NCT04969276

SAP Core Body

Protocol Title:

A Phase II, open-label study to assess the safety and immunogenicity of Fluzone® High-Dose Quadrivalent (Influenza vaccine), 2021–2022 Formulation and a third dose of Moderna COVID-19 Vaccine (mRNA-1273 vaccine) administered either concomitantly or singly in adults 65 years of age and older previously vaccinated with a 2-dose schedule of Moderna COVID-19 Vaccine

Study Code: QHD00028

Study Phase: II

SAP Core Body Version: 2.0

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Protocol Version Number: 4.0

Version History

Previous Version(s)	Date	Comments (optional)
1.0	06 July 2021	Based on protocol version 3.0

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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	3-arm study with either concomitant or single administration of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine
Phase	II
Control method	Active-controlled (single administration versus coadministration)
Study population	Adults 65 years of age and older
Level and method of blinding	Open-label
Study intervention assignment method	Randomization
Number of participants	300 participants 65 years of age and older
Intervention groups	Participants will be randomly assigned to 1 of the 3 study groups in a 1:1:1 ratio, corresponding to *i)* concomitant administration of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine, *ii)* administration of Fluzone High-Dose Quadrivalent vaccine alone, and *iii)* administration of Moderna COVID-19 Vaccine alone
Total duration of study participation	Approximately 180 days (6 months after vaccination) for all participants
Countries	United States
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

Table 1.2: Schedule of activities (simplified compared to the protocol)

Phase II Study, 2 Visits, 2 Telephone Contacts, either 1 or 2 Vaccination, 2 Blood Samples, 180 Days' Duration Per Participant

Visit (V)	***Collection of information in the CRF***	**V01**	**Telephone contact (TC1)**	**V02**	**TC2 6-Month Safety Follow-up**
Study timelines (days [D])		D01	D08	D22	D181
Time interval (days)			V01 + 7 days	V01 + 21 days	V01 + 180 days
Time windows (days)			[+2 days]	[+3 days]	[+14 days]
Visit procedures:					
Informed consent	*X*	X			
Inclusion/exclusion criteria	*X*	X			
Collection of demographic data	*X*	X			
Collection of medical history *	*X* Significant Medical History	X			
History of seasonal influenza and COVID-19 vaccination	*X*	X			
Randomization / Allocation of participant number	*X*	X			
Blood samples (BL) for Ab assays (20 mL) ‡	*X*	BL0001		BL0002	
Vaccination (VAC)	*X*	VAC1 (all groups) VAC2 (Group 1)			
Immediate surveillance (30 min)	*X*	X			
Collection of solicited injection site and systemic reactions	*X*	Up to 7 days after vaccination			
Collection of unsolicited AEs	*X*	Up to 21 days after vaccination			
Collection of concomitant medications	*X* Reportable concomitant medication	X		X	
Collection of SAEs, AESIs, and MAAEs ‡‡	*X*	To be reported at any time during the study			
End of Active Phase participation record***	*X*			X	
End of 6-month safety follow-up ***					X

Abbreviations: Ab, antibody; AE, adverse event; AESI, adverse event of special interest; BL, blood sample (#); CRF, case report form; D, Day; DC, diary card; SAE, serious adverse event; AESI, adverse event of special interest; MAAE, medically-attended adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; V, Visit; VAC, Vaccination.

* Including history of COVID-19 infection.

† Targeted physical examination will be performed at V01. If needed, targeted physical examination based on medical history and Investigator's discretion might be performed at the other vaccination visit(s).

‡ BL0001 must be collected before vaccine injection. Participants that consent to Future Research by ticking the corresponding box in the ICF will provide a 20 mL of blood instead of 10 mL for each BL0001 and BL0002.

§ Participants will use DC1 to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D01 to D08 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D09 to D22.

