRA's booster, if by this time, HIPRA vaccine is not yet included in the European COVID-19 certificate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACE-2	Angiotensin Converting Enzyme 2
ADE	Antibody-Dependent Enhancement
AE	Adverse Event
AESI	Adverse Event of Special Interest
AZ	Vaxzevria Vaccine abbreviation
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Data Base Lock
DSMB	Data Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Clinical Report Form
ECLIA	Electrochemiluminescence immunoassay
ELISpot	Enzyme-Linked Immune Absorbent Spot
EP	Enrolled Population
ETV	Early Termination Visit
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titre
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration 50
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Intracellular Cytokine Staining
ICU	Intensive Care Unit
ID_{50}	Inhibitory dilution 50
IEC	Independent Ethics Committee
IGP	Immunogenicity Population
IM	Intramuscular
LLOQ	Lower Limit of Quantification
MAAE	Medically Attended Adverse Events
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
Moderna	Spikevax Vaccine Abbreviation
mRNA	Messenger RNA
PBMC	Peripheral Blood Mononuclear Cell
PBNA	Pseudovirion-Based Neutralisation Assay
PCR	Polymerase Chain Reaction
PIMMCs	Potentially Immune-Mediated Medical Conditions
PT	Preferred Term
RAT	Rapid Antigen Test
RBD	Receptor Binding Domain
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Coronavirus 2
SD	Standard Deviation
SOC	System Organ Class
SP	Safety Population
SpO_2	Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAR	Unexpected Adverse Reaction
VDE	Vaccine-Dependent Disease Enhancement
VNA	Virus neutralisation assay
VOC	Variants of Concern
WHO	World Health Organization

1. INTRODUCTION

1.1 Disease Overview

At the end of 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[1]. 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 the WHO declared a pandemic[2]. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

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 4 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 protein 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 elicit an immune response that prevents infection in animals.

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 4 to 5 days. Most symptomatic individuals experience symptoms within 2 to 7 days after exposure and almost all symptomatic individuals will experience one or more symptoms before Day 12. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time[3].

The major complication of severe Coronavirus Disease 2019 (COVID-19) is acute respiratory distress syndrome (ARDS), presenting as dyspnoea and acute respiratory failure that requires oxygen/ventilatory support including mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to other 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[4].

The management of COVID-19 cases has developed during 2020, and includes supportive care, which may include fluid therapy, oxygen support, and supporting affected vital organs.

Treatment of patients with COVID-19 encompasses multiple treatments and frequently updated guidelines (for instance www.idsociety.org/COVID19guidelines) that distinguish between the different degrees of severity, hospitalised versus ambulatory, ventilated versus non-ventilated, where anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents (baricitinib and tofacitinib), anticoagulants, antiviral therapy (e.g., remdesivir), monoclonal

antibodies (casirivimab plus imdevimab, sarilumab, tocilizumab, sotrovimab, bamlanivimab plus etesevimab) and antibodies administered from convalescent plasma and hyperimmune immunoglobulins.

These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

While care for individuals with COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for vaccines able to prevent or mitigate COVID-19 infections during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired. Although various vaccines for prevention of COVID-19 have been approved recently, there is still an important need for additional vaccines to meet global demands.

1.2 PHH-1V

Up to date, messenger RNA (mRNA)-based vaccines, recombinant adenovirus vectored vaccines and full spike protein vaccines have established the efficacy of vaccines for SARS-CoV-2 based on full-length Spike (S) protein[5,6,7].

Recombinant S protein produced in mammalian or insect cells has also shown immunogenicity and efficacy[8]. For large volume, low-cost production, however, protein-based vaccines incorporating the receptor binding domain (RBD) subunit remain an important alternative to the full S protein. Antibodies to RBD account for most of the neutralising activity elicited in a natural infection.

HIPRA has developed a recombinant protein RBD fusion dimer vaccine (PHH-1V) with an oil-water adjuvant equivalent to the commonly used adjuvant MF59C.1, for the prevention of COVID-19 caused by SARS-CoV-2, prepared as an emulsion for intramuscular administration in adults.

The adjuvant equivalent to MF59C.1 has been shown to be safe and to enhance immunogenicity of the vaccine in pre-clinical studies.

1.2.1 Phase I/IIa study with PHH-1V in adult healthy subjects

A first-in-human, phase I/IIa, randomised, controlled, observer-blinded, dose-escalation, multicentre clinical trial to evaluate safety and immunogenicity of COVID-19 HIPRA vaccine in adult healthy subjects, was conducted. A total of 30 healthy adults were allocated to one of the following cohorts:

- **Cohort 1**: 5 subjects received 2 doses of COVID-19 vaccine HIPRA containing 10 µg of protein and 1 subject received 2 doses of COMIRNATY (ARNm COVID-19 vaccine, Pfizer-BioNTech)
- **Cohort 2**: 10 subjects received 2 doses of COVID-19 vaccine HIPRA containing 20 µg of protein and 2 subjects received 2 doses of COMIRNATY (ARNm COVID-19 vaccine, Pfizer-BioNTech)
- **Cohort 3**: 10 subjects received 2 doses of COVID-19 vaccine HIPRA containing 40 µg of protein and 2 subjects received 2 doses of COMIRNATY (ARNm COVID-19 vaccine, Pfizer-BioNTech)

The subjects were allocated to the dose escalation cohort according to the order that they have been preselected. Subjects at each cohort were randomised 5:1 to receive COVID-19 vaccine HIPRA or control commercial COVID-19 vaccine.

The safety data evaluated has been the number of subjects with at least solicited local and systemic reactogenicity adverse events (AEs) for 7 days following each vaccination and the number of patients with at least one unsolicited AE for 28 days following.

The analysis related to the solicited AEs was performed as follow:

- Number (%) of subjects with at least one solicited systemic AE, in general and by kind of systemic AE.
- Number (%) of subjects with at least one solicited local AE, in general and by kind of local AE.
- Number (%) of subjects with at least one systemic or local AE.

All analyses described above for the solicited AEs for 7 days following each vaccination were also performed by day and grade of intensity (1-mild, 2-moderate, 3-severe or 4 potentially life-threatening). These analyses were also performed for the maximum intensity over 7 days.

After the first vaccination, the major part of the subjects in all the cohorts reported solicited AEs, however, the majority of them were local. After the second vaccination, there were fewer cases of reported solicited AEs than with the first vaccination in subjects vaccinated with HIPRA vaccine. However, 100% of subjects vaccinate with Comirnaty reported solicited AE with the second vaccination. The solicited systemic AE reported with the second vaccination were fewer than with the first vaccination in subjects vaccinated with HIPRA vaccines, while there was an increase in % of solicited local and systemic AE reported, in subjects vaccinated with Comirnaty (see Table 1 for summary % solicited AEs).

Table 1. Summary of Solicited AEs (% of subjects)

Subjects with at least one solicited AE during 7 days (%)	Cohort 10 µg n=5	Cohort 20 µg n=10	Cohort 40 µg n=10	Comirnaty n=5
After 1st vaccination				
Solicited AE	60	90	80	80
Solicited AE grade 3 or above	0	0	0	0
Solicited local AE	60	80	80	80
Solicited local AE grade 3 or above	0	0	0	0
Solicited systemic AE	20	60	60	0
Solicited systemic AE grade 3 or above	0	0	0	0
After 2nd vaccination				
Solicited AE	60	60	50	100
Solicited AE grade 3 or above	0	0	0	0
Solicited local AE	60	60	50	100
Solicited local AE grade 3 or above	0	0	0	0
Solicited systemic AE	0	30	20	60
Solicited systemic AE grade 3 or above	0	0	0	0

Abbreviations: AE = adverse event

Only Grade 1-2 solicited local and systemic AE occurred. The most frequent solicited local AE were local sensitivity and pain at the injection site. The most frequent solicited systemic AE were fatigue/tiredness and headache.

In the case of HIPRA vaccines, the most frequent solicited grade 2 local AE was local sensitivity in all the cases (first and second vaccination), while only one case experimented a solicited systemic grade 2 AE, fatigue/tiredness (see Table 2 for summary solicited AE grade 2). There wasn´t any systemic grade 2 AE after the second vaccination in subjects vaccinated with HIPRA vaccine. Subjects vaccinated with Comirnaty suffered fever (50%), headache (66.7%), fatigue/tiredness (50%) and myalgia/muscle pain (50%).

Table 2. Summary of Solicited AE Grade 2 (% of subjects)

	Cohort 10 µg n=5	Cohort 20 µg n=10	Cohort 40 µg n=10	Comirnaty n=5
After 1st vaccination				
Local AE				
Local sensitive	100	42.9	12.5	50
Headache	0	0	20	0
Systemic AE				
Fatigue / Tiredness	0	33.3	0	0
After 2nd vaccination				
Local AE				
Pain at the injection site	0	0	0	25
Local sensitivity	33.3	50	25	50
Systemic AE				
Fever	0	0	0	50
Headache	0	0	0	66.7
Fatigue / Tiredness	0	0	0	50
Myalgia / Muscle pain	0	0	0	50

Abbreviations: AE = Adverse Event

No DLTs appeared at any dose (10 µg, 20 µg, 40 µg) after the first or the second immunisations. No pre-specified trial halting rules were met.

No relevant laboratory changes from values at the entry of the study were detected in safety laboratory assessment.

Quantification of neutralising antibodies analysed by sero-neutralisation with pseudovirion (PBNA) and live virus (VNA), at baseline, 3 weeks after the first dose and 2 weeks after the second dose of vaccine was performed.

The results have shown a very good response in neutralising antibodies, for all the variants analysed that are specifically alpha, beta, gamma and delta. This response is already evident after the first dose of vaccine and is magnified after the second dose. In this phase, and even with individuals vaccinated with Pfizer vaccine in the study, statistical comparison has not been performed because the sample size, especially of the Pfizer group, is very low and makes no sense. However, by internal data we have from sample panels of people vaccinated with vaccines already registered, we can confirm that the HIPRA vaccine induces a neutralising antibody response that is quite similar to Pfizer vaccine, and even exceeding the Pfizer vaccine for beta variant. No statistics can be done at this step of clinical studies.

In addition to neutralising antibodies, another secondary objective was the analysis of immunogenicity in terms of total antibodies. To evaluate the immunogenicity by means of total antibody against Receptor Binding Domain of the Spike protein of SARS-CoV-2 quantification, measured by an electrochemiluminiscence immunoassay (ECLIA). There is a clear seroconversion both after the first dose and after the second one, at which point the levels increase significantly.

A very important parameter is the fold rise which measures the increase in the level of antibodies between baseline and 3 weeks after the first dose, and between baseline and 2 weeks after the second dose of vaccine. It is accepted that a vaccine induces an antibody response that may be considered relevant, if this value is equal to or greater than 4.

It has been assessed that 2 weeks after the second dose of vaccine 100% of HIPRA vaccinated subjects, from all 3 groups, exceed the fold rise value of 4. Moreover, it is observed that 3 weeks after the first dose, 100% of subjects in the 20 and 40 microgram per dose of HIPRA vaccine groups, and 80% of subjects in the 10 microgram per dose of HIPRA vaccine group, have exceeded the fold rise value of 4.

What concerns cell immunity, in the subjects immunized with COVID-19 Vaccine HIPRA, a T cell mediated immunity was observed after vaccination. Specifically, results showed that vaccination with a 40 µg RBD fusion dimer/dose of COVID-19 Vaccine induced a specific T cell response, with a significant IFN-ɣ production after re-stimulation in vitro with RBD peptide mix from alpha (on D21 and D35), beta (on D21) and delta (on D35) SARS-CoV-2 variants compared with D0 ($P<0.05$).

