Statistical Analysis Plan (SAP) Core Body

Title: A parallel-group, Phase I/II, randomized, modified double-blind, 3-arm, active comparator, multi-center, prevention study to evaluate the immunogenicity and safety of two adjuvanted dose levels of Panblok H7+MF59 influenza vaccine compared with an unadjuvanted Dose of Panblok H7 in participants 18 years of age and older

Study Code: VAM00001

NCT number: NCT05608005

Study Phase: Phase I/II

SAP Core Body Version: 1.0

SAP Core Body Date: 27May2022

Protocol Version Number: 1.0

The SAP Code Body should be used in conjunction of the study protocol and the SAP TLFs.

Version History

Not applicable as this is the first version of the SAP Core Body.

Previous Version(s)*	Date	Comments (optional)
NA	27MAY2022	

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1 Overall Design

The design of the study is summarized in Table 1.1

Table 1.1: Overall design

Type of design	Randomized study, enrolling naive participants, 2-dose, modified double-blind. As the study will include adjuvanted study vaccines that may have a different appearance than the unadjuvanted vaccine, personnel assessing the immunogenicity and safety of the investigational vaccines with the goal of dose selection for the pivotal Phase III study in adults
Phase	I/II
Control method	Active comparator (comparator = Panblok H7 (45 µg) unadjuvanted)
Study population	Healthy adults 18 - 64 and ≥ 65 years of age
Level and method of blinding	Modified double-blind (participant, Sponsor, and Investigator blinded)
Study intervention assignment method	Randomization and stratification by age group Randomization ratio is: 3:3:1 (Study Group 1, Group 2, and Group 3)
Number of participants	Approximately 700 adult participants (350 adults 18 - 64 years of age and 350 adults ≥ 65 years of age)
Intervention groups	Two of the three Investigational Medicinal Products (IMPs) include the MF59 adjuvant. The IMPs included in this study are: **Panblok H7 (7.5 µg) + MF59 (Group 1):** Monovalent Recombinant H7 influenza vaccine [A/Guangdong/17SF003/2016 (H7N9)] with MF59 **Panblok H7 (15 µg) + MF59 (Group 2):**

	Monovalent Recombinant H7 influenza vaccine [A/Guangdong/17SF003/2016 (H7N9)] with MF59 **<u>Panblok H7 (45 µg) unadjuvanted (Group 3):</u>** Monovalent Recombinant H7 influenza vaccine [A/Guangdong/17SF003/2016 (H7N9)]
Total duration of study participation	A pre-vaccination (baseline) blood sample will be taken during Visit (V) 01 (D01) and post-vaccination blood samples will be taken during V02, V03, V04, and V05 (i.e., D22, D43, D202, and D387) for HIH and SN testing to assess the immune response after Dose 1 and Dose 2 of the study intervention and to assess the persistence of the immune response at 6 and 12 months after the last vaccination
Countries	United States of America
Use of an Independent Data Monitoring Committee, Dose-Escalation Committee, or similar review group	Periodic safety management team (SMT) meetings

Number of Participants:

A total of 700 participants is expected to be randomized with the aim to obtain a total of 630 evaluable participants.

	Group 1: Panblok H7 (7.5 µg) + MF59		**Group 2: Panblok H7 (15 µg) + MF59**		**Group 3: Panblok H7 (45 µg) unadjuvanted**		**Total**
	18 - 64 years	**≥ 65 years**	**18 - 64 years**	**≥ 65 years**	**18 - 64 years**	**≥ 65 years**	
Planned number of Participants	150	150	150	150	50	50	700

Estimation of the Number of Sites: Approximately 14 active sites

The graphical design of Study VAM00001 is presented in Figure 1.1.

