

16.1.9 Documentation of Statistical Methods

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STATISTICAL ANALYSIS PLAN

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PROTOCOL TITLE: A Phase IIb/III, open label, single arm, multi-centre, trial to assess the immunogenicity and safety of an additional dose vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults with pre-existing immunosuppressive conditions vaccinated against COVID-19.

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APPROVAL SIGNATURE PAGE

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By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Approval Signature	Job Title
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
229E	Human Coronavirus-229E
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANOVA	Analysis of variance
ATC	Anatomic Therapeutic Class
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CD25	Cluster of Differentiation 25 - Interleukin 2 receptor subunit alpha
CD69	Cluster of Differentiation 69 - CD69 molecule
CD137	Cluster of Differentiation 137 - Tumor necrosis factor receptor superfamily, member 9
CD4+/CD8+	Cluster of Differentiation 4/8
CI	Confidence Interval
cm	Centimetres
Comirnaty	Pfizer–BioNTech COVID-19 Vaccine
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
°C	Degrees Celsius
DSMB	Data Safety Monitoring Board
ECLIA	Electrochemiluminescence Immunoassay
eCRF	Electronic Case Report Form
EDTA tube	Ethylenediamine tetraacetic acid tube
ELISpot	Enzyme-Linked Immune Absorbent Spot
EP	Enrolled Population
ETV	Early Termination Visit
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titre
HKU1	Human Coronavirus-HKU1
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
IC ₅₀	Inhibitory Concentration 50
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Intracellular Cytokine Staining

Abbreviation	Definition
ICU	Intensive Care Unit
ID	Identifier
ID ₅₀	Inhibitory dilution 50
IgG	Immunoglobulin G
IGP	Immunogenicity Population
ITT	Intent-to-treat
kg	Kilogram
LLOQ	Lower limit of quantification
LS	Least Squared
MAAE	Medically Attended Adverse Event
mL	Millilitre
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome-related Coronavirus
mITT	Modified Intention-to-treat
MMRM	Mixed Effects Model for Repeated Measures
mRNA	Messenger RNA
NCI	National Cancer Institute
NL63	Human Coronavirus-NL63
OC43	Human Coronavirus-OC43
OOW	Out-Of-Window
PBMC	Peripheral Blood Mononuclear Cell
PBNA	Pseudovirion-Based Neutralisation Assay
PCR	Polymerase Chain Reaction
%	Percent
PDF	Portable Document Format
PHH-1V	Study Drug
PIMMC	Potentially Immune-Mediated Medical Conditions
PT	Preferred Term
RAT	Rapid antigen test
RBD	Receptor Binding Domain
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Coronavirus 2
SAS	Statistical Analysis System
Sc-RNA seq	Single Cell Transcriptomics Analyses
SD	Standard Deviation
SI	International System of Units
SOC	System organ class
SP	Safety Population
SQBA	Squalene Based Adjuvant

Abbreviation	Definition
TEAE	Treatment-emergent Adverse Event
TLF	Tables, Listings and Figures
UNS	Unscheduled visit
UK	United Kingdom
VNA	Virus Neutralisation Assay
VOC	Variants of Concern
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

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 published¹. 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 pandemic². The pandemic is ongoing despite unprecedented efforts to control the outbreak.

HIPRA has developed a recombinant protein (RBD) fusion heterodimer vaccine (PHH-1V) with an oil-water adjuvant equivalent to the commonly used adjuvant Squalene Based Adjuvant (SQBA), for the prevention of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, prepared as an emulsion for intramuscular administration in adults.

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

- Phase I/IIa randomised, controlled, observer-blinded, dose-escalation, multicentre study to evaluate safety and immunogenicity of two PHH-1V doses in adult healthy subjects.
- Phase IIb double-blind, randomised, active-controlled, multicentre, non-inferiority study to assess immunogenicity and safety of a booster vaccination with PHH-1V in adults fully vaccinated against COVID-19.
- Phase III, open label, single arm, multi-centre study to assess the safety and immunogenicity of a booster vaccination with PHH-1V against SARS-CoV-2 in adults vaccinated against COVID-19.

1.1.2. Statistical Analysis Plan Objectives

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data to answer the primary and secondary study objectives. Analyses of exploratory immunogenicity objectives will be outlined in [Appendix 2](#). Populations for analysis, data handling rules, and statistical methods are provided. Formats for data presentation are provided in a separate tables, listings, and figures (TLFs) shell document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.1.3. Study Objectives

1.1.3.1. Primary Objective

The primary objectives of the study are:

- To determine immunogenicity measured by pseudovirus neutralization against Omicron BA.1 at Baseline and at Day 14 after administration of HIPRA's vaccine (PHH-1V).
- To determine immunogenicity measured by live virus neutralization for the HIV cohort against Omicron at Baseline and Day 14 after administration of HIPRA's vaccine (PHH-1V).

1.1.3.2. Secondary Objectives

The secondary objectives of this study are:

- To determine and compare the changes of the immunogenicity measured by pseudovirus neutralization against Omicron, D614G, Beta and any other relevant Variants of Concern (VOC) in the epidemiologic moment at Baseline and Days 14, 91 and 182, and 365 only for Spanish participants, after administration of HIPRA's vaccine (PHH-1V).
- To determine and compare the changes of the immunogenicity measured by live virus neutralization for the HIV cohort against Omicron at Days 91, 182 and 365 after administration of HIPRA's vaccine (PHH-1V).
- To determine and compare the changes of the immunogenicity measures by live virus neutralization for the HIV cohort against D614G and any other relevant VOC in the epidemiologic moment at Baseline and Days 14, 91, 182 and 365 after administration of PHH-1V.
- To evaluate the immunogenicity measured by means of total antibody against Receptor Binding Domain of the Spike protein of SARS-CoV-2 quantification, measured by an electrochemiluminescence immunoassay (ECLIA) at Baseline and at Days 14, 91 and 182, and 365 only for Spanish participants, after administration of HIPRA's vaccine (PHH-1V).
- To assess the safety and tolerability of PHH-1V as an additional dose in adult individuals with pre-existing immunosuppressive conditions.

1.1.3.3. Exploratory Objectives

- To assess the number and percentage of participants with SARS-CoV-2 infections ≥ 14 days after PHH-1V administration.
- To assess the number and percentage of COVID-19 severe infections ≥ 14 days after PHH-1V administration.
- To further evaluate humoral responses by measuring Immunoglobulin G (IgG) subclasses usage and avidity of humoral immunity at Baseline and Days 14 91, and 182, and 365 only for Spanish participants in exploratory analysis as [Appendix 2](#).