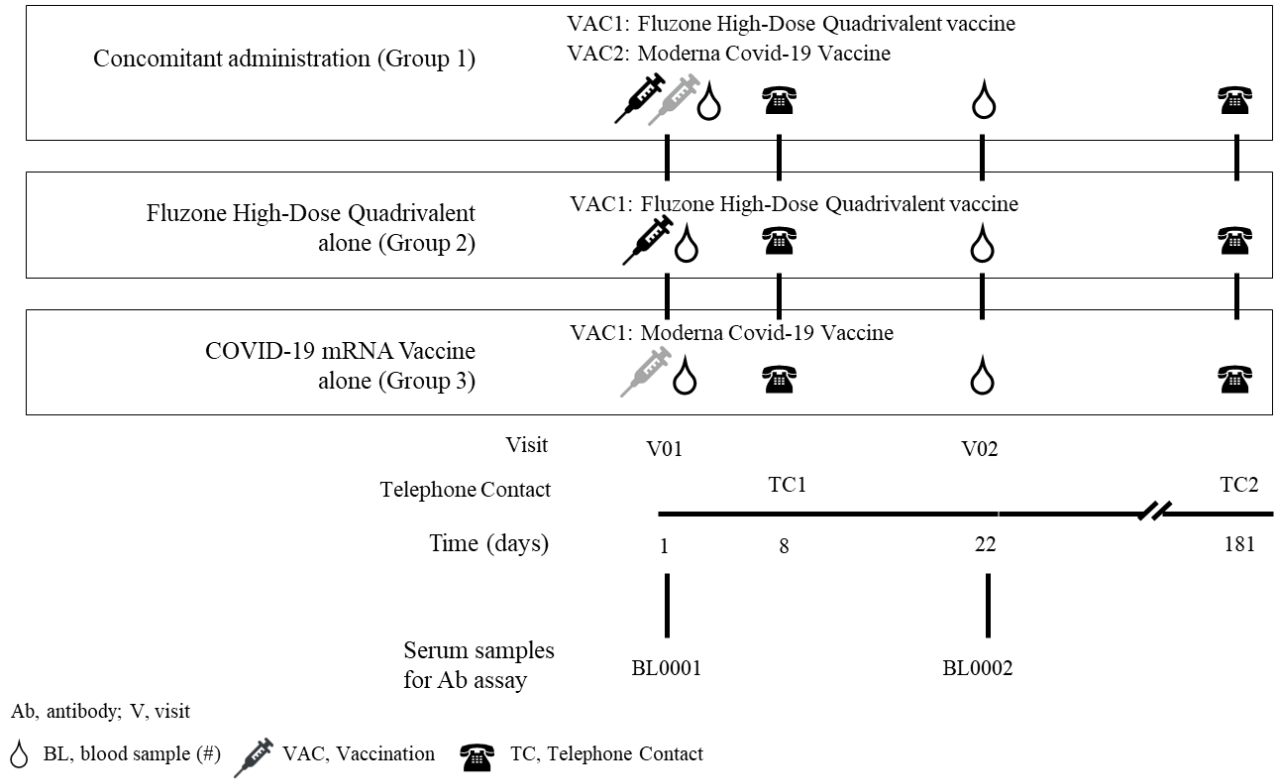
** The Investigator or an authorized designee will remind the participants to bring back the DC at the next visit and will answer any questions.

†† The Investigator or an authorized designee will interview the participants to collect the information recorded in the DC1 and will attempt to clarify anything that is incomplete or unclear.

‡‡ AESIs (serious and non-serious) will be collected throughout the study as SAEs to ensure that events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causal relationship. Full list of AESIs is available in Section 8.3.6 of the protocol.

*** Participants will be in the Active Phase from enrollment (D01) until completion of V02 and in the 6-Month Safety Follow-Up from completion of V02 until approximately 6 months after V01.

Figure 1.1: Graphical study design



Detailed design is provided in Sections 4.1 and 1.2 of the protocol.

2 Objectives and Endpoints

Table 2.1: Objectives and endpoints

Objectives	Endpoints
Safety Objective	
• To describe the safety profile of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine administered concomitantly or singly, up to 21 days after injection in each study intervention group.	• Presence of immediate unsolicited systemic adverse events (AEs) reported in the 30 minutes after injection • Presence of solicited (pre-listed in the participant's diary card [DC] and CRF) injection site reactions and systemic reactions occurring up to 7 days after injection • Presence of unsolicited AEs reported up to 21 days after injection • Presence of serious adverse events (SAEs) reported up to 6 months after injection • Presence of adverse events of special interest (AESIs) reported up to 6 months after injection • Presence of medically-attended AEs (MAAEs) reported up to 6 months after injection
Immunogenicity Objectives	
1) To describe the immune response elicited by Fluzone High-Dose Quadrivalent vaccine administered concomitantly or singly, in each study intervention group.	<u>Endpoints for Immunogenicity Objective #1</u> • Hemagglutination inhibition (HAI) individual titer on Day (D) 01 and 21 days after injection of Fluzone High-Dose Quadrivalent vaccine (D22) • Individual HAI titers ratio D22/D01 • Detectable HAI titer, ie, with a titer ≥ 10 (1/dil) at D01 and 21 days after injection of Fluzone High-Dose Quadrivalent (D22) • Seroconversion (titer < 10 [1/dil] at D01 and post-vaccination titer ≥ 40 [1/dil] at D22, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold-rise in titer [1/dil] at D22) • HAI titer ≥ 40 (1/dil) on D01 and 21 days after injection of Fluzone High-Dose Quadrivalent (D22)
2) To describe the immune response elicited by Moderna COVID-19 Vaccine administered concomitantly or singly, in each study intervention group.	<u>Endpoints for Immunogenicity Objective #2</u> • Individual anti-S binding IgG concentration on D01 and 21 days after injection of Moderna COVID-19 Vaccine (D22) • Individual anti-S binding IgG concentration ratio

	D22/D01 • 2-fold-rise and 4-fold-rise in anti-S binding IgG concentration 21 days post-injection D01

3 Statistical Considerations

3.1 Statistical Hypothesis

No hypothesis testing will be performed in this study.