Table 1.2: Schedule of activities

Phase I/II Study, 5 Visits, 2 Vaccinations, 5 Blood Samples, 13 Months' Duration Per Participant

Visit/Contact	*Collection of information in the CRF*	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Study timelines (days)		D01	21 days post V01 (D22)	21 days post V02 (D43)	6 months post V02 (D202)	12 months post V02 (D387)
Time windows (days)			[+7 D]	[+7 D]	[+14 D]	[+14 D]
Visit procedures:						
Informed consent	X	X				
Inclusion/exclusion criteria	X	X				
Collection of demographic data	X	X				
Urine pregnancy test (if applicable)		X	X			
Collection of Medical history	X Significant Medical History	X				
Physical examination		X	X			
Temporary and definitive contraindications	X		X			
Pre-vaccination temperature		X	X			
Randomization	X	X				
Allocation of participant number	X	X				
Dose assignment by IRT		X	X			
Blood sampling (BL) [40 mL/visit]	X	BL0001 Pre-vac	BL0002 Pre-vac	BL0003	BL0004	BL0005
Vaccination (vac)	X	X	X			

Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Diary card/eDiary provided†		DC1/eDC	DC2	DC3	DC4	
Diary card/eDiary reviewed			DC1/eDC	DC2/eDC	DC3/eDC	DC4/eDC
Diary card collected‡			DC1	DC2	DC3	DC4
Collection of solicited injection site and systemic reactions	X	X	X	X		
Collection of unsolicited adverse events (AEs)	X	X	X	X		
Collection of concomitant medications	X Reportable concomitant medication	X	X	X		
Collection of serious adverse events (SAEs), including AESIs	X	To be reported at any time during the study				
Collection of pregnancies	X	To be reported at any time during the study				
End of Study Intervention Phase§	X			X		
End of study**	X					X

AESI: adverse event of special interest; CRF: case report form; D: day; DC: diary card; IRT: interactive response technology; V: visit

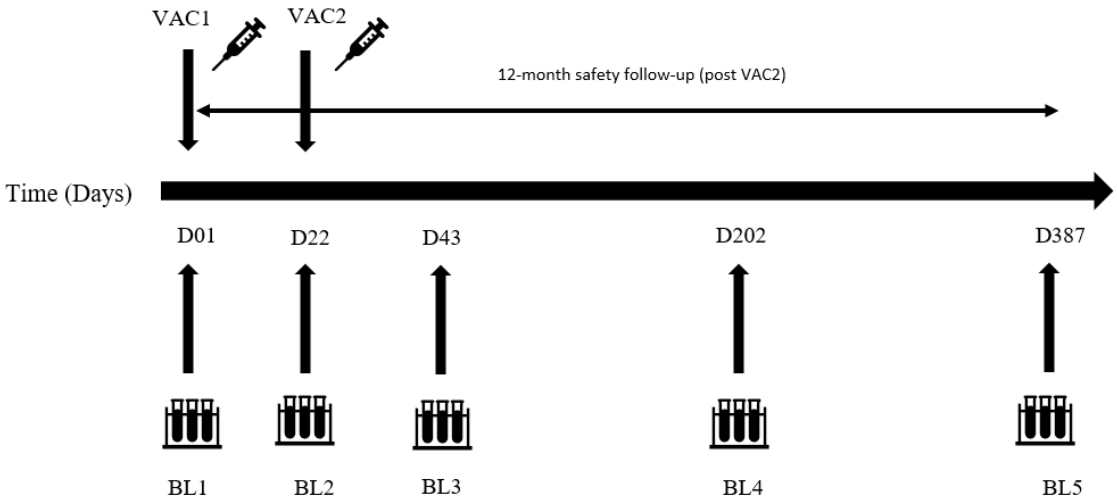
† The investigator or an authorized designee will remind the participants to bring back the DC at the next visit and will answer any questions.

‡ The investigator or an authorized designee will interview the participants to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear.

§ In case of participant discontinuation at a visit, the entire visit will be completed.

** All participants will be scheduled to attend V05 for blood sampling and safety follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted by phone to identify the occurrence of any SAEs and AESIs that had not yet been reported. The site should attempt to contact them and complete the 12-month safety follow-up (and all other scheduled safety follow-ups), except if they specified that they do not want to be contacted again and it is documented in the source document.

Figure 1.1: Graphical study design



BL: Blood sample
VAC: vaccination

Detailed design is provided in Section 4.1 of the protocol.