In summary, we can confirm that the HIPRA vaccine induces a powerful immune response at both the level of total antibodies and neutralising antibodies. Furthermore, it has been shown that the neutralising antibody response is balanced among all tested variants.

Further details on the investigational vaccine and information on nonclinical studies can be found in the Investigator's Brochure (IB).

1.2.2 Phase IIb double-blind, randomised, active-controlled, multicentre, non-inferiority trial to assess immunogenicity and safety of a booster vaccination with PHH1V in adults fully vaccinated against COVID-19

In the Phase IIb study, 782 eligible subjects who have received two doses of the Comirnaty vaccine, and were at least 182 days and less than 365 days after their second dose, were randomly assigned to the following two treatment arms in a PHH-1V: Comirnaty 2:1 ratio:

- Cohort 1: single booster dose of PHH-1V on Day 0
- Cohort 2: single booster dose of Comirnaty on Day 0

765 subjects were vaccinated: 512 subjects received the booster dose of PHH-1V, and 253 subjects received the booster dose of Comirnaty.

Subjects were provided with a paper diary to record local and systemic reactions after vaccination from Day 0 through Day 7. Unsolicited adverse events were reported through Day 28. SAEs, AESI and MAAE were reported during all the duration of the study. Subjects were contacted through telephone on Day 7 for a safety assessment. Subjects returned to the site on Days 14, 28, 182, and 364 (final visit) for blood sample collection and safety follow-up.

Find below the Topline results collected up to the cut-off date of 10-Jan-2022.

Regarding SAFETY:

Table 3. Treatment-emergent adverse events (TEAEs) reported during the study until the data cut off (Safety Population)

	PHH-1V (N=512)		Comirnaty (N=253)		Overall (N=765)	
	Events	Subjectsn (%)	Events	Subjectsn (%)	Events	Subjectsn (%)
Total number of TEAEs	1329	401 (78.3)	924	213 (84.2)	2253	614 (80.3)
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[a]						
Mild	1150	296 (57.8)	763	130 (51.4)	1913	426 (55.7)
Moderate	164	96 (18.8)	148	76 (30.0)	312	172 (22.5)
Severe	12	8 (1.6)	11	7 (2.8)	23	15 (2.0)
Missing	3	1 (0.2)	2	0	5	1 (0.1)
Relationship to study treatment[a]						
Not related	96	18 (3.5)	48	4 (1.6)	144	22 (2.9)
Unlikely related	36	4 (0.8)	9	1 (0.4)	45	5 (0.7)
Possibly related	310	71 (13.9)	198	39 (15.4)	508	110 (14.4)
Probably related	236	67 (13.1)	170	26 (10.3)	406	93 (12.2)
Related	650	240 (46.9)	498	142 (56.1)	1148	382 (49.9)
Not Applicable	0	0	1	1 (0.4)	1	1 (0.1)
Missing	1	1 (0.2)	0	0	1	1 (0.1)
Unrelated[b]	132	22 (4.3)	57	5 (2.0)	189	27 (3.5)
Related[c]	1197	379 (74.0)	867	208 (82.2)	2064	587 (76.7)

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event

Note: A TEAE is defined as an AE that started on or after the date of administration of study treatment until 28 daysthereafter.

[a] If a subject experienced more than one TEAE, the subject is counted once at the most severe or most relatedevent.

[b] Unrelated AEs are those classified as not related and unlikely related.

[c] Related AEs are those classified as possibly, probably, and related. If a TEAE has a missing relationship, it isassumed to be related to the study treatment for analysis purposes.

Table 4. Summary of Treatment-emergent Adverse Events Occurring in ≥1.0% of Overall Subjects (Safety Population)

System organ class Preferred term	PHH-1V (N=512)		Comirnaty (N=253)		Overall (N=765)	
	Events	Subjectsn (%)	Events	Subjectsn (%)	Events	Subjectsn (%)
Total number of TEAEs	1329	401 (78.3)	924	213 (84.2)	2253	614 (80.3)
General disorders and administration site conditions	855	356 (69.5)	614	200 (79.1)	1469	556 (72.7)
Injection site pain	625	341 (66.6)	408	197 (77.9)	1033	538 (70.3)
Fatigue	129	115 (22.5)	97	89 (35.2)	226	204 (26.7)
Injection site induration	34	33 (6.4)	35	34 (13.4)	69	67 (8.8)
Injection site erythema	30	30 (5.9)	31	31 (12.3)	61	61 (8.0)
Pyrexia	12	11 (2.1)	17	16 (6.3)	29	27 (3.5)
Asthenia	11	10 (2.0)	3	3 (1.2)	14	13 (1.7)
Axillary pain	6	3 (0.6)	6	6 (2.4)	12	9 (1.2)
Injection site swelling	3	3 (0.6)	7	6 (2.4)	10	9 (1.2)
Nervous system disorders	173	141 (27.5)	107	91 (36.0)	280	232 (30.3)
Headache	162	134 (26.2)	102	87 (34.4)	264	221 (28.9)
Musculoskeletal and connective tissue disorders	94	86 (16.8)	91	78 (30.8)	185	164 (21.4)
Myalgia	82	76 (14.8)	81	72 (28.5)	163	148 (19.3)
Gastrointestinal disorders	88	61 (11.9)	21	16 (6.3)	109	77 (10.1)
Diarrhoea	34	33 (6.4)	6	5 (2.0)	40	38 (5.0)
Nausea	32	25 (4.9)	11	10 (4.0)	43	35 (4.6)
Vomiting	9	8 (1.6)	1	1 (0.4)	10	9 (1.2)
Infections and infestations	24	24 (4.7)	16	16 (6.3)	40	40 (5.2)
COVID-19	9	9 (1.8)	9	9 (3.6)	18	18 (2.4)
Blood and lymphatic system disorders	10	10 (2.0)	15	15 (5.9)	25	25 (3.3)
Lymphadenopathy	8	8 (1.6)	15	15 (5.9)	23	23 (3.0)
Investigations	8	8 (1.6)	2	2 (0.8)	10	10 (1.3)
SARS-CoV-2 test positive	6	6 (1.2)	3	3 (1.2)	9	9 (1.2)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

Vaccination with the PPH-1V and Comirnaty vaccines was generally well tolerated.

There were no deaths, other SAEs, or any TEAEs that led to discontinuation from the study.

Other significant events reported during the study related to SARS-CoV2 infections in both treatment groups. The percentage of subjects for which a breakthrough SARS-CoV2 infection was reported was higher in the Comirnaty group when compared to the PHH-1V group. Also, the number of subjects who received the PHH-1V vaccine was significantly higher than the number of subjects who received the Comirnaty vaccine. The statistical significance of this observation is still to be determined. SARS-CoV2 infections reported for both treatment groups were asymptomatic or mild. This infers protection against severe, life-threatening and fatal forms of the disease to both vaccines.

The absence of immune-mediated adverse events other than the SARS-CoV2 infection provides evidence to and supports a good safety profile for both vaccines.

Vaccination with PHH-1V shows a good safety profile during the observation period included in this report compared to Comirnaty. There is a low incidence of severe AEs, no SAEs and no SUSARs reported at this time.

Preliminary results show that the booster with PHH-1V may even have a better safety profile than the booster with Comirnaty.

Regarding IMMUNOGENICITY:

Per the Statistical Analysis Plan, the PHH-1V would be considered non-inferior to Comirnaty if the upper bound from the 95% confidence interval surrounding the Geometric Mean Ratio (GMR) from the above model falls below the cutoff of 1.4 for Wuhan. The comparison of the immunogenicity response for the VOCs was included as secondary endpoints in the protocol of this study.

At the cut-off date of 10 January 2022, a total of 257 subjects assigned PHH-1V and 126 assigned Comirnaty had baseline neutralization titre measurement. 497 assigned PHH-1V and 242 assigned Comirnaty had a Day 14 neutralization titre measurement.

Results collected at present allow to conclude that:

- Regarding the binding antibodies titres: The percentage of subjects that after a booster havea ≥4-fold change in binding antibodies titre from Baseline and Days 14 and 28 are similarbetween both groups and a response in antibody titres was observed in most vaccinated subjects.
- Regarding neutralizing antibodies against Delta: With a geometric mean ratio of 1.02 anda 95% confidence interval (CI) between 0.87 and 1.19, the topline results do show non- inferiority of PHH-1V to the Comirnaty vaccine in immune response to the Delta SARS- CoV-2 variant.
- Regarding neutralizing antibodies against Beta: The topline results do show superiority ofPHH-1V to the Comirnaty vaccine in immune response to the Beta SARS-CoV-2 variant expressed in a subset of 92 subjects that received PHH-1V and 48 subjects that received the Comirnaty (geometric mean ratio 0.54, 95%CI: 0.38-0.76).

- Regarding neutralizing antibodies against Omicron: The analysis of the first 30 vaccinated subjects (20 with PHH-1V and 10 with Comirnaty) shows higher levels of neutralizing antibodies against Omicron SARS-CoV2 variant among those treated with PHH-1V than Comirnaty. The analysis of the rest of the samples is on-going and formal comparison hasnot been executed.
- Regarding neutralizing antibodies against Wuhan: For the Wuhan SARS-CoV-2 variant, the topline results do not demonstrate non-inferiority of PHH-1V to the Comirnaty vaccinein immune response at 14 days after the booster. However, due to the current status of theWuhan SARS-CoV2 variant in the pandemic, and that Delta and mostly Omicron, are currently the main concerns together with new variants which may appear in the future, theneutralization against these variants has become much more relevant than that against Wuhan.
- Regarding the number of subjects with SARS-CoV-2 infections during the study: The lownumber of breakthrough SARS-CoV2 infections reported during the study, being asymptomatic or mild may indicate that both vaccines provide protection to moderate, severe, life-threatening, and fatal forms of SARS-CoV2 infections. This preliminary data indicates a slightly lower percentage of Covid cases in PHH-1V group compared to Comirnaty group. This preliminary data will be closely followed up during the study.

1.3 Study Design Rationale

Several vaccines against COVID-19 are in development and/or already approved for emergency use of in Europe. As of July 2021, approved vaccines have been developed using several different platforms, such as adenovirus-vectored vaccines (e.g., Vaxzevria / Covishield from AstraZeneca/Oxford and Ad26.COV2.S from Janssen/Johnson & Johnson), nanoparticles, mRNA vaccines (e.g., Comirnaty from Pfizer and Spikevax from Moderna) and recombinant protein (e.g. Nuvaxovid from Novavax). These vaccines have been approved for emergency use in adults and adolescents and are administered as a single vaccination or two vaccinations separated between 3 to 12 weeks.

Little immunogenicity data for these vaccines are available beyond 6 months after completed vaccination and it is expected that the duration of the immune response may be affected by the waning of immunity elicited by vaccines. Additionally, there are serious concerns about the emergence of new variants of the SARS-CoV-2 virus (e.g., Alpha [lineage B.1.1.7], Beta [lineage B.1.351], Gamma [lineage P.1], Delta [lineage B.1.617] and more recently Omicron [lineage B.1.1.529]) following mutations to the spike protein, enabling the antigens' escape. Some of these new variants are associated with high transmissibility and/or moderate or full resistance to the antibody response elicited by the current generation of COVID-19 vaccines, resulting in an increase in the number of COVID-19 cases, more hospitalisations, and potentially more deaths and incurring in a higher demand of healthcare resources.

To address morbidity and mortality secondary to new SARS-CoV-2 variants, protect high-risk or vulnerable populations, and maintain long-term immunogenicity, several approaches are in development. New vaccines with broad panels of coverage for current and new variants are under exploration, as well as the periodic administration of booster doses of known and new COVID-19

vaccines, which are being administered to population as a third dose to the general population and as a fourth dose to the higher risk population, 3 months after the third, in some countries.