- To evaluate T-cell mediated responses, their immune phenotype polyclonally with potential cross-reactivity capacity and gene-expression profiles against the SARS-CoV-2 RBD proteins at Baseline and at Days 14, 91, 182, and 365 in a subset of approximately 50% of participants in exploratory analysis as [Appendix 2](#).

1.2. Study Estimands

The primary estimand for the study, which follows the ‘While On Treatment’ strategy is:

The geometric mean titres (GMTs) for the target subject population for the neutralising antibody titres measured as inhibitory concentration 50 (IC₅₀) by Pseudovirion-Based Neutralisation Assay (PBNA) for Omicron BA.1 at Day 14 after the booster dose, regardless of study discontinuation and COVID-19 infections. The Estimand components are:

- A. The population is restricted to the modified intention-to-treat (mITT) as defined in **Section 2.1**
- B. The variable is the neutralising antibody titres measured as IC₅₀ by PBNA, for Omicron BA.1 and reported as GMT at Day 14 after the booster dose.
- C. The intervention effect is regardless of study discontinuation and COVID-19 infections.
- D. The population-level summary measure is the GMT.

For the HIV cohort, the GMTs of the neutralising antibody titres measured by ID₅₀ (the reciprocal dilution inhibiting 50% of the infection) will be reported using a live virus neutralisation assay to measure cytopathic effect in Vero E6 cells. In this case, the estimand components are:

- A. The population is restricted to the modified intent-to-treat (mITT) as defined in **Section 2.1**.
- B. The variable is the neutralising antibody titres measured as ID₅₀ by a live virus neutralisation assay (VNA) for Omicron BA.2 and reported as GMT at Day 14 after the booster dose.
- C. The intervention effect is regardless of study discontinuation and COVID-19 infections.
- D. The population-level summary measure is the GMT.

The estimands for the GMFR of the primary and secondary endpoint will follow a similar strategy as above.

1.3. Study Design

1.3.1. Synopsis of Study Design

This is a phase IIb/III, open label, single arm, multi-centre clinical trial that aims to determine safety, reactogenicity, tolerability and immunogenicity of additional vaccination with a recombinant protein RBD fusion heterodimer candidate against SARS-CoV-2 developed by HIPRA (PHH--1V) in subjects with pre-existing immunosuppressive conditions.

Approximately 400 eligible subjects who have received primary vaccination against COVID-19 with 3 doses of messenger RNA (mRNA) vaccine (or 2 doses plus a documented history of COVID-19) with the last dose being administered at least minimum of 91 days will be included. Subjects recruited in Turkey who received a primary vaccination regimen using a combination of Coronavac and/or Comirnaty with or without additional boosters of the same vaccines will be included provided that last booster dose being administered is at least 91 days before day 0. Subjects with history of COVID-19 disease will be allowed to be included if diagnosed at least 91 days prior, or if hospitalisation had been required, a minimum of 30 days should have passed from hospital discharge prior to inclusion and provided they are not suffering from long COVID-19 (Post-acute COVID-19 syndrome).

All subjects will receive a single dose of PHH-1V on Day 0 and will be observed for 15 minutes, except for those subjects reporting previous allergy reactions to vaccination that will be observed for 30 minutes.

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 except for COVID-19 cases that will be recorded in eCRF throughout the study. Serious adverse events (SAEs),

adverse events of special interest (AESIs) and medically attended adverse events (MAAEs) will be reported during all the study.

On-site follow-up visits will be performed on Days 14, 91, 182, and 365 for Spanish subjects, and Days 14, 91 and 182 for Turkish subjects. Subjects who have one of the following SARS-CoV-2 vaccination schemes will be included:

For sites in Spain, the following vaccination schemes will be allowed:

Three doses of mRNA vaccines (Comirnaty and/or Spikevax) with or without past history of positive test for COVID-19, provided that last vaccination and diagnose of COVID-19 is at least 91 days before Day 0, and if hospitalisation was required, subject was discharged from hospital at least 30 days before Day 0.

Two doses of mRNA vaccines (Comirnaty and/or Spikevax) and previous history of positive test for COVID-19, provided that last vaccination and diagnose of COVID-19 is at least 91 days before Day 0, and if hospitalisation was required, subject was discharged from hospital at least 30 days before Day 0.

For sites in Turkey where vaccination with Coronavac was started, the following vaccination schemes will be allowed:

A complete primary scheme of the following vaccines: Coronavac and/or Comirnaty, with or without additional boosters of the same vaccines, being the last vaccination at least 91 days before Day 0. Subjects with or without history of a positive test for COVID-19 are allowed. The infection (first day of positive test, RAT or PCR) must have been at least 91 days before Day 0.

In Spain, each participant will be followed for approximately 52 weeks (365 days) after the administration of the vaccination on Day 0.

In Turkey, each participant will be followed for approximately 26 weeks (182 days) after the administration of the vaccination on Day 0.

1.3.2. Stopping Rules

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.

1.3.3. Study Procedures

The schedule of events, as outlined in the study protocol, is provided in [Table 1](#) and [Table 2](#).

Table 1. Schedule of Events (Spanish Participants)

Visit number	1	2	3	4	5	6/ETV	USC visit
Visit description	Pre-Screening (on-site or remote)	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 and Prior medication		x					
Demographics ^b		x					
Physical examination		x	x	x	x	x	
Vital signs ^c		x	x	x	x	x	
Concomitant medication ^d		x	x	x	x	x	
Vaccination		x					
Participant Diary provided/ collected ^e		x	x				
Adverse events		x	x	x	x	x	
Pregnancy test ^f		x					
Haematology ^g		x (5 mL)	x (5 mL)	x (5 mL)	x (5 mL)	x (5 mL)	
Biochemistry ^h		x (5 mL)	x (5 mL)	x (5 mL)	x (5 mL)	x (5 mL)	
Lymphocyte subpopulations		x (4 mL)					

Visit number	1	2	3	4	5	6/ETV	USC visit
Visit description	Pre-Screening (on-site or remote)	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)	-
Quantitative serum Immunoglobulin tests		x (5 mL)					
Quantitative COVID-19 serology per local laboratories		x (5 mL)	x (5 mL)	x (5 mL)	x (5 mL)	x (5 mL)	
Serum for humoral immunogenicity assays ¹ : COVID-19 serology (N-specific) Binding antibody assays Neutralisation (PBNA/VNA) IgG subclasses quantification Cross-Reactivity to other COV Avidity		x (26 mL)	x (26 mL)	x (26 mL)	x (26 mL)	x (26 mL)	
PBMCs for cellular immunology assays (Cellular Immunogenicity subset - 50% of participants) ¹ ELISPOT ICS (Flow cytometry) Sc-RNA seq		x (80 mL)	x (80 mL)	x (80 mL)	x (80 mL)	x (80 mL)	
Total		50 / 130 mL	41 / 121 mL	41 / 121 mL	41 / 121 mL	41 / 121 mL	Total 214 / 614 mL

Abbreviations: BUN = blood urea nitrogen; WBC = white blood count; ETV = early termination visit; PBMC = peripheral blood mononuclear cells; PCR = polymerase chain reaction; USC = unscheduled visit. Sc-RNA seq = single cell transcriptomics analyses.