3.2 Sample Size Determination

The study will enroll approximately 300 participants 65 years of age or older: approximately 100 participants will be concomitantly administered of Fluzone High-Dose Quadrivalent vaccine and Moderna COVID-19 Vaccine (Group 1), approximately 100 participants will be administered Fluzone High-Dose Quadrivalent vaccine alone (Group 2), and approximately 100 participants will be administered Moderna COVID-19 Vaccine alone (Group 3).

3.3 Populations for Analyses

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

Participant Analysis Set	Description
Randomized	All participants that have a randomization number
Safety Analysis Set (SafAS)	Participants who received at least 1 dose of study vaccine. All participants will have their safety analyzed according to the vaccine they actually received and study intervention group. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Immunogenicity analysis set (IAS)	Subset of randomized participants who received at least 1 dose of study vaccine. Participants will be analyzed according to the vaccine they actually received and study intervention group.

3.4 Statistical Analyses

3.4.1 General Considerations

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the SAS® software, Version 9.4 or above (SAS Institute, Cary, North Carolina, USA).

For descriptive purposes, the following statistics will be presented:

Table 3.1: Descriptive statistics produced

Disposition and follow-up description	**Categorical data**	At least number of participants (Percentage of participants are also possible).
	Continuous data	Mean, standard deviation, minimum and maximum.
Baseline characteristics	**Categorical data**	Number of participants. Percentage of participants.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs for main endpoints) of participants. Unsolicited: Number and percentage (95% CIs for main endpoints) of participants and number of events.
Immunogenicity results	**Categorical data (seroconversion, cutoff)**	Number and percentage (95% CIs for main endpoints) of participants.
	Continuous data (titer / concentration)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (1), 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.

For each participant, randomized study group will be assigned from the randomization number assigned to the participant, and injected vaccine/study group will be derived from the label of the vaccine(s) injected on D01, as collected in the CRF.

3.4.2 Safety Endpoints

The SafAS will be used. Safety will be assessed in all 3 study groups, however the assessment of the safety of the co-administration with regards to single administration will focus on groups 1 and 3, as influenza vaccine is expected to be less reactogenic.

Safety endpoints will be summarized, with 95% CI for the main endpoints, by actual study group. Injection site reactions will be summarized by actual study group and vaccine received; for subjects having received the 2 concomitant administrations, injections site reactions will be assigned to one of the 2 vaccines according to the side of vaccination/reaction.

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 analyses will also be performed as complementary analyses; in particular, the main safety endpoints will be described according to gender and age group, as appropriate according to number of participants in the respective subgroups.

3.4.3 Immunogenicity Endpoints

The IAS will be used. Immunogenicity endpoints will be summarized with 95% CI by actual study group and vaccine received, for each timepoint. Cumulative distribution frequencies will also be provided to support that concomitant vaccine administration does not interfere with the assay readout, particularly at the extremes of high and low titer results.

In addition, the ratios of post-vaccination GMTs between concomitant and single injections will be presented for the five antigens with 2-sided 95% CIs. A baseline adjustment will be applied using an ANCOVA model of the D22 log10 titer/concentration with vaccine group and D01 log10 titer as factor and covariate, respectively.

Subgroup analyses will also be performed as complementary analyses; in particular, immunogenicity will be described according to serostatus at baseline (pre-vaccination < or >= to LLOQ), previous influenza vaccination, gender and age group, as appropriate according to number of participants in the respective subgroups.

3.4.4 Handling of Missing Data and Outliers

3.4.4.1 Safety

Generally, no replacement will be done for Safety Missing Data and Outliers.

3.4.4.1.1 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.

3.4.4.1.2 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 CRF 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(s) at the time of analysis.
- The missing relationship to study procedures for SAEs will not be imputed.

3.4.4.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

3.4.4.1.4 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 considered 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.

3.4.4.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.4.4.2 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 4.2.3.1.

3.5 Interim Analysis

The statistical analysis will be performed in two or three steps, depending on the availability of immunogenicity data: the safety objectives up to D22 will be analyzed first and the immunogenicity objectives will be analyzed in a second step, after immunogenicity data have been released. No impact is expected on immunogenicity results as the conduct of

immunogenicity assays will remain blinded. At last, the final analysis will be performed when safety data up to D181 is released.