As of end of June 2021, efforts to assess the role of the administration of a booster vaccine (either with extra doses of the original prime vaccine [homologous booster], or with new or marketed vaccines different that the prime [heterologous booster]) were started. A "booster dose" refers to another dose of a vaccine that is given to vaccinated people to restore protection after it has waned (also known as waning immunity). Preliminary clinical data suggests that both the homologous and heterologous booster regimes can be effective and safe [9,10,11,12,13]. In Spain, a booster dose was recommended in September 2021 to subjects with solid organ transplant, receptors of hematopoietic stem cell transplantation, post CAR-T cell treatment, on immunosuppressive treatment, or having graft-versus-host disease regardless of the time since HSCT, as well as subjects with onco-haematological disease and solid organ cancer, all primary immunodeficiencies, excluding IgA deficiency and antibody formation defect, very high risk patients with certain immunosuppressive treatments, people with renal replacement therapy (haemodialysis and peritoneal dialysis), cystic fibrosis, Down syndrome aged 40 or over.

Booster dose was also recommended for people residing in long term care facilities, given their profile of frailty, multiple pathologies and closed environments, and those on treatment with anti-CD20 drugs (including rituximab, ocrelizumab, ofatumumab, tositumomab, and ibritumomab). As of 5th of October 2021, the Public Health Commission approved the administration of a booster to all subjects aged above 70 years old and previously vaccinated at least 6 months prior to the booster dose. Subjects older than 18 years will receive a third dose from January 2022 onwards.

A Phase I/IIa study with HIPRA COVID-19 vaccine (PHH-1V) is being conducted to generate initial data on the safety, reactogenicity, and immunogenicity of two doses, administered 21 days apart, to adults between 18 and 39 years of age.

Also, a Phase IIb is being conducted to compare the immunogenicity and safety of a booster dose of HIPRA's recombinant protein RBD fusion dimer vaccine as a heterologous booster (to subjects who have received the second dose of the Pfizer–BioNTech (Comirnaty) COVID-19 vaccine at least 182 days prior to the booster dose in this study) versus a homologous booster (subjects who received the second dose of the Comirnaty COVID-19 vaccine at least 182 days prior to the booster dose in this study will receive a third dose of the Comirnaty vaccine).

This Phase III clinical trial aims to assess the safety and tolerability of a booster dose of HIPRA's recombinant protein RBD fusion dimer vaccine as a heterologous booster to subjects who are vaccinated (following local authorities recognized vaccination scheme) at least 91 days before administration of study vaccine. People who had a non-severe or asymptomatic COVID-19 infection will be included. Immunogenicity will also be assessed in a subset of subjects vaccinated with homologous doses of Vaxzevria or Spikevax vaccines and with heterologous doses.

1.4 Rationale for safety and immunogenicity of phase III

Based on the efficacy to prevent COVID-19 demonstrated in phase 3 clinical trials, to date, many COVID-19 vaccines have been granted an emergency use authorization and or have been fully approved. However, the manufacturing challenges posed by the global demand for doses, the need for safe and effective vaccines that are accessible and affordable to diverse populations, the current lack of efficacy data in certain populations (e.g., pediatrics, pregnant women, and autoimmune or immunocompromised individuals), and the emergence of more-transmissible viral variants highlight the need for approval of a larger number of COVID-19 vaccines to achieve vaccine equity worldwide.

Vaccine-induced immune responses are often multifaceted. However, single components (such as antibody responses) may correlate with the level of protection. Also, antibody responses are easier to measure and more clinically useful than cellular responses. Many studies connect neutralizing antibody responses to SARS-CoV-2 with vaccine efficacy, which has been considered a correlate of protection for vaccines against COVID-19. However, no absolute correlate of protection has been established to date for COVID-19 vaccines due to the continuing research and a fast-mutating virus.

Evidence shows that COVID-19 vaccines remain highly effective against COVID-19 related hospitalizations and deaths despite the waning immunity. This waning immunity increases the risk of acquiring a new variants of concern (VOC) despite of the assumption that we are moving from a pandemic to an endemic scenario. For this reason, it is paramount that given the current circulating variants and the current state of the pandemic (even with the establishment of natural immunity in the population and high vaccination rates) that the levels of protection remain high to lessen the burden in healthcare systems and to preserve lives.

Preliminary data from phase IIb of the PHH-1V vaccine has shown potent neutralization capabilities against the delta variant 14 post vaccination (With a geometric mean titre ratio of 1.02 and a 95% confidence interval (CI) between 0.87 and 1.19) comparable to Comirnaty and superior to Comirnaty against beta 14 post vaccination (with a geometric mean titre ratio of 0.54 and a 95% confidence interval (CI) between 0.38 and 0.76) which, along with omicron, are the VOCs that to date, have shown high immune escape properties from the currently approved and or authorized vaccines. Furthermore, the analysis of the samples of the first 30 vaccinated subjects (20 with PHH-1V and 10 with Comirnaty) 14 days post vaccination shows higher levels of neutralizing antibodies against the omicron variant after the administration of the PHH-1V booster dose than after the administration of Comirnaty booster

Considering the public health implications of emerging SARS-CoV-2 VOC on the performance of all COVID-19 vaccines, faster development and approval of new vaccines with a better performance against the VOC is urgent. It is also important to add that to meet global demands, many more vaccines will need to be approved, especially if it is considered that vaccination against COVID-19 will most likely become, at least, a yearly occurrence.

1.5 Risk-Benefit Assessment

1.5.1 Known Potential Risks

Nonclinical studies show that PHH-1V at different antigenic dose levels are well-tolerated in relevant animal species without identified safety risks. Regarding the adjuvant, as with every vaccination and based on previous clinical experience with influenza vaccines containing MF59, local reactions (e.g., pain, tenderness, erythema/redness, and induration/swelling at the injection site) and systemic AEs (e.g., fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhoea) are expected side effects that typically resolve within 24 hours after the vaccination with or without treatment.

As for every vaccine, the occurrence of allergic/anaphylactic reactions cannot be excluded and emergency equipment for the treatment of such reactions must be available at the study site. These events are unexpected and constitute a potential important medical risk. The subjects will be closely observed on site for at least 15 minutes after vaccination.

Vaccine-dependent disease enhancement (VDE) describes a phenomenon in which pre-existing immunity is not enough to neutralise viral infection and may lead to severe disease progression. The risk of antibody-dependent enhancement (ADE) is defined as when the antibodies generated during an immune response recognise and bind to a pathogen, but they are unable to prevent infection. The risks of developing either VDE or ADE is considered low after the administration of PHH-1V. The factors that are postulated to contribute to VDE (based on observations in animal studies for SARS or MERS) are the use of inactivated virus, recombinant wild-type non stabilised S protein, nucleoprotein vaccines, aluminium, or other adjuvants inducing a Th2 bias; by design these factors are not applicable to PHH-1V.

Furthermore, PHH-1V induces a balanced immune response, as observed in nonclinical studies and documented in the IB in which cellular response was also assessed and a Th1 response was observed.

Subjects who experience COVID-19 disease during the study will be followed closely to ensure clinical symptoms and safety data are collected and disease progression is monitored and reported. Developmental toxicity studies have not been performed for HIPRA COVID-19 vaccine. The teratogenicity risk is deemed low. However, given that human data on pregnancies is not yet available, the teratogenic risk associated with PHH-1V administration cannot be ruled out at this moment. For this reason, inclusion of female subjects of childbearing potential age requires use of a highly effective contraceptive measure from the Screening through 8 weeks after vaccination (Day 0) or sexual abstinence beginning at least 21 days before Screening.

In addition, a list of AEs of special interest (AESIs) will be monitored following administration of PHH-1V. If any suspected AESI occurs in a subject who received PHH-1V, a diagnostic workup should be performed by a specialist depending on the type of suspected reaction (e.g., endocrinologist for suspected autoimmune thyroiditis) and this condition will be monitored and documented throughout the study.

PHH-1V has not been investigated in combination with other drugs or vaccines. Given the mechanism of action, which relies on building up an adequate immune response, it is expected that immunosuppressive drugs like steroids may inhibit the desired pharmacological effect of the

induction of a specific immune response against the SARS-CoV-2 RBD of S protein. Similarly, drugs that enhance the immune response like certain cytokines (IFN-α, IL-2) may increase the response to the vaccines, which could theoretically result in increased efficacy, but also in an increased risk of toxicity.

Risks from phlebotomy for blood sampling are well known and minimal. Venepuncture is a routine procedure that the medical community commonly uses to obtain blood samples. Immediate complications may include slight pain during puncture of the skin and, rarely, dizziness and syncope. Additionally, a hematoma may result from the venepuncture, but this has minimal risk. Subject monitoring and aseptic techniques, such as using sterile disposable blood collection apparatuses and adhering to standard medical precautions, reduce any risk to a minimum. The amount of blood to be taken for sampling will not be harmful to the subject's health.

1.5.2 Known Potential Benefits

Subjects receiving PHH-1V may or may not mount a similar immunogenicity response (measured by the increase in the levels of neutralising antibodies) depending on primary vaccination schemes. Data obtained in Phase I/IIa indicate that PHH-1V is a good vaccine candidate in terms of safety and immunogenicity and also data obtained in Phase IIb indicate that HIPRA's heterologous booster produces similar protection in terms of neutralising antibodies than Comirnaty's homologous booster. In terms of safety, HIPRA's booster demonstrated a good safety profile after Comirnaty's primary vaccination scheme. Proceeding with clinical studies Phase III is of public health interest.

More detailed information about the known and expected benefits and risks of PHH-1V can be found in the phase III.

1.5.3 Overall Benefit/Risk Conclusion

In the current pandemic scenario, the two objectives of COVID-19 vaccination are the direct protection of the vaccinated individuals against future infection and the indirect protection of the population (even for those who have not been vaccinated) by reducing overall viral transmission and, thereby, the risk of infection.

The overall benefit/risk assessment for this study is considered acceptable for the following reasons:

1. The selection criteria include provisions to minimise the risk and protect the well-being of subjects in the study. Eligibility will be re-assessed before the administration of the vaccine.
2. Safety will be closely monitored during the study.
3. The data gathered in the phase IIb study has shown that HIPRA's booster efficacy is similar to the already marketed Pfizer's vaccine. Therefore, the benefit of a booster dose with HIPRA, associated with its good safety profile, justifies its assessment as a booster in previously vaccinated subjects in a larger clinical trial where different primary vaccination schemes are included. The safety profile of HIPRA vaccine in Phase IIb is indicating that this vaccine has a low reactogenicity profile and is considered well tolerated between subjects.

2. STUDY OBJECTIVES

2.1 Study Objectives

2.1.1 Primary Objective

- To 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.

2.1.2 Secondary Objectives

- To determine and compare the changes of the immunogenicity measured by pseudovirus neutralisation against Wuhan strain (also known as L strain) and against Omicron, and any other relevant Variants of Concern (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.
- 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.

2.1.3 Exploratory Objectives

- To assess number of subjects with SARS-CoV-2 infections ≥14 days after PHH-1V booster.
- To assess number of COVID-19 severe infections ≥14 days after receiving PHH-1V.
- To evaluate 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. T-cell mediated response will be performed in a subset of 30 subjects.
- To assess 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. Th-1/Th2 T cell mediated response will be performed in a subset of 30 subjects.

3. STUDY PLAN

3.1 Overall Design

This is a phase III, open label, single arm, multi-centre clinical trial that aims to determine safety, reactogenicity, tolerability and immunogenicity of a booster vaccination with a recombinant protein receptor binding domain (RBD) fusion heterodimer candidate against SARS-CoV-2 developed by HIPRA (PHH-1V).