2 Objectives and Endpoints

Table 2.1: Objectives and endpoints

Objectives	Endpoints
Primary	
To assess the antibody response induced by each study dose group of Panblok H7+MF59 vaccine (7.5 µg and 15 µg) compared with unadjuvanted Panblok H7 (45 µg) by hemagglutination inhibition using horse red blood cells (HIH) and seroneutralization (SN) measurement methods at day (D) 22 and D43 (i.e., 21 days after each vaccination) in participants 18 - 64 years and ≥ 65 years of age	***Immunogenicity*** The following immunogenicity endpoints will be summarized: <u>*Immunogenicity by HIH measurement method:*</u> • Hemagglutination inhibition (HAI) antibody (Ab) titers obtained on D01, D22, D43, D202, and D387 • Individual HAI Ab titers ratio D22/D01, D43/D01, D202/D01, D387/D01, D22/D202, D22/D387, D202/D43 and D387/D43 • Seroconversion defined as titer < 10 (1/dilution [1/dil]) on D01 and post-injection titer ≥ 40 (1/dil) on D43 or defined as titer ≥ 10 (1/dil) on D01 and a ≥ 4-fold increase in titer (1/dil) on D43. Seroconversion defined as titer < 10 (1/dilution [1/dil]) on D01 and post-injection titer ≥ 40 (1/dil) on D22 or defined as titer ≥ 10 (1/dil) on D01 and a ≥ 4-fold increase in titer (1/dil) on D22. • Individual HAI Ab titers ≥ 40 (1/dil) on D01, D22, D43, D202, and D387 • Detectable HAI Ab titer, i.e., with a titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387 <u>*Immunogenicity by SN measurement method:*</u> • Neutralization (NT) Ab titer obtained on D01, D22 D43, D202, and D387 • Individual NT Ab titers ratio D22/D01, D43/D01, D202/D01, D387/D01, D22/D202, D22/D387, D202/D43 and D387/D43 • NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) on D01, D22, D43, D202, and D387

Objectives	Endpoints
	• Fold increase in NT Ab titer [D43/pre-vaccination] ≥ 2 and ≥ 4 on D43 Fold increase in NT Ab titer [D22/pre-vaccination] ≥ 2 and ≥ 4 on D22 • Detectable NT Ab titer, i.e., with a titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387
Secondary	
Safety To assess the safety profile in each study vaccine group in participants 18 - 64 years and ≥ 65 years of age throughout the study	***Safety*** The following safety endpoints will be summarized: • Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination • Presence of solicited (prelisted in the participant's diary card [DC] / electronic diary card [eDC] and case report book [CRB]) injection site reactions and systemic reactions occurring up to 7 days after each / any vaccination • Presence of unsolicited AEs up to 21 days after each / any vaccination • Presence of adverse events of special interest (AESIs) throughout the study • Presence of serious adverse events (SAEs) (including AESIs) throughout the study

3 Statistical Considerations

3.1 Statistical Hypotheses

All analyses will be descriptive; no hypotheses are planned to be tested.

3.2 Sample Size Determination

Assuming a dropout rate of approximately 10%, a total of approximately 630 participants evaluable for immunogenicity is anticipated.

No study power was calculated for this study. However, examples were given in the table below showing the probability of 2-sided 95% lower being greater than the CBER thresholds (1), if the proportion of participants with HAI antibody titer ≥ 1:40 reach a certain proportion; or if the proportion of participants with seroconversion reach a certain proportion.

Table 3.1 shows the expected number of evaluable participants in each study group and each age stratum, and the probability that the lower bound of the 95% CI exceeding the threshold defined by Center for Biologics Evaluation and Research (CBER) requirement for seroconversion and percentage of participants achieving an HAI antibody titer ≥ 1:40 (1).

Table 3.1: Probability of exceeding the CBER lower bound if a certain proportion is achieved

Age in Years	Evaluable Number of Participants (Study Group)	Expected Proportion	CBER: Lower Bound of 2-Sided 95% CI Greater Than	Probability (%)
Percentage of participants with HAI antibody titer ≥ 1:40				
≥ 18	270 (Groups 1 or 2)	0.80	70%	96%
18 to < 65	135 (Groups 1 or 2)	0.82	70%	88%
≥ 65	135 (Groups 1 or 2)	0.72	60%	82%
≥ 18	90 (Group 3)	0.85	70%	93%
18 to < 65	45 (Group 3)	0.85	70%	< 80%
≥ 65	45 (Group 3)	0.80	60%	83%
Percent of participants with seroconversion for antibody				
≥ 18	270 (Groups 1 or 2)	0.50	40%	90%
18 to < 65	135 (Groups 1 or 2)	0.52	40%	<80%