3.6 Data Monitoring Committee (DMC)

Not applicable

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 Method

Not applicable.**Complementary Information on Derived Endpoints: Calculation Methods**

4.2.1 Safety

4.2.1.1 Solicited Reactions

4.2.1.1.1 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) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as "No" and with all daily records missing (Unknown) then 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. Note 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 on 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.

4.2.1.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.2.1.1.3 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.

4.2.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.1.1.1. 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, D1-D4, D5-D8.

4.2.1.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

4.2.1.1.6 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 - 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.

4.2.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.1.1.1 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).

4.2.1.1.8 Vaccination

For participants having received 1 vaccine, solicited reactions will be assigned to the vaccine received. For participants having received the 2 concomitant administrations, solicited injections site reactions will be assigned to the vaccine injected on the same side as the solicited reaction, and solicited systemic reactions will be assigned to both vaccines.

4.2.1.2 Unsolicited AEs

4.2.1.2.1 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.

4.2.1.2.2 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 in adults).

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

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

4.2.1.2.3 Vaccination

For participants having received 1 vaccine, unsolicited AEs will be assigned to the vaccine received. For participants having received the 2 concomitant administrations, unsolicited injections site reactions will be assigned to the vaccine injected on the same side as the reaction, and other AEs will be assigned to both vaccines.

4.2.1.2.4 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 D1 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 vaccination, which corresponds to AEs with a time of onset between D1 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 D1-D4, D5-D8, D9-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.

4.2.1.2.5 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 of the start and end dates of the unsolicited AE is missing or partially missing.

4.2.1.2.6 Medically-Attended Adverse Event

An event will be considered as an MAAE if "Yes" is checked for "Is the event an MAAE?" in the CRF. MAAE will be analyzed within 21 days after vaccination, from D22 to 180 days after vaccination, and within 180 days after vaccination.

4.2.1.2.7 Serious Adverse Events

An event will be considered as a serious event if "Yes" is checked for "Serious" in the CRF.

SAEs will be analyzed within 21 days after vaccination, from D22 to 180 days after vaccination, and within 180 days after vaccination.

4.2.1.2.8 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 CRF.

AESIs will be analyzed within 21 days after vaccination, from D22 to 180 days after vaccination, and within 180 days after vaccination.

4.2.2 Other Safety Endpoints

4.2.2.1 Pregnancy

Not applicable

4.2.2.2 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.2.2.3 Seriousness

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

4.2.2.4 Outcome

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

4.2.2.5 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 3.4.4.1.2. Relationship to study procedure is only presented in the listing.

4.2.2.6 Adverse Events Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation before the end of active phase.

In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Active 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 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.

4.2.3 Immunogenicity

4.2.3.1 Computed Values for 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 HAI 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 particular blood sample.

For the analysis of SARS COV-2 immune response, the serological results will be received in ELU/mL (ELISA Laboratory Unit) but will be expressed in BAU/mL (Binding Antibody Unit) for the analysis. The following formula will be used for converting the concentration units from ELU/mL to BAU/mL:
Result (BAU/mL) = Result (ELU/mL)/7.9815

4.2.3.2 Fold-rise

For the HAI and SARS COV-2 immune response, the derived endpoint fold-rise is driven by both baseline (D01) and post-baseline (D22) computed values as described in Section 4.2.3.1 and is computed as individual ratio:

- 21 days after vaccination divided by D01.

For the SARS COV-2 immune response:

- If the computed fold-increase is ≥ 2, the derived ≥ 2-fold rises indicator will be "Yes", otherwise ≥ 2-fold rises will be "No".
- If the computed fold-increase is ≥ 4, the derived ≥ 4-fold rises indicator will be "Yes", otherwise ≥ 4-fold rises will be "No".

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

4.2.3.3 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 21 days after vaccination (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) value is missing, the seroconversion is missing.

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.

For randomization stratification and subgroup analyses, the 2 following classes of age will be used: < 75 years and ≥ 75 years.

5 Changes in the Conduct of the Trial or Planned Analyses

This section summarizes major changes in the SAP amendment.

Table 5.1: Major statistical changes in SAP amendment

Amendment Number	Approval Date	Changes	Rationale
Amendment 1 (SAP v2.0)		Addition of 6-month f-up analysis	Protocol Amendment 2

6 Supporting Documentation

6.1 Appendix 1 List of Abbreviations

AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
BAU	Binding Antibody Unit
CRF	Case report form
ELU	ELISA Laboratory Unit
GCP	Good Clinical Practice
GM	Geometric mean
GMT	Geometric mean of titer
GMC	Geometric mean of concentration
LLOQ	Lower level of quantitation
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
RCDC	Reverse cumulative distribution curve
SAE	Serious adverse events
SafAS	Safety analysis set
SAP	Statistical analysis plan
SOC	(Primary) System organ class
PT	Preferred term
TC	Telephone Contact
ULOQ	Upper level of quantitation

7 References

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