- 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. For the different groups, information detailed in section 6.3.1 of the protocol will be recorded for each of the underlying disease.
- c Vital signs will include pulse, blood pressure, temperature, and oxygen saturation.
- d Current concomitant medication, except for immunosuppressive therapy for the last 6 months. See details on section 5.8 of the protocol for immunosuppressive therapy history.
- e A paper Participant Diary will be provided to all the participants to collect solicited local and systemic reactions after vaccination. The Participant 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 WBC, 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 Three serum separator tubes (SST tubes) (8.5 mL each) will be obtained to isolate at least 6 mL of serum for all humoral immunogenicity assays. Additional serum will be aliquoted for storage. The COVID-19 serology against N protein will be performed if deemed necessary for the interpretation of the results at any timepoint during the study. Serology will be done at HIPRA central laboratory to assess if the participant has never had a COVID-19 infection.
- j Eight ethylenediamine tetraacetic acid (EDTA) tubes (10 mL each) will be extracted to obtain PBMC for the study of T cell responses in the immunogenicity subset (50% of participants of each group).

Table 2. Schedule of Events (Turkish Participants)

Visit number	1	2	3	4	5/ETV	USC visit
Visit description	Pre-Screening (on-site or remote)	Screening and Baseline Vaccine	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)	-
Informed consent ^a		x				
Eligibility criteria	x	x				
Medical history and Prior medication		x				
Demographics ^b		x				
Physical examination		x	x	x	x	
Vital signs ^c		x	x	x	x	
Concomitant medication ^d		x	x	x	x	
Vaccination		x				
Participant Diary provided/ collected ^e		x	x			
Adverse events		x	x	x	x	

Visit number	1	2	3	4	5/ETV	USC visit
Visit description	Pre-Screening (on-site or remote)	Screening and Baseline Vaccine	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)	-
Pregnancy test ^f		x				
Haematology ^g		x (5 mL)	x (5 mL)	x (5 mL)	x (5 mL)	
Biochemistry ^h		x	x (5 mL)	x (5 mL)	x (5 mL)	
Lymphocyte subpopulations		x				
Quantitative serum Immunoglobulin tests		x				
Serum for humoral immunogenicity assays ⁱ : COVID-19 serology (N-specific) Binding antibody assays Neutralisation (PBNA) IgG subclasses quantification Cross-Reactivity to other COV Avidity		x (26 mL)	x (26 mL)	x (26 mL)	x (26 mL)	

Visit number	1	2	3	4	5/ETV	USC visit
Visit description	Pre-Screening (on-site or remote)	Screening and Baseline Vaccine	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)	-
Total		45 mL	36 mL	36 mL	36 mL	Total 153 mL

Abbreviations: BUN = blood urea nitrogen; WBC = white 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. For the different groups, information detailed in section 6.3.1 of the protocol will be recorded for each of the underlying disease.

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

d Current concomitant medication, except for immunosuppressive therapy for the last 6 months. See details on section 5.8 of the protocol for immunosuppressive therapy history.

e A paper Participant Diary will be provided to all the participants to collect solicited local and systemic reactions after vaccination. The Participant 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 WBC, 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 Three SST tubes (8,5ml each) will be obtained to isolate at least 6ml of serum for all humoral immunogenicity assays. Additional serum will be aliquoted for storage. The COVID-19 serology against N protein will be performed if deemed necessary for the interpretation of the results at any timepoint during the study. Serology will be done at HIPRA central laboratory to assess if the participant has ever had a COVID-19 infection.

1.3.4. Study Parameters

1.3.4.1. Immunogenicity Parameters

The primary endpoints are:

- Neutralization titre against Omicron BA.1 measured as IC₅₀ by a PBNA and reported as reciprocal concentration for each individual sample and GMT for descriptive statistics analysis at Baseline and at Day 14.
- The geometric mean fold rise (GMFR) in neutralising antibody titre from baseline to Day 14.
- Neutralization titer against Omicron measured as a ID₅₀ (the reciprocal dilution inhibiting 50% of the infection) by a VNA to measure cytopathic effect in Vero E6 cells at Baseline and Day 14 after PHH-1V administration.

The secondary endpoints are:

- Neutralization titre against Omicron, D614G, Beta strains, and any other relevant VOC in the epidemiologic moment, measured as IC₅₀ by a PBNA and reported as reciprocal concentration for each individual sample and GMT for descriptive statistics analysis at Baseline and at Days 14, 91 and 182 for all participants, and 365 only for Spanish participants.
- Neutralization titre against Omicron measured as ID₅₀ (the reciprocal dilution inhibiting 50% of the infection) by a VNA to measure cytopathic effect in Vero E6 cells at Days 91, 182 and 365 after PHH-1V administration.
- Neutralization titer against D614G and any other relevant VOC in the epidemiologic moment, measured as a ID₅₀ (the reciprocal dilution inhibiting 50% of the infection) by a VNA to measure cytopathic effect in Vero E6 cells at Baseline, and at Days 14, 91, 182 and 365 after PHH-1V administration.
- Binding antibodies titre measured for each individual sample and GMT for descriptive statistics analysis at Baseline and Days 14, 91 and 182 for all participants, and 365 only for Spanish participants.
- The GMFR in binding antibody titre from baseline to Day 14
- The percentage of subjects that after PHH-1V vaccine have a ≥ 2 -fold and 4-fold change in binding antibodies titre from Baseline to Day 14

The exploratory endpoints are:

- Quantification of IgG subclasses (IgG1, IgG2, IgG3 and IgG4) measured by ELISA at Baseline and Days 14, 91 and 182 for all participants, and 365 only for Spanish participants.
- Cross reactivity with Spike glycoproteins from other coronavirus (SARS-CoV, MERS-CoV, HKU1, OC43, NL63, 229E) measured at Baseline and Days 14, 91 and 182 for all participants, and 365 only for Spanish participants.