Age in Years	Evaluable Number of Participants (Study Group)	Expected Proportion	CBER: Lower Bound of 2-Sided 95% CI Greater Than	Probability (%)
≥ 65	135 (Groups 1 or 2)	0.42	30%	82%
≥ 18	90 (Group 3)	0.55	40%	80%
18 to < 65	45 (Group 3)	0.70	40%	97%
≥ 65	45 (Group 3)	0.50	30%	<80%

3.3 Populations for Analyses

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Randomized	All participants randomized by study IRT to one of the 3 study doses (one of three study groups).
Safety Analysis Set (SafAS)	Participants who have received at least one study intervention. All participants will have their safety analyzed after each dose according to the intervention received, and after any dose according to the intervention received at the 1st dose. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of randomized participants who received at least 1 dose of the study vaccine and had a post-vaccination blood sample for D22 or D43. Participants will be analyzed according to the study dose group to which they were randomized.
Per-protocol analysis set (PPAS)	To be able to compare and present the results of immunogenicity in the same table, only one PPAS will be derived in this study. Subset of the FAS participants. Participants presenting with at least one of the following relevant protocol conditions will be excluded from the PPAS: • Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participant did not complete the vaccination schedule • Participant received a vaccine other than the one that he / she was randomized to receive • Preparation and / or administration of vaccine was not done as per-protocol • Participant did not receive vaccine in the proper time window

Participant Analysis Set	Description
	• Participant did not provide a post-dose serology sample at D22 (+7 days) and D43 (+7 days) in the proper time window or a post-dose serology sample was not drawn • Participant received a medication impacting or that may have an impact on the immune response as described in Section 6.8 of the protocol. • Re-randomized participants Any other deviation identified during the study conduct and judged by the clinical team during data review as having a potential impact on the assessment of immunogenicity will be used to exclude a participant from the PPAS. These deviations will be determined during the protocol deviations review and will be flagged for excluding a participant from PPAS. In the event of a local or national immunization program with a SARS-CoV-2 or other vaccine, participants who receive 1 or more doses of the vaccine listed above at any time during the study will not be withdrawn from the study.

3.4 Statistical Analyses

The SAP Core Body should be used in conjunction with the study protocol and the SAP TLFs. The Core Body and TLFs are available before the first interim analysis (without considering SMT analysis).

3.4.1 General Considerations

The statistical analysis referring to primary and secondary objectives will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 or later.

The statistical analysis will be conducted as follows:

- The database will be locked, and the study will be unblinded after all immunogenicity and safety data are collected for the follow-up period of 3 weeks after D22 (i.e., 21 days after the last vaccination).
- The final database lock will occur after the 12-month follow-up.

No adjustment for multiplicity regarding multiple comparisons between study doses is planned in this study.

For descriptive purposes, the following statistics will be presented:

Table 3.2: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number and percentage of participants
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum
Safety results	**Categorical data**	Solicited: Number and percentage (95% confidence intervals [CIs]) of participants Unsolicited: Number and percentage (95% CIs) of participants, and number of events
	Continuous data	At least mean, standard deviation, minimum, and maximum
Immunogenicity results	**Categorical data (seroprotection, seroconversion, cutoff)**	Number and percentage (95% CIs) of participants
	Continuous data (titer / data)	Log_{10}: Mean and standard deviation Anti-Log_{10} (work on Log_{10} distribution, and anti-Log_{10} applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum Graphical representation by Reverse Cumulative Distribution Curve (RCDC) Graphical representation showing geometric mean titer (GMT) kinetics Graphical representation showing boxplot

The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (2), i.e., using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

3.4.2 Primary Endpoints

Primary Immunogenicity Objective

The immunogenicity parameters will be calculated with their 95% CIs using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed for GMTs and GMTs ratio. The 95% CI of proportions difference (i.e., difference between vaccine groups in seroconversion) will be calculated using Wilson Score method without continuity correction (3). All analyses will be conducted by study group and by age stratum.