In this phase III study, approximately 3000 eligible subjects who have received:

- One dose of: Comirnaty + COVID-19 infection (before or after the vaccination) or,
- One dose of: Spikevax + COVID-19 infection (before or after the vaccination) or,
- One dose of: Vaxzevria + COVID-19 infection (before or after the vaccination) or,
- One dose of: Janssen + COVID-19 infection (before or after the vaccination) or,
- One dose of: Janssen or,
- Two homologous doses of: Comirnaty + Comirnaty (with or without COVID-19 infection, before, in between or after the two doses) or,
- Two homologous doses of: Spikevax + Spikevax (with or without COVID-19 infection, before, in between or after the two doses) or,
- Two homologous doses of: Vaxzevria + Vaxzevria (with or without COVID-19 infection, before, in between or after the two doses) or,
- Two homologous doses of: Janssen + Janssen (with or without COVID-19 infection, before, in between or after the two doses) or,
- Two heterologous doses of: Comirnaty + Spikevax (or vice-versa) (with or without COVID-19 infection, before, in between or after the two doses) or,
- Two heterologous doses of: Vaxzevria + Comirnaty (with or without COVID-19 infection, before, in between or after the two doses) or,
- Two heterologous doses of: Vaxzevria + Spikevax (with or without COVID-19 infection, before, in between or after the two doses)

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, will be vaccinated with a single booster dose of PHH-1V on Day 0.

For the safety assessment, subjects who have had a COVID-19 infection before, after or in between the two doses of the vaccines can be enrolled.

Immunogenicity will be evaluated in a subset of 8% of the enrolled subjects (250 subjects). The immunogenicity subset will be conformed of subjects vaccinated with:

- Approximately 100 subjects with two doses of Vaxzevria (Adenoviral vector vaccine platform) at least 91 days before PHH-1V booster administration.

    - Approximately in 30 of these 100 subjects, cellular immunogenicity response will be evaluated as an exploratory objective.

- Approximately 100 participants who have received heterologous priming with two doses of different authorised vaccines (Vaxzevria combined with mRNA vaccine) at least 91 days before PHH-1V booster administration.

- Approximately 50 subjects with two doses of Spikevax (mRNA vaccine platform) at least 91 days before PHH-1V booster administration.

Immunogenicity will be evaluated in all the participants of 16 or 17 years old in Spain, never been infected with COVID-19 and vaccinated with:

- Two doses of Pfizer vaccine at least 91 days before PHH-1V booster administration.

For the immunogenicity assessment, subjects who have passed a COVID-19 infection will be excluded.

All subjects will be provided with a paper diary on Day 0 to record solicited local and systemic reactions after vaccination through Day 7. Unsolicited adverse events will be reported through Day 28. SAEs, AESI and MAAE will be reported during all the duration of the study. Subjects will return to the site on Days 14, 91, 182 (final visit for 92% of participants) and 365 (final visit for 8% of participants in the immunogenicity assessment) for blood sample collection and safety follow-up.

Subjects will receive a single booster dose, on Day 0 and will be observed for 15 minutes after vaccination.

A DSMB will be available and may review safety data at any time point during the study as necessary and/or if requested by any of the involved IPs in case of observation of serious adverse events (SAEs).

Once the first 1000 enrolled subjects have completed Day 14 safety assessments, a first interim analysis will be performed to assess the safety of PHH-1V.

Once the first 2500 enrolled subjects have completed Day 14 safety assessments, a second interim analysis will be performed to assess the safety of PHH-1V.

Also, once data of Day 14 of all enrolled subjects in the immunogenicity subset will be available, a third interim analysis will be performed to assess the observed immunogenicity response of the PHH-1V booster dose.

3.2 Study Endpoints

3.2.1 Safety Endpoints

Primary:

- Number, percentage, and characteristics of solicited local reactions and systemic events through Day 7 after vaccination.
- Number, percentage, and characteristics of unsolicited local and systemic adverse events (AEs) through Day 28 after vaccination.
- Number and percentage of serious adverse events (SAEs) through the end of the study.
- Number and percentage of adverse event of special interest (AESI) through the end of the study.
- Number and percentage of medically attended adverse events (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.

3.2.2 Immunogenicity Endpoints

Secondary:

- Neutralisation titre against Wuhan and Omicron strains, and any other relevant VOC in the epidemiologic moment, measured as inhibitory concentration 50 (IC_{50}) 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 geometric mean fold rise (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.

3.2.3 Exploratory Endpoints

Safety

- Number and percentage of subjects with SARS-CoV-2 infections according to COVID-19 infection criteria ≥14 days after PHH-1V booster and throughout the study duration.
- Number and percentage of COVID-19 severe infections ≥14 days after PHH-1V booster and through the end of the study.
- Number and percentage of hospital admissions associated with COVID-19 ≥14 days after PHH-1V booster and through the end of the study.
- Number and percentage of intensive care unit (ICU) admissions associated with COVID-19 ≥14 days after PHH-1V booster and through the end of the study.
- Number and percentage of non-invasive ventilation administration associated with COVID-19 ≥14 days after PHH-1V booster and through the end of the study.
- Number and percentage of deaths associated with COVID-19 ≥14 days after PHH-1V booster and through the end of the study.

Immunogenicity

- 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 will be performed in 30 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 30 subjects.

3.3 Study Termination

This study may be prematurely terminated if there is sufficient reasonable cause, including, but not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or not evaluable
- Regulatory authorities requested

If the study is prematurely terminated, the Investigator will promptly inform study subjects and the authorities as applicable. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule. The Investigator will assure appropriate follow-up for the subjects, as necessary.

The Sponsor will notify regulatory authorities as applicable.

3.4 End of Study

The end of the study is defined as the date of the last visit of the last subject enrolled in the study.

4. STUDY POPULATION

4.1 Number of Subjects

In this Phase III approximately 3000 subjects will be administered with HIPRA's COVID-19 vaccine as a booster dose.

4.2 Inclusion Criteria

The inclusion criteria for enrolling are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study.

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

1. Male or female, ≥ 16 years old at Day 0.
2. Participant must provide consent indicating that she or he understands the purpose and potential risks and is willing and able to participate in the study and comply with all the study requirements and procedures (scheduled visits, laboratory tests, complete diaries, etc). In subjects of 16 and 17 years old, participation in the study must be approved by their legal tutors though informed consent form.
3. Participant who have a SARS-CoV-2 vaccination scheme recognized by the authorities of the country with any of the following vaccines: Comirnaty, Spikevax, Vaxzevria or Janssen vaccine at least 91 days before Day 0. Homologous and heterologous prime vaccinations and non-severe COVID-19 infection are allowed.

   Following local authorities recognized vaccination scheme, subjects can participate in the following cases:

   <u>For safety assessment:</u>

   – two doses of any of the vaccines mentioned above (homologous or heterologous)

   – two doses of any of the vaccines mentioned above (homologous or heterologous) + non-severe COVID-19 infection (before, in between or after the second dose).

   – one dose of any of the vaccines mentioned above + non-severe COVID-19 infection (before or after the dose).

   – one dose of Janssen vaccine.

   NOTE: Non-severe COVID-19 infections are permitted if passed at least 30 days before Day 0 (30 days from the day of COVID-19 infection confirmation via PCR or RAT).

For immunogenicity assessment:

- Two doses of Vaxzevria with no previous COVID-19 infection
- Two doses of Spikevax with no previous COVID-19 infection
- Two heterologous doses of different authorised vaccines (Vaxzevria combined with mRNA vaccine) with no previous COVID-19 infection
- In subjects of 16 or 17 years old in Spain, two doses of Comirnaty with no previous COVID-19 infection

4. Participants may have underlying illnesses if are stable and well-controlled according to the investigator judgment. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months prior to screening and for which neither a significant change in treatment or hospitalization for worsening is expected in the near future.
5. Participant is willing to avoid receiving live attenuated vaccines (licensed) within 4 weeks before screening or after receiving any study vaccine, or other not live vaccines (licensed) within 14 days before and after receiving any study vaccine.
6. Participant agrees not to donate blood, blood products and bone marrow at least 3 months before and after vaccination.
7. Contraceptive use should be consistent with local regulation for participants in clinical trials.
    a. Female participants of childbearing potential [defined as any female who has experienced menarche and until becoming postmenopausal* (defined as having ≥ 12 months amenorrhea prior to screening without an alternative cause) unless is surgically sterile]:
        i. Have a negative pregnancy test on the day of screening and day 0 prior to vaccination.
        ii. Use of any acceptable contraceptive method that should be started on day 0 and until 8 weeks after vaccination. Acceptable contraceptive methods are:
            1. Hormonal contraception (progestogen-only or combined): oral, injectable or transdermal (patch).
            2. Intrauterine device.
            3. Vasectomized partner (the vasectomized partner should be the sole partner for that participant).
            4. Sexual abstinence **, as a form of contraception, is acceptable if in line with the participant's lifestyle.
            5. Condom

b. Male participants:

i. Vasectomized participants.

ii. Refrain from donating sperm for at least 28 days after day 0.

iii. Agree to use a male condom may be considered in women of childbearing potential partners, from screening and for at least 28 days after day 0.

iv. Sexual abstinence**, as a form of contraception, is acceptable if in line with the participant's lifestyle.

* A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

** Sexual abstinence is considered an effective method only if defined as refraining from heterosexual intercourse from screening until 8 weeks after receiving the vaccine for female participants and from screening until 4 weeks for male participants. Periodic abstinence (e.g., calendar, ovulation) and withdrawal are not acceptable methods of contraception.

4.3 Exclusion Criteria

The exclusion criteria for enrolling are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study.

Participants meeting any of the following criteria will be excluded from the study:

8. History of anaphylaxis to any prior vaccine.

9. Previous severe SARS-CoV-2 infections are not permitted.
   Note: Severity explained as any episode of COVID-19 requiring ≥ 24hrs of hospitalization.

10. Participant received or plans to receive:
    a. Live attenuated vaccines (licensed) within 4 weeks before or after receiving any study vaccine.
    b. Other not live vaccines (licensed) within 14 days before and after receiving any study vaccine

11. Pregnancy or breast-feeding at screening or Day 0 (vaccination time-point) or willingness/intention to become pregnant during the study.

Medical conditions

12. Participant has a clinically significant acute illness (this does not include minor self-limited illness such as mild diarrhoea) or fever (temperature ≥38º C (100.4ºF) at screening or within 48 hours prior to the planned vaccination (Day 0).

13. Participant had a surgery requiring hospitalization (defined as inpatient stay for > 24 hours) before vaccination and he/she has not received the hospital discharge at day 0; or has a surgery requiring hospitalization planned within 12 weeks after study vaccine administration.

14. Participant has any active malignancy even if under treatment except for (at the discretion of the investigator):
    c. Non-melanoma adequately treated skin cancer without evidence of disease
    d. Adequately treated uterine cervical carcinoma in situ without evidence of disease
    e. Adequately treated anal carcinoma in situ without evidence of disease
    f. Localized prostate cancer

15. Participant has ongoing severe and non-stable psychiatric condition likely to affect participation in the study (e.g., ongoing and non-stable severe depression, recent suicidal ideation, severe eating disorder, psychosis)

16. Participant has a problematic or risk use of substances including alcohol (except tobacco) that can compromise the study follow-up. Problematic or risk use of psychoactive substances is understood as the one that causes evident damage, whether it is dependence or any other physical, psychological, or social problem or that carries a high risk of suffering these damages. The negative consequences that consumption causes to third parties could be included.

17. Participant has a bleeding disorder (e.g., factor deficiency, platelet disorder), blood dyscrasia, or continuous use of anticoagulants or has any condition that in the opinion of the investigator contraindicates intramuscular injections or frequent phlebotomy. The use of ≤ 325mg of aspirin or ≤ 75mg of clopidogrel per day as prophylaxis is permitted but not combined.