- Avidity of the main antibodies elicited against the Spike glycoproteins determined by ELISA at Baseline and Days 14, 91 and 182 for all participants, and 365 only for Spanish participants.
- Frequency of IFN γ positive T-cells measured by enzyme-linked immune absorbent spot (ELISpot) covering the RBD sequence of D614G, RBD Omicron BA.1 and BA.2, RBD Beta and RBD Delta and any other relevant VOC in the epidemiologic moment at Baseline and at Days 14, 91, 182, and 365 in a subset of approximately 50% of subjects.
- Immune phenotype of SARS-CoV-2 specific CD4⁺/CD8⁺ T-cell responses measured by intracellular cytokine staining (ICS) flow-cytometry at Baseline and at Day 14 in a subset of 50% of subjects.
- T-cell transcriptional profiles and TCR usage of RBD-specific T-cells isolated using cell sorting with CD25, CD69 and CD137 activation markers and subjected to single cell transcriptomics analyses (sc-RNAseq) at Baseline and at Days 14, 182, and 365 in a subset of 50 subjects selected based on the humoral, ELISpot and Flow cytometry data.

Above exploratory endpoints analysis information will be detailed in [Appendix 2](#).

1.3.4.2. Safety Parameters

The secondary endpoints are:

- 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 SAEs through the end of the study.
- Number and percentage of AESIs through the end of the study.
- Number and percentage of MAAEs 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 for all participants, and 365 only for Spanish participants, after vaccination.

The exploratory endpoints are:

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

- Number and percentage of deaths associated with COVID-19 ≥ 14 days after PHH-1V administration and through the end of the study.

2. SUBJECT POPULATION

2.1. Population Definitions

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

- **Enrolled (EP):** All individuals who have signed the Informed Consent Form (ICF).
- **Intention-to-treat (ITT):** All subjects who are enrolled, regardless of the individual's treatment status in the study. "Enrolled" is defined as "Answer - Yes to the Has subject been recruited into the study?" in eCRF.
- **Modified Intention-to-treat (mITT):** All individuals in the ITT who meet the inclusion/exclusion criteria, received a dose of study vaccine and did not test positive for COVID-19 within 14 days after receiving study vaccine. Subjects in Spain should have a valid serology (N-specific) result at screening or baseline.
- **Immunogenicity (IGP):** All individuals in the mITT who had a valid immunogenicity test result, based on neutralization titre, before receiving study vaccine and at least one valid result after dosing. Subjects will be analysed according to their underlying disease, history of prior COVID-19 and/or positive N-serology and primary vaccination schemes (mRNA or CoronaVac/mRNA).

For exploratory analyses in [Appendix 2](#), a subset of about 50% of the enrolled individuals -or approximately 200 individuals - will be further characterized in terms of T cell responses that require PBMC isolation. This subset will be selected based on pre-existing conditions.

- **Safety (SP):** All enrolled individuals who received the study vaccine. This population will be used for all analyses of safety. Subjects will be analysed according to their underlying disease and primary vaccination schemes (mRNA or CoronaVac/mRNA).

2.2. Protocol Deviations

Major protocol deviations are any intentional or unintentional change, divergence or departure from the study design or procedures defined in the clinical trial protocol or from Good Clinical Practice (GCP) that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

At the discretion of the Sponsor, major protocol deviations, as determined by a review of the data prior to CSR analysis of the study results and the conduct of statistical analyses, may result in the removal of a subject's data from the subject populations. The Sponsor or designee will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file), in collaboration with the data monitoring group as applicable; this file will include a description of the protocol deviation and clearly identify whether this deviation warrants exclusion from the subject populations. This file will be finalised prior to hard database lock.

Major and minor protocol deviations will be presented in a data listing based on the ITT.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

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

A sample size of 400 subjects is proposed, with 60-80 subjects per condition. This is an exploratory study to assess safety and immunogenicity in special populations with some underlying immunosuppressive conditions. No formal sample size calculation is envisioned. As a means to characterise the statistical properties of this study, the table below presents the probability of observing zero, at least one, and two or more safety endpoints among the 400 subjects for various “true” event rates:

Event rate	P(0 events n=400)	P(≥ 1 event n=400)	P(≥ 2 events n=400)
1%	1.8%	98.2%	91%
5%	0%	100%	100%
10%	0%	100%	100%
15%	0%	100%	100%
25%	0%	100%	100%

P=Probability

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

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Study Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study treatment which is designated as Day 0. The preceding day is Day 1, the day after that is Day 2, etc.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labelled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Demographic, baseline and safety analyses will be presented by 5 underlying disease groups and overall group. Immunogenicity analyses will be presented by 5 underlying disease groups.

Tabulations will be produced for appropriate demographic, baseline, safety, and immunogenicity parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, standard deviation (SD), median and Q1, Q3, minimum, and maximum values will be presented, where appropriate.

For the immunogenicity variables, the geometric mean titer (GMT) and geometric SD, GMFR and fold rise will be presented, as appropriate. Standard error and 95% confidence intervals (CI) will be also provided, as appropriate.

In the case where a variable is recorded as “> x”, “≥ x”, “< x” or “≤ x”, then for analysis purposes a value of x will be taken. Where a range of values is quoted the midpoint of the range will be taken.

Summary statistics will be presented, as well as confidence intervals on selected parameters, as described in the sections below.

3.3. Data Presentations

For demographics, baseline data and safety tables, data will be summarised by 5 underlying disease groups and overall group in Safety (SP) population:

- HIV infection
- Kidney transplant
- Hemodialysis/ peritoneal dialysis
- Primary antibody deficiencies
- Autoimmune diseases
- Total

For immunogenicity tabulations, data will be summarised by 5 underlying disease groups and overall group, in mITT and IGP populations:

- HIV infection
- Kidney transplant
- Hemodialysis/ peritoneal dialysis
- Primary antibody deficiencies
- Autoimmune diseases
- Total

Analysis sets will be summarised for all enrolled subjects. Background and demographic characteristics will be summarised using the SP. The immunogenicity data will be summarised using the mITT and IGP. All other data will be summarised using the SP, unless otherwise stated.

Only scheduled post-baseline laboratory and vital signs will be tabulated, post-baseline repeat/unscheduled assessments will be disregarded, although they will be listed and in particular if available, any clinically significant values will be noted.

Safety listings will be based on the SP. Analysis sets, eligibility study completion data will be based on the Enrolled population. Demographic and baseline characteristics will be based on the Safety population. All other listings will be based on the ITT, unless otherwise stated.

Listings will be sorted for each study part by subject number, and date/time of assessment.

3.4. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 or higher. Concomitant medications will be coded using the WHO Drug Dictionary Version B3 Global March 2022 or higher version.