The time windows used for collecting blood samples are: D01, D22 [+7], D43 [+7], D202 [+14], and D387 [+14]. To avoid redundancy and typing errors, these time windows will not be reported in all sections of this document.

- Immunogenicity by HIH measurement method
  - GMTs of HAI Ab titers obtained on D01, D22, D43, D202, and D387
  - Geometric mean of individual ratios of HAI Ab titers D22/D01, D43/D01, D202/D01, D387/D01, D22/D202, D22/D387, D202/D43 and D387/D43
  - Percentage of participants with seroconversion defined as HAI Ab titer < 10 (1/dilution [1/dil]) on D01 and post-injection titer ≥ 40 (1/dil) on D43 or defined as titer ≥ 10 (1/dil) on D01 and a ≥ 4-fold increase in titer (1/dil) on D43.

    Percentage of participants with seroconversion defined as HAI Ab titer < 10 (1/dilution [1/dil]) on D01 and post-injection titer ≥ 40 (1/dil) on D22 or defined as titer ≥ 10 (1/dil) on D01 and a ≥ 4-fold increase in titer (1/dil) on D22.

    The interpretation of the results will account for seroconversion thresholds reported in FDA guideline (1) for participants 18 – 64 years and ≥ 65 years of age.

  - Percent of participants with HAI Ab titers ≥ 40 (1/dil) on D22, and percent of participants with HAI Ab titers ≥ 40 (1/dil) on D43. The same statistic will be calculated for D01, D202, and D387.

    The interpretation of the results will account for sero-protection thresholds reported in FDA guideline (1) for participants 18 – 64 years and ≥ 65 years of age.
  - Percent of participants with detectable HAI Ab titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387.
  - Difference and its 95% CI in seroconversion between the 3 study doses (Group 1 - Group 3; Group 2 - Group 3, and Group 2 - Group 1) at D22 and D43.
  - Ratio of GMTs and its 95% CI for: Group1/Group3, Group2/Group3, and Group2/Group1 at D22, and at D43.
  - The RCDCs of pre-vaccination titer prior to the first vaccination (D01), and post-vaccination titer at D22, D43, D202, and D387 will be generated for each study dose. The RCDCs will include the plots of the 3 doses on the same figure.

- Immunogenicity by SN measurement method
  - GMTs of NT Ab titer obtained on D01, D22, D43, D202 and D387.
  - Geometric mean of individual ratios of NT Ab titers D22/D01, D43/D01, D202/D01, D387/D01, D22/D202, D22/D387, D202/D43 and D387/D43
  - Percentage of participants with NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥80 (1/dil) on D01, D22, D43 D202 and D387.
  - Percent of participants with fold increase in NT Ab titer [D43/pre-vaccination] ≥ 2 and ≥ 4 on D43

Percent of participants with fold increase in NT Ab titer [D22/pre-vaccination] ≥ 2 and ≥ 4 on D22

- Percent of participants with detectable NT Ab titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387.
- Difference and its 95% CI in percentage of participants with fold increase between the 3 study doses (Group 1 - Group 3, Group 2 - Group 3, and Group 2 - Group 1) on D22, and on D43.
- Ratio of GMs and its 95% CI for: Group1/Group3, Group2/Group3, and Group2/Group1 on D22, and on D43.
- The RCDCs of pre-vaccination titer prior to the first vaccination (D01) and post-vaccination titer at D22, D43, D202, and D387 will be generated for each study dose. The RCDCs will include the plots of the three doses on the same figure.

For each immunogenicity measurement method, the analysis will be conducted for each immunogenicity variable on the PPAS and the FAS.

In addition, subgroup analysis will be performed on FAS; in, immunogenicity will be described according to sex, race, age subgroups and sero-status at baseline as appropriate according to number of participants in the respective subgroup(s).

3.4.3 Secondary Endpoints

Safety

For the main safety parameters, 95% CIs of point estimates will be calculated using exact binomial method (Clopper-Pearson method) for single proportions and using the normal approximation for quantitative data.

All analyses will be descriptive; no hypotheses will be tested.