18. Participant has abnormal function of the immune system as in autoimmune diseases, asplenia, recurrent infections or congenital/acquired immunodeficiency. Participants with stable clinical conditions (e.g., autoimmune thyroiditis, celiac disease, type 1- diabetes) under non-immune-modifying treatment (e.g., hydroxychloroquine in lupus erythematosus, rituximab in psoriasis, cyclosporine in atopic dermatitis) and participants living with HIV with CD4 T cell count ≥ 400 cells/mm3 under stable antiretroviral treatment with a fully suppressed viral load ≥ 1 year are permitted [one or two non-consecutives blips (HIV viral load ≤ 500 viral copies) are permitted].

19. Participants have clinically significant and unstable cardiovascular, respiratory, hepatic, neurological, gastrointestinal, renal, or any other medical disorder as judged by the investigator and defined as disease requiring hospitalization or addition of new treatments or major dose adjustments within 3 months before screening.

Prior/Concomitant Therapy and Clinical Study Experience.

20. Chronic or recurrent administration (during at least 14 days) of systemic immunosuppressant medication (defined as given by oral or parenteral routes) within 12 weeks preceding the planned administration of study vaccine (Day 0). The use of a prednisone dose < 10mg per day or equivalent, ocular, topical, inhaled and nasal corticoids are allowed.

21. Subject has received immunoglobulins and/or blood-derived products 12 weeks prior vaccination (Day 0) or expects to receive them during the study.

22. Participant received any immunotherapy (monoclonal antibodies, plasma) aimed to prevent or treat COVID-19 within 90 days preceding the planned administration of study vaccine.

23. Participation in any research involving an investigational product (drug, biologic, device) within 12 weeks prior to vaccination and during the study.

24. Participant has donated ≥ 450ml of blood products within 12 weeks before screening.

25. Participant has any medical condition and/or finding that in the investigator opinion might increase participant risks, interfere with the study or impair interpretation of study data.

4.4 Subject Identification and Registration

Subjects who are candidates for enrolment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria (see Sections 4.2 and 4.3) have been satisfied and that the subject is eligible for participation in this clinical study.

Once a subject is determined to be eligible by the clinical study site, the subject will be registered and assigned a sequential and unique patient number. Once a subject number has been assigned, it cannot be reused.

No subject may be enrolled or begin treatment prior to registration and assignment of a subject number.

4.5 Withdrawal and Replacement of Subjects

A subject may discontinue study participation for any of the following reasons:

- If he/she is unwilling or unable to meet the protocol requirements.
- If the subject or the Investigator considers it best to end his/her participation in the study.
- Lost to follow-up.
- Withdrawal of consent from the subject or legal tutors.

All subjects have the right to withdraw their consent at any time during the study without prejudice to them.

If possible, the subject withdrawing consent or discontinuing the study should complete an early termination visit.

The date and reason for discontinuation or consent withdrawal will be documented in the eCRF.

Subjects who withdraw or discontinue from the study will not be replaced.

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Reasonable efforts will be made, and documented, by site personnel to contact the subject to continue with their follow-up before determination that the subject is lost to follow-up.

5. STUDY TREATMENTS

5.1 Study Drug Supply and Storage

HIPRA SCIENTIFIC S.L.U. is responsible for manufacturing PHH-1V in accordance with Good Manufacturing Practice.

PHH-1V will be supplied in a vial containing 10 doses of 0.5 ml (40 µg), ready to use. There is no need to dilute or reconstitute. PHH-1V will be shipped to clinical sites and must be stored in a refrigerator (between 2ºC and 8ºC). Vials must not be frozen.

5.2 Study Drug Dose and Administration

In Phase III, subjects will receive a single dose of PHH-1V (40 µg) on Day 0, administered via IM injection into the deltoid muscle, preferably into the nondominant arm. Refer to the Laboratory Manual for details of PHH-1V administration.

5.3 Method of Assigning Subjects to Treatment

All subjects will be administered with a PHH-1V booster dose.

Subjects will be assigned a unique Subject ID and will be identified only by the Subject ID number to protect confidentiality. The site will keep its own subject identification log to match the Subject ID number with the subject's personal data, in accordance with applicable regulatory data protection requirements.

5.4 Blinding, Packaging, and Labelling

5.4.1 Packaging and Labelling

PHH-1V will be packaged, labelled and supplied by the Sponsor in accordance with European regulation (as set in Annex VI of the Regulation EU No 536/2014).

5.5 Duration of Subject Participation

For the Phase III of the study, the study consists of a Pre-screening visit (by phone) maximum at -28 days before the Screening/Vaccination Visit and a Follow-up Period of 182 days in the safety assessment subset and 365 days in the immunogenicity assessment subset. Therefore, an individual subject may participate in this study for up to 7 or 13 months.

5.6 Assessment of Treatment Compliance

All doses of PHH-1V will be administered at the study site by site personnel. The time and date of dose administration will be recorded in the eCRF. No other assessments of compliance will be conducted.

5.7 Study Drug Accountability

During the study, investigational product accountability will be monitored by the pharmacy receipt, dispensing log, and accountability log (that includes all the information related to the investigational product dispensed and returned).

The site personnel who administer the injection will be responsible for ensuring that the return of the used vials is recorded in the accountability log at the end of the immunisation.

For the Phase III, study drug accountability will be monitored by the CRA.

At the completion of the study, used and unused vials of the investigational product will be destroyed onsite by pharmacy staff or returned to the supplier according to local pharmacy guidelines and applicable regulations. Authorisation must be granted by the Sponsor before destruction takes place. Final disposition will be registered in the disposition records.

5.8 Prior and Concomitant Treatment

Prior medications will be defined as those taken within 90 days before Screening and including medications taken through Day -1. Concomitant medications will be defined as those started on or after Day 0. All prior and concomitant medications will be recorded on the eCRF and will include the name of the drug, dose, route, and start and stop dates as well as the reason or indication for administration.

Concomitant medications will include prescription drugs, over-the-counter drugs, herbal medicines, vitamins, and supplements.

Medications prohibited during the Phase III include anticoagulants, immunosuppressants, or other immune-modifying treatments within 2 months before Day 0 and throughout the study.

Medications prohibited during the study include:

- A continuous use of anticoagulants, except the use of ≤ 325mg of aspirin or ≤ 75mg of clopidogrel per day (not combined), that are allowed.
- Systemic immunosuppressant medication (defined as given by oral or parenteral routes) within 90 days preceding the planned administration of study vaccine (Day 0), except the use of prednisone (<10 mg/day) or equivalent, via ocular, topical inhaled and nasal corticoids, that are allowed.
- Immunoglobulins or other blood-derived products within 90 days before Day 0 and throughout the study.
- Any other experimental product against COVID-19 (drug, biologic, device) within 90 days before Day 0 and throughout the study.

6. STUDY ASSESSMENTS

6.1 Schedule of Events

Table 3. Schedule of Events (Safety subset)

Visit number	1	2	3	4	5/ETV	USC visit
Visit description	Pre-Screening	Screening and Baseline Vaccine	Safety assessment	Safety assessment	Safety assessment	As required
Day (+/-days)	-28 to -1	0	14 (-3/+3)	91 (±15)	182 (±15)	-
Informed consent[a]		x				
Eligibility criteria	x	x				
Medical history		x				
Demographics[b]		x				
Physical examination		x	x	x	x	
Vital signs[c]		x	x	x	x	
Concomitant medication		x	x	x	x	
Vaccination		x				
Telephone or on-line[d]	x					
Subject Diary provided/ collected[e]		x	x			
Adverse events		x	x	x	x	
Pregnancy test[f]		x				
Haematology[g]		x	x	x	x	
Biochemistry[h]		x (10 mL)	x (10mL)	x (10 mL)	x (10 mL)	

Visit number	1	2	3	4	5/ETV	USC visit
Visit description	Pre-Screening	Screening and Baseline Vaccine	Safety assessment	Safety assessment	Safety assessment	As required
Day (+/-days)	-28 to -1	0	14 (-3/+3)	91 (±15)	182 (±15)	-
Serum for binding antibody assays[i]		x (10 mL)	x (10 mL)			
Serum for neutralisation assays[i]		x (10 mL)	x (10 mL)			
TOTAL BLOOD		**30 mL**	**30 mL**	**10 mL**	**10 mL**	**Total 80ml**

Abbreviations: BUN = blood urea nitrogen; CBC = complete blood count; ETV = early termination visit; PBMC = peripheral blood mononuclear cells; PCR = polymerase chain reaction; USC = unscheduled visit.

a Informed consent will be provided via email to the participant after the Pre-Screening and once the study is approved by the ethics committee and competent authorities. ICF will be signed and dated at Baseline Vaccine visit.

b Demographics will include gender, race, ethnicity, and age.

c Vital signs will include pulse, blood pressure, temperature, and oxygen saturation.

d Telephone or on-line visit will be performed at pre-screening to assess eligibility criteria and to ask for email address to send the ICF.

e A paper Subject Diary will be provided to all the subjects to collect solicited local and systemic reactions after vaccination. The Subject Diary will be collected at the Day 14 visit.

f Urine pregnancy test to be performed at the study site, only for women of childbearing potential on Day 0. A negative urine pregnancy test should be verified before vaccination.

g Haematology will include CBC, haemoglobin, and platelets.

h Biochemistry will include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, BUN or urea (urea can be measured), creatinine, glucose, potassium, sodium, and total protein. 10 mL of blood will be required for haematology and biochemistry.

i Additional samples of blood will be extracted to obtain serum of all the subjects at baseline and Day 14 for future further analysis if required. These subjects will still participate in the safety subset but extra samples will be taken.

Table 4. Schedule of Events (Immunogenicity subset)

Visit number	1	2	3	4	5	6/ETV	USC visit
Visit description	Pre-Screening	Screening and Baseline Vaccine	Immunogenicity and safety assessment	Immunogenicity and safety assessment	Immunogenicity and safety assessment	Immunogenicity and safety assessment	As required
Day (+/-days)	-28 to -1	0	14 (-3/+3)	91 (±15)	182 (±15)	365 (±15)	-
Informed consent[a]		x					
Eligibility criteria	x	x					
Medical history		x					
Demographics[b]		x					
Physical examination		x	x	x	x	x	
Vital signs[c]		x	x	x	x	x	
Concomitant medication		x	x	x	x		
Vaccination		x					
Telephone or on-line [d]	x						
Subject Diary provided/ collected[e]		x	x				
Adverse events		x	x	x	x	x	
Pregnancy test[f]		x					
SARS-CoV-2 PCR[g]		x					
Serology[h]		x					

Visit number	1	2	3	4	5	6/ETV	USC visit
Visit description	Pre-Screening	Screening and Baseline Vaccine	Immunogenicity and safety assessment	Immunogenicity and safety assessment	Immunogenicity and safety assessment	Immunogenicity and safety assessment	As required
Day (+/-days)	-28 to -1	0	14 (-3/+3)	91 (±15)	182 (±15)	365 (±15)	-
Haematology[i]		x	x	x	x		
Biochemistry[j]		x (10 mL)	x (10mL)	x (10 mL)	x (10 mL)		
Serum for binding antibody assays		x (10 mL)	x (10 mL)	x (10 mL)	x (10 mL)	x (10 mL)	
Serum for neutralisation assays		x (10 mL)	x (10 mL)	x (10 mL)	x (10 mL)	x (10 mL)	
PBMCs for cellular[k] immunology assays		x (60 ml)	x (60 ml)				
TOTAL BLOOD		**30 / 90[k] mL**	**30 / 90[k] mL**	**30 mL**	**30 mL**	**20 mL**	**Total 140/260[k] ml**

Abbreviations: BUN = blood urea nitrogen; CBC = complete blood count; ETV = early termination visit; PBMC = peripheral blood mononuclear cells; PCR = polymerase chain reaction; USC = unscheduled visit.

a Informed consent will be provided via email to the participant after the Pre-Screening and once the study is approved by the ethics committee and competent authorities. ICF will be signed and dated at Baseline Vaccine visit.

b Demographics will include gender, race, ethnicity, and age.

c Vital signs will include pulse, blood pressure, temperature, and oxygen saturation.

d Telephone or on-line visit will be performed at pre-screening to assess eligibility criteria and to ask for email address to send the ICF.

e A paper Subject Diary will be provided to all the subjects to collect solicited local and systemic reactions after vaccination. The Subject Diary will be collected at the Day 14 visit.

f Urine pregnancy test to be performed at the study site, only for women of childbearing potential on Day 0. A negative urine pregnancy test should be verified before vaccination.

g SARS-CoV-2 PCR only performed in those individuals with primovaccination with two doses of Vaxzevria

h Serology only performed in those individuals with primovaccination with two doses of Vaxzevria to check if they had had a previous COVID-19 infection
i Haematology will include CBC, haemoglobin, and platelets.
j Biochemistry will include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, BUN or urea (urea can be measured), creatinine, glucose, potassium, sodium, and total protein. 10 mL of blood will be required for haematology and biochemistry.
k Only for a subset of 30 subjects with primovaccination with two doses of Vaxzevria included in the cellular immunogenicity.