3.5. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior or equal to the administration of study drug.

No statistical comparisons will be performed for any of the baseline characteristics.

3.6. Methods of Pooling Data

Data will be pooled across study sites.

3.7. Adjustments for Covariates

Analysis of the immunogenicity endpoints will be adjusted, and the covariates will be detailed in [Section 4.3](#).

3.8. Multiple Comparisons/Multiplicity

No multiplicity concerns for this study, only descriptive statistics in the analyses.

3.9. Subpopulations

3.9.1. Primary Vaccination and COVID-19 Test Groups

The following 3 primary vaccination and COVID-19 test groups will have subgroup analysis for all immunogenicity tables ([Section 4.3](#)):

- Primary vaccination and COVID-19 test groups 1: 2 or 3 doses of Comirnaty and/or Spikevax, with history of positive rapid antigen test (RAT)/PCR test for COVID-19 or positive in COVID-19 N-specific serology result, subjects enrolled in Spain.
- Primary vaccination and COVID-19 test groups 2: 3 doses of Comirnaty and/or Spikevax, without history of positive RAT/PCR test for COVID-19 or negative in COVID-19 N-specific serology result, subjects enrolled in Spain.
- Primary vaccination and COVID-19 test groups 3: A complete primary scheme of the following vaccines for sites in Turkey: Coronavac and/or Comirnaty, with or without additional boosters

of the same vaccines, being the last vaccination at least 91 days before Day 0. Participants with or without history of a positive test for COVID-19 are allowed. The infection (first day of the positive test, RAT or PCR) must have been at least 91 days before Day 0.

3.9.2. Evusheld Groups

A sensitivity analysis will be carried out of the following groups for secondary endpoints (1.1.3.2). If the subjects with Evusheld subgroup have less than 10 subjects, only the summary table will be presented:

- For HIV, Kidney transplant, Hemodialysis/ peritoneal dialysis, Primary Antibody Deficiency and Autoimmune diseases groups
 - Subjects with Evusheld (ATC: J06BD03) after Day 14
 - Subjects without Evusheld (ATC: J06BD03) after Day 14

3.10. Withdrawals, Dropouts, Loss to Follow-up

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 listing.

Subjects who are withdrawn 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.

3.11. Missing, Unused, and Spurious Data

There will be no substitutions made to accommodate missing data points. All data below LLOQ will be provided as LLOQ. All data recorded on the electronic case report form (eCRF) will be included in data listings that will accompany the CSR.

When tabulating adverse event data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and

month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment.

Only the collected date will be reported in the listings.

3.12. Visit Windows

Visit windows as per the schedule of events are as follows in [Table 3.](#):

Table 3. Evaluation Intervals

Evaluation	Protocol-Specified Interval	Interval for Analysis
Pre-Screening	Day -28 to Day -1	Day -28 to Day 1 (Prior to treatment)
Baseline	Day 0	Day 1
Visit 3	Day 14 (± 3)	Day 11 to Day 17
Visit 4	Day 91 (± 15)	Day 76 to Day 106
Visit 5	Day 182 (± 15)	Day 167 to Day 197
Visit 6/ETV	Day 365 (± 15)	Day 350 to Day 380

*ETV = early termination visit.

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

For Efficacy analysis, out-of-window (OOW) data:

- Day 14 visit
 - If the study visit date is “ahead more than 3 days of Day 14 (i.e., Day 1, Day 2, Day 3, ..., Day 10) then the OOW value will be excluded from Day 14 analysis.
 - If the study visit date is “delayed more than 3 days of Day 14 (i.e., Day 18 onwards), then the OOW value will still be used in the Day 14 analysis.
- Other visits will follow the original eCRF visit guideline as Table 2 for the OOW data.

For Safety analysis, all OOW visit data will follow the original eCRF visit guideline as Table 2.

3.13. Interim Analyses

3.13.1. Safety Review

A Data Safety Monitoring Board (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 SAEs.

3.13.2. Interim Analysis

An interim analysis is envisioned after data on humoral response at Day 91 of all enrolled participants in Spain will be available. A final analysis will include exploratory humoral and cellular objectives and the analysis of long-term immunogenicity response of the PHH-1 V vaccination.

Outputs to be produced for the IA are indicated in **Section 8, Appendix 1**.

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated and include the number enrolled, the number in each subject population for analysis, the number of subjects who completed the study, and who withdrew prior to completing the study and reason(s) for withdrawal. Study duration in months will also be summarised and is derived as follows:

$$\frac{(\text{Date of study completion/early withdrawal} - \text{Date of booster vaccination} + 1)}{30.4375}$$

For the IA outputs, study duration will be calculated using date of data cut off as well as above.

A by-subject data listing of study completion information including informed consent data and the reason for premature study withdrawal, if applicable, will be presented.

4.2. Demographics and Baseline Characteristics

Screening demographic characteristics will be presented using summary statistics for the following variables:

- Age (year)
- Age groups: ≥ 18 to < 65 years; ≥ 65 years.
- Sex: Male; Female; Unknown; Undifferentiated.
- Ethnicity: Hispanic or Latino; Not Hispanic or Latino; Not reported; Unknown.
- Race: American Indian or Alaska; Native; Asian; Black or African American; Native Hawaiian or Other; Pacific Islander; White; Other.
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Baseline vital signs (systolic and diastolic blood pressures [mmHg], pulse rate [beats per minute], pulse oximetry [%] and body temperature [$^{\circ}\text{C}$]).
- Prior COVID-19 infection status: Yes; No.
- Test type of prior COVID-19 infections: RAT; PCR.
- Severity of prior COVID-19 infections: Severe; Non-severe.
- Serology COVID-19 anti-NC IgG (HIPRA): Positive; Negative.

- Subjects who reported no previous COVID-19 infection but positive in Serology COVID-19 test (N-specific)
- Hospitalisation required due to prior COVID-19 infections: Yes; No.
- Study sites: Site 1, Site 2...etc. in Spain; Site N...etc. in Turkey.

Lymphocyte, Quantitative serum Immunoglobulin and Quantitative COVID-19 anti-S IgG will also be summarised for test items.

Medical history will be summarised using the MedDRA coding system (version 25.1 or higher) and displayed using system organ class (SOC) and preferred term (PT).

All demographic and baseline data for each subject will be provided in data listings.

4.2.1. Immunosuppression Condition and History

To address the condition of immunosuppression, additional information and history on their underlying conditions will be summarised and listed.

4.2.2. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (version GLOBAL B3 Mar22). Results will be tabulated by anatomic therapeutic class (ATC) and preferred term (PT).