The number of participants with documented safety will be used as denominator of the frequencies:

- For solicited reactions, the denominator will be the total number of participants who have non-missing data for the endpoint considered.
- For unsolicited AEs, the denominator will be the total number of participants who were vaccinated with the dose analyzed.

In terms of contents, solicited reactions will be presented by time to onset, maximum severity, number of days of occurrence and action taken; unsolicited AEs will be presented by causal relationship, time of onset, maximum severity, and duration; SAEs will be presented by causal relationship, seriousness, and outcome.

Subgroup analysis will also be performed; in particular, the main safety endpoints will be summarized according to age subgroups, sex, and race, as appropriate according to number of participants in the respective subgroups.

3.4.4 Handling of Missing Data and Outliers

3.4.4.1 Immunogenicity

No imputation of missing values and no search for outliers will be performed. LLOQ and ULOQ management will be performed as described in Section 4.2.1.1.

3.4.4.2 Safety

No replacement will be done for Safety Missing Data and Outliers.

3.4.4.2.1 Immediate

For unsolicited systemic AEs, a missing response to the "Immediate" field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

3.4.4.2.2 Causal Relationship

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the eCRF are also considered as related to vaccination and will be considered as reactions.

- For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis
- The missing relationship to study procedures for SAEs will not be imputed

3.4.4.2.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.2.1.2. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

3.4.4.2.4 Start Date and End Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be set to missing. If either the start date or end date is missing or partially missing, the duration will be considered missing.

Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed.

3.4.4.2.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.5 Interim Analysis

The blind will be broken at the participant level after collecting all immunogenicity and safety data up to 21 days after last vaccination, data are cleaned, and database is locked. The study participants and the laboratory personnel who analyze the blood samples will remain blinded throughout the study. The study team will strive not to communicate the study unblinded data to the sites until the interim CSR sign-off, to minimize the bias in collecting the follow-up safety data.

The main analysis of immunogenicity (HIH and SN measurement methods) data and safety will include all data up to 21 days after the last vaccination. The results of this analysis will help in selecting the dose formulation for further clinical development. The results of this main analysis may be reported in an interim clinical study report (CSR).

HIH and/or SN results will be evaluated, discussed, and used in selecting the best Panblok formulation with the most suitable immunogenicity response and safety for further clinical development.

A final database lock will occur after all data, including up to the 12-month follow-up period, are collected. A final CSR would include the analysis of the safety and immunogenicity data at 6- and 12-month after the last vaccination to assess the persistence of the antibody levels.

No hypothesis will be tested, thus adjustment for multiplicity is not necessary.

Unblinded early looks at the safety data may take place to assess safety.

3.6 Data Monitoring Committee (DMC)

No independent Data Monitoring Committee (DMC) is planned. Participant safety data will be continuously monitored by the Sponsor's internal safety management team (SMT), led by the Global Safety Officer, to detect any safety signals during the study period.

A separate SAP will be dedicated to SMT summaries and analysis.

4 Complementary Information on Assessment Methods

Study assessments and procedures are detailed in Section 8 of the protocol. This section focusses on complementary/additional information not detailed in the protocol.

4.1 Complementary Information for Endpoints Assessment Methods

Not applicable.

4.2 Complementary Information on Derived Endpoints: Calculation Methods

4.2.1 Immunogenicity

4.2.1.1 Computed Values for Statistical Analysis

For the derivation of immunogenicity endpoints, all values strictly under the lower limit of quantification (LLOQ) will be treated as LLOQ/2, and all values above or equal to the upper limit of quantification (ULOQ) will be treated as ULOQ.

For the analysis of the results of HIH assay, which is performed in duplicate, the individual geometric mean (GM) of both values will be computed for each blood sample and each strain, after managing extreme values as described above. The computed value is then considered the titer for that blood sample.

Only 1 titer value will be recorded for SN assay.

To appropriately manage extreme values (LLOQ and ULOQ) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample (BL) drawn:

For HAI

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the value ULOQ

For SN:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the value ULOQ

4.2.1.2 Fold-rise

For both the HAI and SN immune response, the derived endpoint fold-rise is driven by both baseline (D01) and post-baseline (D22 or D43) computed values as described in Section 4.2.1.1 and is computed as individual ratio:

- 22 days after the last vaccination divided by D01.