6.2 Immunogenicity Measurements

Handling of samples for immunogenicity measurements for the subjects in the immunogenicity subset, will be detailed in the Laboratory Manual. Also, it will be detailed the handling of samples in the safety subset at baseline and D14.

6.2.1 Antibody Binding Immunity Assays

For the 250 subjects in the immunogenicity subset, immunoassay for the in vitro quantitative determination of antibodies to the SARS-CoV-2 S protein RBD in human serum will be used.

The assay uses a recombinant protein representing the RBD of the S antigen in a double-antigen sandwich assay format, which favours detection of high affinity antibodies against SARS-CoV-2. The test is intended as an aid to assess humoral immune response to the SARS-CoV-2 S protein.

Antibody binding immunity assays will be conducted at LABORATORIOS HIPRA, S.A.

Electrochemiluminescence immunoassay (ECLIA) will be conducted with a commercial kit. Specimen type: serum collected using standard sampling tubes; Li-heparin, K2-EDTA-, K3-EDTA-, and sodium citrate plasma.

6.2.2 Neutralising Antibody Immunity

6.2.2.1 Pseudovirus

Neutralising antibodies will be assessed for the 250 subjects in the immunogenicity subset. HIV reporter pseudoviruses expressing SARS-CoV-2 S protein and Luciferase will be generated. pNL4-3.Luc.R-.E- will be obtained from the NIH AIDs repository[15].

SARS-CoV-2 SctΔ19 will be generated (Geneart) from the full protein sequence of SARS-CoV-2 spike with a deletion of the last 19 amino acids in C-terminal[16], human-codon optimised and inserted into pcDNA3.1-TOPO.

Expi293F cells will be transfected using Expifectamine Reagent (Thermo Fisher Scientific, Waltham, MA, USA) with pNL4-3.Luc.R-.E- and SARS-CoV-2.SctΔ19 at a 8:1 ratio, respectively. Control pseudoviruses will be obtained by replacing the S protein expression plasmid by a VSV-G protein expression plasmid.

Supernatants will be harvested 48 hours after transfection, filtered at 0.45 µm, frozen and titrated on HEK293T cells overexpressing WT human ACE-2 (Integral Molecular, USA). For neutralisation assay, 200 $TCID_{50}$ of pseudovirus supernatant will be preincubated with serial dilutions of the heat-inactivated serum samples for 1 hour at 37°C and then added onto ACE2 overexpressing HEK293T cells. After 48 hours, cells will be lysed with Britelite Plus Luciferase reagent (Perkin Elmer, Waltham, MA, USA). Luminescence will be measured for 0·2 s with an EnSight Multimode Plate Reader (Perkin Elmer).

Neutralisation capacity of the serum samples will be calculated by comparing the experimental RLU calculated from infected cells treated with each serum to the max RLUs (maximal infectivity calculated from untreated infected cells) and min RLUs (minimal infectivity calculated from

uninfected cells), and expressed as percent neutralisation: %Neutralisation = (RLUmax–RLUexperimental)/(RLUmax–RLUmin)*100. All IC_{50} values will be expressed as reciprocal concentration.

Neutralisation antibody immunity assays (PBNA) will be conducted at Hipra in Parc Científic i Tecnològic of the Universitat de Girona. Method is duly validated.

6.2.3 T-cell Mediated Immunity

T-cell mediated immunity will be assessed by measurement of whole PBMC stimulation by ELISpot at different timepoints and only for a subset of 30 subjects with two doses of Vaxzevria vaccine, and no infection of COVID-19.

To evaluate the SARS-CoV-2-specific T-cell responses, 6 peptide pools of overlapping SARS-CoV-2 peptides each encompassing the SARS-CoV-2 regions S (2 pools), RBD, nucleoprotein, membrane, and envelope will be used.

T-cell responses will be analysed as present or absent and reported as the number and proportion of subjects responding to each peptide pool and for each time point. The total ELISpot responses will be described as the sum of $SFC/10^6$ PBMC of all positive responses per peptide pool, after subtraction of background. Each subject will be classified as a responder if there is at least 1 positive against any of the SARS-CoV-2 peptides pools at any time, and non-responder if ELISpot responses are all negative.

In addition, intracellular cytokine staining (ICS) based T-cell assay will be determined at different timepoints. ICS assays will include Th1/Th2 pathways (e.g., IL-2, IL-4, TNFα, INFγ) CD4 and CD8 T cell determinations using flow cytometry.

An ICS will be considered positive if the percentages of cytokine-positive cells in the stimulated samples are 3 times more than the values obtained in the unstimulated controls and if the background-subtracted magnitudes are higher than 0.02%. Each subject will be classified as a responder if there are at least 1 positive IFN-γ ICS response against any of the SARS-CoV-2 peptide pools at determined timepoints and as a non-responder if responses at these timepoints are all negative.

T-cell mediated response analysis will be conducted at the IDIBAPS of Hospital Clínic of Barcelona, Spain, and IRSICaixa del Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain.

6.2.4 Biological samples for future studies

All the subjects in the study will be asked to provide consent for the use of the remaining samples obtained during the safety or immunologic assessment for future studies. If the subject consents, leftover samples will be kept and sent to a sample collection located in HIPRA SCIENTIC, S.L.U. (Amer, Girona) for future studies related to COVID-19.

If the subject does not consent the storage of the remaining samples for their use in future studies, samples will be destroyed once they are analysed for the purpose of this study in compliance with the law 14/2007 Biomedical Research.

Samples obtained from screening failures will be also kept and sent to the sample collection if the subjects have consented their use for future studies.

Subjects will be informed that biological samples and their associated data stored at the central lab in HIPRA SCIENTIC, S.L.U. will be used for biomedical research in the field of COVID-19 infection. These investigations must be previously approved by an Ethics Committee.

Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

6.3 Safety Measurements

6.3.1 Demographics and Medical History

Demographics will include age, gender, race and ethnicity. Prior COVID-19 vaccination schemes (and brand) will be recorded as prior medications (brand of the dose/s + last dose date). Previous COVID-19 infections will also be recorded indicating the date of the RAT or PCR positive test.

6.3.2 Physical Examination

A complete physical examination will be done at each presential study visit.

6.3.3 Vital Signs

Vital signs will be recorded at each study visit before blood samples are collected and will include pulse, blood pressure, body temperature, and oxygen saturation. Abnormal values of vital signs will be recorded as well in eCRF but indicated non clinically significant as per investigator criteria.

Blood pressure and pulse measurements will be assessed while the subject is in a supine position and at rest for 5 minutes. The same method of measurement will be used for the subject at all visits.

6.3.4 Clinical Laboratory Tests

Details of sample collection, storage, and handling will be provided in the Laboratory Manual. Blood samples to determine haematology and biochemistry tests will be analysed at the local laboratory of each study site. After analysis the samples will be destroyed locally.

The following parameters will be evaluated:

- Haematology: white blood cell count, haemoglobin, platelet count.
- Biochemistry: alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN) or urea (as per site common procedures), creatinine, glucose, potassium, sodium, and total protein.
- Urine pregnancy test (only for women with childbearing potential; to be performed locally at the study site on Day 0).
- COVID-19 serology test: only for the participants in the immunogenicity subset and with two doses of AZ vaccine (n∼100), a sample will be taken and sent to HIPRA's Central Laboratories, where a serology will be performed to determine whether these participants have had a previous COVID-19 infection. Even that a positive result is obtained, the participant will remain in the immunogenicity subset.

6.3.5 Subject Diary

All subjects will be dispensed with a Subject Diary to register all the local and systemic reactions from the time of vaccination until 7 days post-vaccination; the diary will be collected at the Day 14 visit. The Subject Diary will collect the following site of injection reaction information:

- Pain
- Tenderness
- Erythema/redness
- Induration/swelling

And the following systemic solicited events:

- Fever
- Chills
- Nausea
- Malaise
- Vomiting
- Diarrhoea
- Headache
- Fatigue
- Muscle pain
- Joint pain

6.3.6 Telephone Contact

For Phase III, subjects will be contacted by the site staff on a pre-screening visit via telephone or on-line to assess some of the eligibility criteria.

6.3.7 COVID-19 Infection

6.3.7.1 COVID-19 Infection

Asymptomatic subjects in close contact with a subject known with COVID-19 post-booster should be assessed with an antigen test (RAT) or Reverse Transcription Polymerase Chain Reaction (RT-PCR) following the standard procedures in the health system. If positive, the patient should contact the study team to inform them about the test. It will be included in the CRF but only confirmed COVID-19 cases happening after ≥14 days post-booster will be considered as an AESI.

Symptomatic cases of COVID-19 happening post-booster should be assessed with an antigen test (RAT) or RT-PCR following the standard procedures in the health system. If positive, the patient should contact the study team to inform them about the test and the symptoms. The investigator will follow up the medical evolution by phone and recommend medical assistance in the hospital

if required. All this information will be included in the CRF but only confirmed COVID-19 cases happening after ≥14 days post-booster will be considered as an AESI.

6.3.7.2 Severe COVID-19 Infection

Severe cases of COVID-19 after booster will be assessed. Severe cases are considered as any episode of COVID-19 requiring ≥ 24hrs of hospitalization.

All this information will be included in the CRF and severe COVID-19 infections will be considered as SAE. However, only confirmed COVID-19 cases happening after ≥14 days post-booster, regardless of severity, will be taken into account for the exploratory endpoints' analysis mentioned in section 3.2.3.

6.3.8 Adverse Events

Adverse events will be coded by preferred term (PT) and system organ class (SOC) using NCI Common Terminology Criteria for Adverse Events. CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade) (version 5.0 of 27Nov2017) (US Department of Health and Human Services).

6.3.8.1 Definitions, Documentation, and Reporting

Adverse event (AE): an AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious adverse event (SAE): an SAE is any untoward medical occurrence that at any dose: Results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a suspected transmission of any infectious agent via a medicinal product, is medically important (according to the treating physician), other important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (e.g., death from anaphylaxis), the event must be reported as a SUSAR even if it is a component of the study endpoint (e.g., all-cause mortality).