Prior medication is defined as any medication taken before Day 0. Concomitant medications will include prescription drugs, over-the-counter drugs, herbal medicines, vitamins, and supplements. Concomitant medications will be defined as those started on or after Day 0. If an end date is missing or the medication is ongoing, the medication will be considered as concomitant. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Prohibited concomitant medications during the study include:

- Any other experimental product against COVID-19 (drug, biologic, device) within 90 days before Day 0 and throughout the study.
- Treatment or immunotherapy (monoclonal antibodies, plasma) aimed to prevent COVID-19 (PrEP) will be prohibited from Day 0 to Day 14.

The use of prior and concomitant medications will listed.

4.2.2.1. Prior Immunosuppressive Medications

Prior and concomitant immunosuppressive medications are of special interest in this study to define type and degree of immunosuppression and will be defined as those taken within last 6 months before Day 0.

To address the immunosuppression medications, following 3 immunosuppressive medications will be summarised by WHO Drug Dictionary ATC level 3 and Preferred Name:

- L04A – Immunosuppressants

- L01F – Monoclonal antibodies and antibody drug conjugates
- H02A – Corticosteroids for systemic use

The use of prior immunosuppressive medications will be summarised. All data will be listed for prior and concomitant immunosuppressive medications.

4.3. Immunogenicity Analysis

Immunogenicity analyses will be conducted using the mITT and IGP population by 5 underlying diseases group and stratified by 3 primary vaccine and COVID-19 test groups as described in [Section 3.9](#).

For Immunogenicity analyses, if a subgroup has less than 10 subjects, only the summary table will be presented and this subgroup will not be considered in the models.

4.3.1. GMT and GMFR Analysis in Neutralizing Antibody Titre in IC₅₀ and ID₅₀

To investigate the primary and secondary endpoints of neutralisation titre against Omicron BA.1, D614G, Beta strains and any other relevant VOC measured as IC₅₀ by PBNA, for HIV cohort, measured as ID₅₀ by VNA at Day 14, 91, and 182 and 365 only for subjects in Spain using same VOCs if available at the time of analysis, mixed effects model for repeated measures (MMRM) will be used for each underlying disease groups.

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

- Fixed effects: visit, primary vaccination and COVID-19 test groups, age groups and primary vaccination and COVID-19 test groups-by visit interaction.
- Random effects: site.
- Repeated measures structure: visits within subject.

A compound symmetry covariance matrix structure will be used. The denominator degrees of freedom will be computed using the Kenward-Roger method. Weights will be applied to the model estimation to account for sample distributions across covariates.

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

The weighted Least Squared (LS) mean estimates will be presented with the associated standard error and 95% CIs. The back-transformed LS mean estimates will also be presented with the corresponding 95% CI.

Summary statistics for the log₁₀ transformations for each individual sample will be calculated based on the log₁₀-transformed titres at Baseline and Day 14, 91, and 182 and 365 only for subjects in Spain and will be presented for the mITT and IGP population. All data will be listed.

A scatter plot of log10-transformed titres with mean estimates and 95% CIs error bars for each visit will be produced. A reverse cumulative distribution function plot of log10-transformed Baseline and Day 14 neutralising antibodies titres by percentage of subject will also be produced.

For GMFR analysis in neutralizing antibody titre, fold rise will be calculated as post-baseline titre (Day 14)/Baseline titre for Omicron BA.1, D614G, Beta strains and any other relevant VOC.

The GMFR in neutralizing antibody titres from Baseline to Day 14 visit will be analysed by Analysis of variance (ANOVA) on log transformed data and will include the following effects.

- Fixed effects: age group, primary vaccination and COVID-19 test groups.
- Random effect: site.

4.3.2. GMT Analysis in Binding Antibody Titre

To evaluate the immunogenicity, total binding antibodies titre are measured for each individual sample and GMT for descriptive statistics analysis at Baseline and Days 14, 91, 182, and 365 will be analysed in a similar manner as described in [Section 4.3.1](#).

4.3.3. GMFR Analysis in Binding Antibody Titre

The GMFR in binding antibody titres from Baseline to Day 14 will be analysed by ANOVA. The ANOVA model will be carried out on log transformed data and will include the following effects.

- Fixed effects: age group, primary vaccination and COVID-19 test groups
- Random effect: site.

4.3.4. GMFR Fold Change Analysis in Binding Antibody Titre

Subjects who after a booster dose, have a ≥ 2 -fold and ≥ 4 -fold change in binding antibody titres from Baseline to Day 14 will be summarised by number and proportion of subjects along with an exact 95% Clopper-Pearson CI for the proportion.

Summary statistics for the GMFR fold change at Day 14 in binding antibody titres will be presented for the mITT and IGP populations. All data will be listed.

4.4. Safety Analyses

Safety analyses will be conducted using the SP population by 5 underlying diseases group, total group and stratified by 3 primary vaccination and COVID-19 test groups as described in [Section 3.9](#).

4.4.1. Study Drug Administration

Subjects receive one dose of the treatment via injection on Day 0 of the study only. Study drug administration data for each subject will be listed only.

Subjects are provided with a subject diary to record the solicited injection site (local) reactions and solicited systemic events at the time of study treatment administration through to Day 7 and is returned at the Day 14 visit; this data will be listed.

Solicited local reactions:

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

Solicited systemic events:

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

4.4.2. Adverse Events

All AEs will be coded using the MedDRA coding system (version 26.1) and displayed in tables and data listings using SOC and PT.

No formal hypothesis-testing analysis of adverse event incidence rates will be performed. All adverse events occurring on-study including data collected via the subject diary will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths, serious adverse events, and adverse events leading to withdrawal. In this study, AE will be analysed as follows:

Treatment-emergent Adverse Events:

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any adverse event with onset on or after the administration of study treatment through Day 28 or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study. A summary of TEAEs by MedDRA SOC and PT will be provided.

The following will be considered when analysing TEAEs:

- Each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes. Therefore, in any tabulation, a subject will contribute only once to the count for a given AE (SOC and PT).
- If dates are incomplete and it is not clear whether the AE is treatment-emergent, it will be assumed to be treatment-emergent.
- A treatment-related TEAE is defined as a TEAE that was related to study drug administration. If the TEAE has a missing relationship, it will be assumed to be related to all study treatments for analysis purposes.

Solicited local and systemic AEs:

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

Unsolicited local and systemic AEs:

Unsolicited local and systemic adverse events from Day 0 through Day 28 after booster vaccination will be presented by intensity and cumulatively.