Note: if pre-vaccination (D01) or post-vaccination (D22 or D43) values is missing, the fold-rise will be missing.

4.2.1.3 Seroconversion

For HAI assay, seroconversion is defined as a binary indicator. If a pre-vaccination (D01) titer < 10 (1/dil): post-vaccination titer ≥ 40 (1/dil) on D43, or ≥ 4-fold-rise for participants with a pre-vaccination titer ≥ 10 (1/dil), the derived seroconversion indicator will be "Yes", otherwise will be "No".

For HAI assay, seroconversion is defined as a binary indicator. If a pre-vaccination (D01) titer < 10 (1/dil): post-vaccination titer ≥ 40 (1/dil) on D22, or ≥ 4-fold-rise for participants with a pre-vaccination titer ≥ 10 (1/dil), the derived seroconversion indicator will be "Yes", otherwise will be "No".

Note: if pre-vaccination (D01) or post-vaccination (D22 or D43) value is missing, the seroconversion is missing.

4.2.2 Safety

4.2.2.1 Solicited Reactions

4.2.2.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing (Unknown).

For the derivation of daily intensities, the following sequential steps will be applied:

1) For solicited reactions (except fever/pyrexia) with eCRF presence recorded as "No" and with all daily records missing (Unknown), all daily intensities will be derived as None.
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions, the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3.

The intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement >0 mm but <25 mm in adults).

Note: The maximum intensity of the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

4.2.2.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.2.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.2.2.1.3 Presence

Presence is derived from the maximum overall intensity over the time-period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing or Unknown: Missing presence

Participants with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

4.2.2.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.2.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None), then the time of onset is the first day of the first occurrence.

Time of onset period is displayed as D01-D04 and D05-D08 after vaccination.

4.2.2.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of presence over the period considered is derived from the daily intensities computed as described in Section 4.2.2.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence over the solicited period with a specified intensity may also be derived.

4.2.2.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of presence is derived from the daily intensities and the end date of the reaction after the end of the solicited period. The overall number of days of presence is:

- (End date - last vaccination date) + (number of days of presence within the solicited period) - length of the solicited period + 1

If the end date is missing or incomplete (contains missing data), the overall number of days of presence will be considered as Missing.

4.2.2.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.2.1.1, and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement will determine the ongoing status of the reaction.

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1.
- Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in the safety tables).

4.2.2.2 Unsolicited AEs

4.2.2.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event.

Grade 0 events are not included in safety analysis but are included in separate listings.

4.2.2.2.2 Intensity

Intensity will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or missing.

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm).

Intensity for the other unsolicited AEs will correspond to the value reported in the eCRF.

The maximum intensity corresponds to the highest intensity for a unique term.

4.2.2.2.3 Last Vaccination

Last vaccination before an unsolicited AE will be derived from the pre-visit numbers provided in the clinical database and will be calculated as follows:

- If an unsolicited AE has a non-missing pre-visit number, the pre-visit number will be used to determine the last vaccination before the unsolicited AE.

- If the pre-visit number is missing and the start date is complete (i.e., including the day), then the start date will be used to determine the last vaccination before the unsolicited AE.
- If an unsolicited AE has a missing pre-visit number and a partial start date (at least the day missing), the unsolicited AE will be considered as post injection 1.

4.2.2.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of vaccination:

Time of Onset = start date of the unsolicited AE - date of vaccination + 1 (if D01 is the first vaccination day).

The time of onset is considered as missing only if one or both dates are missing or partially missing.

The unsolicited AEs will be analyzed "Within 21 days" after each vaccination, which corresponds to AEs with a time of onset between D01 and D22 or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination, so will be included in these tables.

Time of onset period is displayed as D01-D04, D05-D08, D09-D15, D16 or later, and missing.

Note: Unsolicited AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis but will be listed separately.

4.2.2.2.5 Duration

Duration is derived from the start and end dates of the unsolicited AE:

- Duration = End date of unsolicited AE - start date of unsolicited AE + 1

The duration is considered as missing only if one or both start and end dates of the unsolicited AE is missing or partially missing.