Any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalisations for the following: hospitalisations not intended to treat an acute illness or AE (e.g., social reasons

such as pending placement in long-term care facility), surgery or procedure planned before entry into the study.

Adverse reaction (AR): An AR is an AE suspected to be causally related to a medicinal product.

An AR is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out). Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include overdose, misuse, abuse, and medication errors.

Unexpected Adverse Reaction (UAR): Any adverse reaction, whose nature or severity of which is not consistent with the applicable product information (e.g., IB for an unauthorised investigational product or Summary of Product Characteristics for an authorised product).

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both serious and unexpected.

Adverse events of special interest (AESI): An AE for which additional data is required. AESIs in this study will include potential immune-mediated medical conditions (see Appendix 1).

Medically attended adverse events (MAAEs): An AE that leads to hospitalisation, an emergency room visit, or an unscheduled visit to medical personnel for any reason.

6.3.8.2 Assessment of Intensity and Causality

An assessment of intensity will be made using the general categorical descriptors outlined in the toxicity grading scale for healthy adult and adolescent subjects enrolled in preventive vaccine clinical studys[17].

For AEs not identified in the grading table, the following guidelines will be followed:

- Grade 1 – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 – Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL (Activities of Daily Living) *.
- Grade 3 – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 – Life-threatening consequences; urgent intervention indicated.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An assessment of causality will be made based on the following criteria:

- Related: The temporal relationship of the AE with the study drug indicates a possible causal relationship and it cannot be explained by factors such as the patient's clinical condition or therapeutic interventions.
- Unrelated: The temporal relationship of the AE with the study drug indicates an unlikely causal relationship, or other factors (concomitant medication or conditions) or other therapeutic interventions provide a satisfactory explanation for the AE.

6.3.8.3 Procedures for AE and SAE Reporting

Adverse events will be 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 will be recorded in the eCRF.

The following will be recorded for each event: indication, intensity (grade 1, 2, 3 and 4), duration (start and stop dates), severity, causal relationship with the intervention vaccine (according to the previously attributability criteria), actions taken, and outcome. The Investigator should report any underlying condition when a surgical or medical procedure is required as the event term, and the procedure as an action taken. For a pre-existing condition that has worsened in terms of severity or frequency, the meaning of the change should be specified (e.g., worsening of hypertension).

If the AE is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose) and the Investigator shall notify Sponsor or whoever assumes the tasks delegated by the Sponsor, within 24 hours from the time of knowing about the event. The reporting circuit and form will be the same as for the SAE.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as an SAE requiring expedited notification (see Section 6.3.8.4.1). Adverse events should be followed until the event resolves or stabilises at a level acceptable to the Investigator.

Serious AEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs: the event resolves, the event stabilises, the event returns to baseline, if a baseline value/status is available, the event can be attributed to agents other than the study drug or to factors unrelated to study conduct, it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

6.3.8.4 Expedited Reporting of SAEs, AESIs, MAAEs, and SUSARS

6.3.8.4.1 Serious Adverse Events

Any SAE due to any cause, whether or not related to the study medication, occurring from the time of signing the informed consent and up to the last visit of the study, must be reported within 24 hours of occurrence or during the next 24 hours after the Investigator becomes aware of the event. It will only be included in the safety database SAEs occurring in patients that are part of the safety analysis group.

The initial report of SAE should be as complete as possible, including details of the current disease and SAE and assessment of the causal relationship between the SAE and the investigational product. Reporting will be made using the Serious Adverse Event Report Form within 24 hours from first knowledge by the Investigator, completing all information on the form in the following two days.

Serious Adverse Event Report Forms will be sent by email to Asphalion S.L., Veristat, LLC., and the Sponsor.

The information missing at the time of the initial report must be reported in the SAE/AESI/MAASE follow-up form. All documentation relating to the event should be included (e.g., additional laboratory tests, hospital records, death certificates). Additional information may be requested by the study coordinator, the Ethics Committee, or regulatory authorities.

In the case of a medication error or if the investigational medicinal product is used outside the provisions of the protocol, while conducting the study, the Investigator shall notify Asphalion S.L. within 24 hours from the time of knowing about the event using the Serious Adverse Event Report Form.

6.3.8.4.2 Adverse Events of Special Interest and Medically Attended Adverse Events

If an AESI or MAAE occur, the Investigator will notify the Asphalion S.L. within 24 hours from the time of knowing about the event.

6.3.8.4.3 Suspected Unexpected Serious Adverse Reaction

Asphalion S.L. will report any event that is serious and unexpected that may be related to the investigational product to the competent authority in Spain (AEMPS and to the Autonomous Community, if applicable), Portugal and Italy through Eudravigilance in accordance with local regulations.

Reporting will be made using a specific SUSAR form.

The maximum deadline for reporting will be 15 calendar days from the time the Investigator is aware of the SUSAR. For SUSARs causing death or that are life-threatening for the subject, the maximum reporting time will be 7 calendar days from the time the Investigator is aware of them. This information will be completed, when possible, in the following 8 days.

6.3.8.5 Pregnancy

Pregnancy will not be recorded as an AE. However, the Investigator must notify Asphalion S.L. of any pregnancy that occurs during the study within 24 hours of knowing about the event.

To ensure subject safety, female subjects will be asked for consent to be followed up to determine pregnancy and delivery outcome. If the subject consents, a follow-up of the pregnancy to document its outcome and the state of health of the new-born will be completed. If the pregnancy outcome meets the SAE criteria, or if the new-born presents an SAE, the procedures for reporting an SAE will be followed.

The report shall be made using the specific form for the notification of pregnancy, which must be sent by fax or email.

7. STATISTICAL PROCEDURES

7.1 Sample Size Estimation

No formal sample size calculation has been performed for this phase III study.

A sample size of 3000 participants is proposed.

This sample size together with those participants enrolled in Phase IIb fulfil the requirements of the minimum safety population established in the EMEA/CHMP/VWP/164653/05 Rev. 1, 2018; FDA CBER, 2020.

Furthermore, another important aspect has been considered to decide the sample size is that safety profile of PHH-1V vaccine is based on a well-known manufacturing platform (recombinant protein produced in CHO cells) and has a not novel adjuvant (MF59C.1) widely used in Flu vaccines for many years. HIPRA PHH-1V is a recombinant protein vaccine. This type of vaccines has been used in the pharmaceutical industry during years, starting in the mid-1980s with the hepatitis B vaccine, now a routine vaccination around the world.

Overall, we consider that the sample size proposed is considered adequate for this specific kind of vaccine.

7.2 Populations for Analysis

The following analyses populations are included in this study:

- **Enrolled** (EP): All subjects who have signed the Informed Consent Form (ICF).
- **Intent-to-treat** (ITT): All subjects who are randomised, regardless of the subjects' treatment status in the study.
- **Modified Intent-to-treat** (mITT): All subjects in the ITT who meet the inclusion/exclusion criteria, received a dose of study drug and did not tested positive for COVID-19 within 14 days of the receiving study drug
- **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 following primary vaccination schemes.
- **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 their primary vaccination schemes.

7.3 Procedures for Handling Missing, Unused, and Spurious Data

In general, missing data will not be imputed. For the continuous variables related to the immunogenicity endpoints and T-cell, zero values will be imputed to half of the lower limit of quantification (LLOQ). If other parameters are deemed appropriate for imputation, information will be detailed in the Statistical Analysis Plan (SAP).

7.4 Interim Analysis

Once the first 1000 enrolled subjects have completed Day 14 safety assessments, a first interim analysis will be performed to assess the safety of PHH-1V.

Once the first 2500 enrolled subjects have completed Day 14 safety assessments, a second interim analysis will be performed to assess the safety of PHH-1V.

Also, once data of Day 14 of all enrolled subjects in the immunogenicity subset will be available, a third interim analysis will be performed to assess the observed immunogenicity response of the PHH-1V booster dose.

7.5 Statistical Methods

7.5.1 General Methods

No formal statistical analysis will be performed on the primary and secondary endpoints.

Descriptive analysis will be performed for variables overall by time-point. Categorical variables will be presented by means of number of cases and frequencies (%) and continuous variables will be 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 will be presented as frequencies and percentages. 95% confidence intervals (CI) will be also provided, as appropriate.

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

Further details on methodology for summary and statistical analyses of the data collected in this study will be detailed in the study SAP.

7.5.2 Disposition of Subjects

Subject disposition will be tabulated and descriptively summarised for all enrolled subjects. Analysis populations will be summarised. Entry criteria and protocol deviations will be listed.

7.5.3 Baseline Comparisons

7.5.4 Demographic and baseline data will be tabulated using the safety population. No statistical comparisons will be performed for any of the baseline characteristics. Safety Analysis

Solicited local reactions and systemic events from Day 0 through Day 7 after dosing will be presented by intensity and cumulatively across severity levels.

Unsolicited local and systemic reactogenicity adverse events from Day 0 through Day 28 after boost vaccination will be presented by intensity and cumulatively across severity levels.

Adverse Events and SAEs will be categorised according to NCI Common Terminology Criteria for Adverse Events. CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

Summaries of local and systemic solicited AEs will be presented by SOC and PT for events occurring through Day 7. In addition, AEs will be summarised by maximum intensity and causal relationship to study drug. A separate summary of AESIs, including potentially immune-mediated medical conditions (PIMMCs) and MAAEs will be reported.

Laboratory parameters changing to grades 3 or 4, will be summarised as actual values and change from baseline over time. Shift tables from Baseline to worst on-study value and Baseline to Days 14, 91, 182 and 365 (if applicable) value will be reported.

The safety analyses will be performed using the safety population (SP).

7.5.5 Immunogenicity analysis

For each subset of subjects included in the immunogenicity population, the following data will be presented:

- The neutralizing antibody titre and the total binding antibodies measured for each individual sample and the GMT with its 95% confidence intervals at baseline and at Days 14, 91, 82 and 365
- The geometric mean fold rise (GMFR) in neutralizing antibody titre and in total binding antibodies from baseline to Day 14.
- The percentage of subjects that after the booster dose have a ≥4-fold change in total binding antibodies titre from Baseline to Day 14

7.5.6 Procedures for Reporting Deviations to Original Statistical Analysis Plan

A SAP will be written to detail further methodology for summary and statistical analyses. Any deviations on the planned analysis from this SAP would be documented on a SAP amendment and in the Clinical Study Report (CSR).

8. ADMINISTRATIVE REQUIREMENTS

8.1 Good Clinical Practice

This study will be conducted in accordance with the protocol and ethical principles stated in the Declaration of Helsinki or the applicable guidelines on Good Clinical Practice (GCP), and all applicable local laws, rules, and regulations.

Requirements for ethical review as set forth in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical studies on medicinal products for human use or other relevant local regulations for institutional review will be followed.

The Sponsor and his delegates, in collaboration with the Investigator, will be responsible for reporting to the Ethics Committee all changes in research activity, including protocol amendments, updates of IBs, annual safety reports, all unanticipated problems involving risks to human subjects, and study termination.

8.2 Ethics

In parallel to the submission to the Independent Ethics Committee (IEC), the Sponsor must obtain an authorisation from the appropriate competent authority to conduct the clinical study. Subjects must not be entered into the study until the relevant IEC has issued its opinion and the CA has given authorisation to conduct the study.

All substantial amendments must be submitted to the IEC and/or to the Competent Authorities for approval.

Neither the Investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IEC approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC and relevant competent authority.

Documentation of amendment approval by the Investigator and IEC must be provided to the Sponsor. During the study, in situations where a departure from the protocol is unavoidable, the Investigator or other physician in attendance will contact the appropriate Sponsor representative. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF, and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

8.2.1 Independent Ethics Committee

The Protocol, informed consent forms, IB, and other required documents must be approved by the IEC before enrolment of subjects in the study. The letter of approval from the IEC, as well as a list of documents reviewed, will be filed in the Investigator Site File (ISF) and a copy will be filed in the study master file (TMF) held by the Sponsor.