SAEs and other significant AEs:

A separate summary of SAEs will be summarised separately and also presented by causal relationship to study drug, intensity and cumulatively according to National Cancer Institute Common Terminology Criteria (NCI-CTCAE). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, SAEs are listed and accompanied by descriptions of severity (Grade). Separate summaries will also be produced for each of the subgroups defined in [Section 3.9](#).

A separate summary of AESIs, including potentially immune-mediated medical conditions (PIMMCs), and MAAEs through to Day 365 will be reported including causal relationship. PIMMCs are defined in section 10.1 of the Protocol. Derived AESI has been introduced to define AESIs used for reporting

purposes as the definition of AESI for COVID-19 infections changed during the trial. Initially, all COVID-19 infections reported from Day 14 onward after vaccination were considered as AESIs. However, after protocol amendment (Protocol v5.0, dated 07th Sep 2022), COVID-19 infections were reported as AESIs for severe cases only. From Protocol v5.0 approval date, non-severe COVID-19 cases were reported as AEs, thus they will be not counted in the AESI summaries.

4.4.3. Laboratory Data

Clinical laboratory values will be expressed in reported units and ordered as per the eCRF.

The actual value and change from Baseline (Day 0) to each on-study evaluation will be summarised for each clinical laboratory parameter, including haematology, and biochemistry. In the event of repeat values, the last non-missing value per study day/time will be used. If the test results are reported in categorical format, the results will be summarised by subject counts and percentage for each category. Laboratory parameters changing to AE Grades 3 or 4 based on NCI-CTCAE v5.0 in [Appendix 3](#) and [Appendix 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 (timepoint of day 365, only for subjects in Spain) (if applicable) value will be reported.

All laboratory data included pregnancy test results will be provided in data listings.

4.4.4. Vital Signs and Physical Examination

The actual value and change from Baseline (Day 0) to each on-study evaluation will be summarised for vital signs.

Vital sign measurements including body temperature (°C), pulse rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and pulse oximetry (%) will be presented for each subject in a data listing.

All physical examination findings will be presented in a data listing.

4.4.5. COVID-19 Infections

The impact of any subject who are infected with COVID-19 during the study up to Day 365 will be summarised as follows:

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

- Number and percentage of deaths associated with COVID-19 ≥ 14 days after PHH-1V administration and through the end of the study.
- Number and percentage of subjects with anti-NC seroconversion during follow-up. Anti-NC seroconversion is defined as negative for N-serology at baseline and positive in follow-up visits.

Any positive infection recorded as “COVID-19” or “SARS-CoV-2” will be considered a COVID--19 infection for the above endpoints.

An exact 95% Clopper-Pearson CI for the proportion of each endpoint will also be presented. Analyses will be repeated on the mITT population. All COVID-19 testing, and infection data will be listed.

4.5. Sensitivity Analysis

A sensitivity analysis will be performed for the following two groups for secondary endpoints. If the subjects with Evusheld subgroup have less than 10 subjects, only the summary table will be presented.

- Subjects with Evusheld (ATC: J06BD03) after Day 14.
- Subjects without Evusheld (ATC: J06BD03) after Day 14.

To investigate the neutralisation Titre against Wuhan (D614G), Beta, Omicron (BA.1) strains, and any other relevant VOC in the epidemiologic moment, measured as IC50 by a PBNA and reported as reciprocal concentration for each individual sample and GMT for descriptive statistics analysis at Days 14, 91, and 182, and 365 only for subjects in Spain. For the HIV cohort, ID50 will be reported using a VNA to measure cytopathic effect in Vero E6 cells.

5. CHANGES TO PLANNED ANALYSES

The following are changes between the protocol-defined statistical analyses and those presented in this statistical analysis plan:

- Addition of the Estimands Framework per ICH E9 (R1) addendum.
- Clarification of analysis of the exploratory endpoints relating to COVID-19 infections.
- Amendments to the summary statistics for immunogenicity data to only list raw data and summarise the log10 transformations.
- Intent-to-treat (ITT): All subjects who are “enrolled”, not randomised. “Enrolled” is defined as “Answer - Yes to the Has subject been recruited into the study?” in eCRF.
- Modified Intention-to-treat (mITT): Subjects in Spain should have a valid serology N result at screening or baseline. Criteria added.
- Safety (SP): All “enrolled” individuals who received the study vaccine, not randomised.
- Variant of concerns have been further defined: Wuhan (D614G), Beta, Omicron (BA.1).
- D614G, Beta strains and any other relevant VOC are added in the GMFR Day 14 analysis of neutralising antibodies.

6. REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-733.
2. Ghebreyesus TA. WHO director-general's opening remarks at the media briefing on COVID-19—11 March 2020 2020 [Available from: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19%2D%2D11-march-2020>].

7. REVISION HISTORY

Version	Date	Revision Summary
v1.0	26Jul2023	Initial version 1.0
v2.0	05Feb2024	Updated based on protocol v2.0 and Interim analysis comments.

8. APPENDICES

8.1. Appendix 1: Interim Analysis Outputs

A subset of the final TLF outputs will be delivered for the IA as described in **Section 3.13.2**. The table indicates the outputs will be delivered to the Sponsor, in all subjects enrolled in Spain.

Any additional requests that are not listed below by the Sponsor may be provided for the purpose of supporting regulatory decision making at this time.

Note that data/outputs provided at the time of this IA is subject to change as the safety follow up continues. Any output that is affected may be reproduced at the request of the sponsor prior to final TLF provision.

Table 4. Interim Analysis Outputs

Output	Table	Listing	Figure
Subject Disposition and Demography	Table 14.1.1.1 Subject Enrolment and Disposition (Enrolled Population)	Listing 16.2.1.1 Informed Consent and Study Completion Status (Enrolled Population)	
	Table 14.1.2.1 Demographics and Baseline Characteristics (Safety Population)	Listing 16.2.1.2 Inclusion/Exclusion Criteria and Eligibility (Enrolled Population)	
	Table 14.1.2.2 Baseline Characteristics - Lymphocyte, Serum Immunoglobulin, COVID-19 anti-S IgG (Safety Population)	Listing 16.2.3.2 Study Populations (Enrolled Population)	
		Listing 16.2.4.1.1 Demographics and Baseline Information (Safety Population)	
		Listing 16.2.4.1.2 Baseline Characteristics - Lymphocyte, Serum Immunoglobulin, COVID-19 anti-S IgG (Safety Population)	