4.2.2.2.6 Serious Adverse Events

An event will be considered as a serious event if "Yes" is checked for "Serious?" in the eCRF. SAEs will be analyzed within 21 days after each vaccination, from D22 to 387 days after each vaccination, and within 387 days after each vaccination.

4.2.2.2.7 Adverse Events of Special Interest

An event will be considered as an AESI if "Yes" is checked for "Is the event an AESI?" in the eCRF.

AESIs will be analyzed within 21 days after each vaccination, from D22 to 387 days after each vaccination, and within 387 days after each vaccination.

4.2.3 Other Safety Endpoints

4.2.3.1 Pregnancy

This information will be listed separately. No derivation or imputation will be done.

4.2.3.2 Action Taken

This information will be summarized as collected. No derivation or imputation will be done.

4.2.3.3 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.2.3.4 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.2.3.5 Causal Relationship

This information will be summarized as collected in the field "Relationship to study vaccine". Missing causal relationship will be handled as described in Section 3.4.4.2.2. Relationship to study procedure is only presented in the listing.

4.2.3.6 Adverse Events Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs to identify AEs leading to discontinuation before the end of active/intervention phase. In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Active/intervention Phase" form question "What was the participant's status?" has "Adverse Event" checked.

- Safety overview table: A participant who has either on the "Completion at End of Active/intervention Phase" form, question" What was the participant's status?" has "Adverse Event" checked or lists a solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time-period indicated.

- System Organ Class (SOC)/Preferred Term (PT) table: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time-period indicated.

4.2.4 Derived Other Variables

4.2.4.1 Age for Demographics

The age of a participant in the study will be the calendar age in years at the time of inclusion, as collected in the eCRF.

4.2.4.2 Duration of a Participant in the Trial

The duration of a participant in the trial, including the D387 safety follow-up, is computed as follows:

- Maximum (visit dates, termination date, safety follow-up date) – V01 date + 1.

The duration of a participant in the active phase of the trial is computed as follows:

- Maximum (V02 or V03 dates, termination during the active/intervention phase) − V01 date + 1.

4.2.4.3 Duration of the Study

The duration of the study is computed in days as follows:

- Maximum (Visit dates, Termination and safety follow-up date) – minimum (V01 date) + 1

The duration of the active phase of the study is computed in days as follows:

- Maximum (latest date of V02 or V03, date of termination during the active/intervention phase) − minimum (V01 date) + 1,

The duration of the D387 safety follow-up phase of the study is computed in days as follows:

- Maximum (date of D387 safety follow-up) − minimum (V02 or V03 dates, termination dates during the active/intervention phase) + 1

Note: Some participants will be vaccinated only with 1 dose and may decide not drop-out of the study.

5 Changes in the Conduct of the Trial or Planned Analyses

Not applicable.

6 Supporting Documentation

6.1 Appendix 1 List of Abbreviations

Ab	antibody
AE	adverse event
AESI	adverse events of special interest
BL	blood sample
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CRF	case report form
CSR	clinical study report
D	day
DC	diary card
Dil	dilution
DMC	Data Monitoring Committee
eCRF	electronic case report form
eDC	electronic diary card
FAS	Full Analysis Set
GMT	geometric mean titer
H7	rHA of A/Guangdong/17SF003/2016 (H7N9)
HAI	hemagglutination inhibition
HIH	hemagglutination inhibition using horse red blood cells
IMP	investigational medicinal product
IRT	interactive response technology
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MF59	adjuvant
mm	millimeter
NM	non-measurable
NT	neutralization test
PPAS	Per-protocol Analysis Set

PT	preferred term (MedDRA)
RCDC	reverse cumulative distribution curve
rHA	recombinant hemagglutinin protein
SAE	serious adverse events
SafAS	Safety Analysis Set
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMT	Safety Management Team
SN	Sero-neutralization
SOC	(primary) system organ class
TLF	tables, listings, and figures
ULOQ	upper limit of quantitation
V	visit
VAC	vaccination (as in vaccination #)

7 References

1. Food and Drug Administration. Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines. May 2007. Available at: https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Guidance-for-Industry--Clinical-Data-Needed-to-Support-the-Licensure-of-Pandemic-Influenza-Vaccines.pdf

2. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.

3. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998;17(8):873-90.