8.3 Data and Safety Monitoring Board

The DSMB is a group of experts that monitors the main safety and tolerability outcome measures and the overall conduct of the study with the aim of protecting the safety and interests of the study subjects. The membership, frequency, and method of the DSMB and the study aspects to be reviewed would be specified in the DSMB Charter.

After any DSMB meetings, DSMB would make a recommendation to continue the study, to stop vaccination administration new subjects in the same part of the study or terminate the study.

The DSMB Chairman will be responsible for providing a written report of findings and recommendations to the Sponsor in a timely manner. Veristat LLC. would be responsible for informing the study sites and the Sponsor will be responsible for informing appropriate regulatory authorities of any DSMB recommendation relating to conduct of the study.

8.4 Subject Information and Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICFs must be signed before performance of any study related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IEC and be in a language that the subject can read and understand. The ICF(s) should be in accordance with principles that originated in the Declaration of Helsinki (updated according to its last version, Fortaleza, Brazil, 2013), current ICH and GCP guidelines, applicable regulatory and Sponsor policy. Before enrolment in the study, the Investigator or an authorised member of the study site must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort that the participation in the study may entail.

Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Finally, they will be told that the Investigator will maintain a subject identification register and that their records may be accessed by health authorities and authorised Sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations.

The subject will be given enough time to read the ICF(s) and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature and their legal tutor if the subject is 16 or 17 years old. After having obtained the consent, a copy of the ICF(s) must be given to the subject.

8.5 Subject Confidentiality

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfil the objectives of the study. Subject data will be codified to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Subjects will be codified with a Subject ID that prevents their identity from being deduced.

The Investigator and duly authorised collaborators will maintain personal data strictly confidential, according to regulatory requirements. The link between the numeric code and real personal data from subjects will be rigorously kept by the Investigator. The ICF(s) obtained from the subject includes explicit consent for the processing of personal data and for the Investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC review, and regulatory inspection.

In the eCRF, the subject will only be identified by the assigned Subject ID. The name of subjects will not appear in any publication or report of the study results.

Duly authorised persons by the Sponsor and the health authorities and the IEC may audit or inspect the study. Personal information will not be publicly available, in compliance with General Data Protection Regulation (GDPR) (EU) 2016/679 of 27th April 2016.

In addition, the Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or Investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Only data collected for the study that does not bear any information that could directly identify the subject will be transferred to third parties or other countries. Should this transfer occur, it will be for the same purposes as the study and guarantee confidentiality with at least the level of protection afforded by applicable regulations.

Subjects will be informed that their clinical data will be incorporated into an automated study-specific file after, and the results of the clinical studies and different studies conducted with samples can be communicated at scientific meetings, medical conferences or publications. However, the subject's identity or identifiable data will never be disclosed.

8.6 Personal Data Protection

According to the Council of 27 April 2016 on the protection of natural persons as to the processing of personal data and the free circulation of data, and in accordance with the provisions of the Article 9 of the EU Regulation 2016/679 the following personal data protections will be followed in this study.

The data collected for the study will be collected only identified by a code, so that no information will be included to identify the subjects. Data will be processed with the only purpose of carry out all activities related to the clinical study in compliance with pharmacovigilance regulations (for the drug safety control). The legal basis for the processing of the data is the subject consent and

Article 9.2 of the Regulation. Only the Investigator and his collaborators have the right to access the source data (clinical history) and will be able to relate the data collected in the study with the subject's medical history.

The identity of the subject will not be available to any other person except for a medical emergency or legal requirement. Health authorities, the Research Ethics Committee and personnel authorised by the Sponsor of the study, may have access to the personal data identified when necessary to verify data and study procedures, but always maintaining confidentiality in accordance with current legislation.

Only encrypted data will be transferred to third parties and to other countries, which in no case will contain information that can identify the subject directly (such as name and surnames, initials, address, social security number, etc.). If this assignment occurred, it would be for the same purpose of the study described and guaranteeing confidentiality.

If a transfer of encrypted data is carried out outside the EU, either in entities related to the hospital where the subject participates, to service providers or to researchers who collaborate with them, the data of the subjects will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

The Sponsor of the study commits to carry out the data processing according to EU Regulation 2016/679 and, therefore, to keep a record of the processing activities to carry out and to make a risk assessment of the data processing, to establish what measures will be applied and how it will be done.

In addition to the rights already covered by the previous legislation (access, modification, opposition and cancellation of data, deletion in the new Regulation) subjects can now limit the processing of data collected for the project that has to be rectified, request a copy, or move to a third party (portability). To exercise these rights, the subject should be directed to the Investigator of the study or the Data Protection Delegate of their site. The subject also has the right to contact the Data Protection Agency if not satisfied.

The data cannot be deleted even if a subject discontinues the study, to guarantee the validity of the investigation and comply with the legal duties and the medication authorisation requirements.

The Investigator and the Sponsor are obliged to keep the data collected for the study at least up to 25 years after its completion. Subsequently, personal information will only be kept by the site for the care of their health and by the Sponsor for other scientific research purposes if the subject has given their consent to do so, and if the law and applicable ethical requirements so permit.

In accordance with the provisions of recital 33 of the regulations and the corresponding provisions of each country involved in the study regulations, the data may be preserved in such a way that the clinical data are kept separate from the identifiers, to be used in future investigations, applying all technical precautions necessary to avoid their re-identification, and in accordance with all ethical and legal requirements.

8.7 Quality Assurance and Quality Control

According to ICH/GCP guidelines, the Sponsor should ensure that the study is adequately monitored.

The purpose of monitoring is to verify that the rights and wellbeing of human subjects are protected; that the study is accurate, complete, and verifiable with source data and that the study is conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

A monitoring plan will be designed by Veristat, LLC. The monitoring plan will establish the guideline for conducting all the monitoring activities.

To ensure homogeneity and the same quality standards, monitors in all study centres will be trained with the same procedures. The training sessions will be done before the initiation of the study and training periodic updates if new sites or personnel are included or when overall quality of data collected through the eCRF is not optimal. The training session will be focused on the protocol implementation, target population and recruitment, electronic CRF and site initiation visit (SIV) procedures and monitoring forms to be used along the study conduct.

During the SIV, the monitors will train the local Investigators and collaborators about study protocol, requirements, interventions, visits, follow-up activities and electronic CRF completion. These tasks will ensure the quality of the data and the quality of the conduct of the clinical study.

Source data will be verified during on-site monitoring visits. During the visits, the monitor will compare the data entered in the eCRF with the source documents. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the monitor and study-site personnel and are accessible for verification. During monitoring visits, the relevant study-site personnel should be available, the source documentation accessible, and a suitable environment provided for review of study-related documents. The monitor will meet the Investigator The number of visits will be described in detail in the monitoring plan.

A close-out visit will be performed before the final closure of each centre. During this visit, medication accountability will be checked and arranged according to the indications of the final version of the protocol. Besides, a general overview and a final revision of pending queries will be implemented, ensuring that all data and corresponding source documents are in place before the site closure.

8.7.1 Direct Access to Source Data

Investigators will ensure access to the source documents of the staff responsible for guaranteeing data quality and data analysis. In addition, access to documentation will be provided, if necessary, to the staff duly authorised by the Sponsor (study monitors), to regulatory authorities, and to the IEC if they request to inspect the study.

Source documents will be stored in the Investigator´s File. These documents will be kept for a minimum period of 25 years by the Investigator, after which they will be destroyed.

8.7.2 Electronic Case Report Form Completion

Data generated and/or collected at clinical sites will be registered using an electronic data management system with remote data entry. Completeness and plausibility checks will ensure the collection of high-quality data. An eCRF will be designed, validated and implemented and will provide electronic data capture functionality (EDC) to the Investigators. The electronic data management system consists in two modules: the eCRF design and the SQL database; and so allows the link between case forms and the database in order to make the generated eCRF consistent and valid, as well as project customised. It complies with the standard[18] and specific[19], GCP as well as the higher software[20,21,22,23] validation requirements, with restricted access based on user level, and with inconsistency filters and traceability of all data until the database closure.

The eCRF and its database are developed and maintained by the Data management group of the Veristat, LLC.

An eCRF for each subject will be completed by authorised personnel.

Each study site will have access to their subjects only and access will be secured using unique personal logins. Each data recording or editing event will be logged in the database to allow better monitoring and database coordination.

The Sponsor or its delegates must ensure that data are recorded in the eCRF correctly and completely by authorised personnel. The Investigator must confirm the integrity of the data transferred to the eCRF by signature.

The data entered in the eCRF must be consistent with the project source documents (specific project records, medical history, medical and nursing notes, laboratory reports, etc.) The data must be entered by authorised personnel, after receiving specific training in the use of the eCRF.

Any change in the initial data recorded will be justified and traceable to make the data as clean and accurate for analysis. Data quality will be enhanced by a series of scheduled checks that automatically detect out-of-range or abnormal data.

The data entry should not be delayed regarding the obtaining of the data sources, trying to be as simultaneous as possible, to avoid the loss of data.

The eCRF will be designed to require only the necessary data following a system of locks and dependencies.

Those data not registered in the source data will be considered lost data.

8.7.3 Data Handling

Demographic and biological data will be collected at each clinical site and entered in an eCRF. Defined Investigators at each of the study sites will be in charge of data entry to an eCRF. The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfil the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection, European, and National regulations. Appropriate technical and organisational measures to protect the personal data against unauthorised disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place. The clinical Investigator team at

each clinical centre will compromise to keep the identity of subjects confidential. For this aim, subjects will be assigned an alphanumeric code (Subject ID). The link between the code and real personal data will be safely stored at the study site, and only the local Investigator will have access to it.

8.8 Record Retention

The Investigator is responsible for maintaining all records which enable the conduct of the clinical study at the site to be fully documented, in compliance with ICH GCP filing standard. Timeliness and completeness of the documentation will be regularly checked by the clinical monitor. The documentation of the clinical study including all the relevant correspondence should be kept by the Investigator for the minimum period required by applicable regulatory.

All completed study related documents (e.g., eCRF, ICF, drug accountability logs, staff signature lists, subject identification log) must be archived for 25 years.

8.9 Financing, Liability, and Insurance

The Sponsor or his delegate will procure insurance for this clinical study to cover study related injuries of the subjects according to local regulatory requirements.

Clinical study subjects will be provided on request with the conditions of insurance along with the ICF.

8.10 Publication of Study Findings and Use of Information

All data generated as a result of this study will be considered confidential and remain the sole property of the Sponsor.

The Sponsor, in agreement with the Investigators of the study will publish the results of the study in internationally indexed journals. Authorship will consider members of the study management, participating Investigators and persons responsible for coordination, data analysis and article writing.

8.11 Return of Research Results and Management of Incidental Findings

All data generated as a result of this study will be considered confidential and remain the sole property of the Sponsor.

The Sponsor, in agreement with the Investigators of the study, will publish the results of the study in internationally indexed journals. Authorship will consider members of the study management, participating Investigators, and persons responsible for coordination, data analysis, and article writing.

8.12 Post-Study Access

No post-study access to the study drugs will be provided.

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10.APPENDICES

10.1 Appendix 1. List of Adverse Events of Special Interest

Potential Immune-Mediated Medical Conditions (PIMMCs)

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.

Categories	**Diagnoses** (as **MedDRA Preferred Terms)**
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 lgA 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[a], diabetes mellitus type 1, Addison's disease
Other Disorders	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anaemia, sarcoidosis, hypersensitivity.

[a] For Hashimoto thyroiditis: new onset only