Output	Table	Listing	Figure
		Listing 16.2.4.1.3 Baseline Characteristics - Serum Immunoglobulin and COVID-19 anti-S IgG (Safety Population)	
Immunogenicity	Table 14.2.1.1.1 Summary of IC₅₀ and ID₅₀ (HIV) GMT in Neutralising Antibodies Titres against All Variants (Modified Intention-to- treat Population) Table 14.2.1.1.2 Analysis of IC₅₀ and ID₅₀ (HIV) GMT in Neutralising Antibodies Titres against All Variants (Modified Intention-to- treat Population) Table 14.2.1.1.5 Summary of IC₅₀ and ID₅₀ (HIV) GMT in Neutralising Antibodies Titres against All Variants - by Primary Vaccination and COVID-19 Test Groups (Modified Intention-to-treat Population) Table 14.2.1.1.6 Analysis of IC₅₀ and ID₅₀ (HIV) GMT in Neutralising Antibodies Titres against All Variants	Listing 16.2.6.1 PBNA Neutralisation Data (Intention-to-treat Population) Listing 16.2.6.2 VNA Neutralisation Data (Intention-to-treat Population)	Figure 14.2.1.1.1 Log₁₀ IC₅₀ and ID₅₀ (HIV) in Neutralising Antibodies Titres against All Variants Over Time (Modified Intention-to-treat Population) Figure 14.2.1.1.3 Log₁₀ IC₅₀ and ID₅₀ (HIV) in Neutralising Antibodies Titres against All Variants Over Time - by Primary Vaccination and COVID-19 Test Groups (Modified Intention-to-treat Population)

	- by Primary Vaccination and COVID-19 Test Groups (Modified Intention-to-treat Population) Table 14.2.1.2.1 Summary of IC₅₀ and ID₅₀ (HIV) GMFR Fold Rise in Neutralising Antibodies Titres (Modified Intention-to-treat Population) Table 14.2.1.2.2 Analysis of IC₅₀ and ID₅₀ (HIV) GMFR in Neutralising Antibodies Titres (Modified Intention-to-treat Population) Table 14.2.1.2.5 Summary of IC₅₀ and ID₅₀ (HIV) GMFR in Neutralising Antibodies Titres - by Primary Vaccination and COVID-19 Test Groups (Modified Intention-to-treat Population) Table 14.2.1.2.6 Analysis of IC₅₀ and ID₅₀ (HIV) GMFR in Neutralising Antibodies Titres - by Primary Vaccination and COVID-19 Test Groups (Modified		
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Output	Table	Listing	Figure
	Intention-to-treat Population)		
Study Drug Administration		Listing 16.2.5.1 Diary and Dosing Information	
Safety	Table 14.3.1.1 Summary of Adverse Events (Safety Population) Table 14.3.1.2 Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population) Table 14.3.1.5.1 Summary of Solicited Local Reactions from Day 0 through Day 7 (Safety Population) Table 14.3.1.5.3 Summary of Solicited Systemic Events from Day 0 through Day 7 (Safety Population)	Listing 16.2.7.1 Adverse Events (Safety Population)	

8.2. Appendix 2. Exploratory Endpoints SAP

To be provided by FLS-IrsiCaixa team.

8.3. Appendix 3. Hematology Parameters of NCI-CTCAE V5.0

Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology								
Hemoglobin - Low	Decrease	Blood and lymphatic system disorders	Anemia	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80 g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.								
Hemoglobin - High	Increase	Investigations	Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL		-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal.								
Leukocytes/ White blood cell	Decrease	Investigations	White blood cell decreased	<LLN - 3000/mm ³ ; <LLN - 3.0 x 10 ⁹ /L	<3000 - 2000/mm ³ ; <3.0 - 2.0 x 10 ⁹ /L	<2000 - 1000/mm ³ ; <2.0 - 1.0 x 10 ⁹ /L	<1000/mm ³ ; <1.0 x 10 ⁹ /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of white blood cells in a blood specimen.								
Leukocytes/ White blood cell	Increase	Blood and lymphatic system disorders	Leukocytosis	-	-	>100,000/mm ³	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.								
Platelet count (PLT)	Decrease	Investigations	Platelet count decreased	<LLN - 75,000/mm ³ ; <LLN - 75.0 x 10 ⁹ /L	<75,000 - 50,000/mm ³ ; <75.0 - 50.0 x 10 ⁹ /L	<50,000 - 25,000/mm ³ ; <50.0 - 25.0 x 10 ⁹ /L	<25,000/mm ³ ; <25.0 x 10 ⁹ /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.								

8.4. Appendix 4. Chemistry Parameters of NCI-CTCAE V5.0

Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Chemistry								
Albumin	Decrease	Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.								
Alkaline phosphatase (ALP)	Increase	Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal (Baseline grade: >ULN - 2.5 x ULN)	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal (Baseline grade: >2.5 - 5.0 x ULN)	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal (Baseline grade: >5.0 - 20.0 x ULN)	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. (Baseline grade: >20.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.								
Alanine aminotransferase (ALT)	Increase	Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal (Baseline grade: >ULN - 3.0 x ULN)	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal (Baseline grade: >3.0 - 5.0 x ULN)	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal (Baseline grade: >5.0 - 20.0 x ULN)	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. (Baseline grade: >20.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.								

Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase (AST)	Increase	Investigations	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal (Baseline grade: >ULN - 3.0 x ULN)	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal (Baseline grade: >3.0 - 5.0 x ULN)	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal (Baseline grade: >5.0 - 20.0 x ULN)	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. (Baseline grade: >20.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.								
Total Bilirubin	Increase	Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal (Baseline grade: >ULN - 1.5 x ULN)	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal (Baseline grade: >1.5 - 3.0 x ULN)	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal (Baseline grade: >3.0 - 10.0 x ULN)	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal. (Baseline grade: >10.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.								
Creatinine	Increase	Investigations	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN (Baseline grade: >1.5 - 3.0 x ULN)	>3.0 x baseline; >3.0 - 6.0 x ULN (Baseline grade: >3.0 - 6.0 x ULN)	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.								
Potassium - Low	Decrease	Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.								
Potassium - High	Increase	Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.								

Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Sodium - Low	Decrease	Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood. Specified for programming use: Grade 1: <LLN - $\geq$ 130 mmol/L; Grade 2: $\geq$ 125 - < 130; Grade 3: $\geq$ 120 - < 125; Grade 4: < 120 mmol/L.								
Sodium - High	Increase	Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.								
Glucose - Low	Decrease	Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.								
Gamma-Glutamyl Transferase (GGT)	Increase	Investigations	GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal. (Baseline grade: >ULN - 2.5 x ULN)	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal. (Baseline grade: >2.5 - 5.0 x ULN)	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal. (Baseline grade: >5.0 - 20.0 x ULN)	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. (Baseline grade: >20.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.								