SAP Core Body

Title: A Phase I/II study to investigate the safety and immunogenicity of Quadrivalent Influenza mRNA Vaccines MRT5421, MRT5424, and MRT5429 in healthy participants aged 18 years and above

Study Code: VAV00045

Study Phase: Phase I/II

SAP Core Body Version: v2.0

SAP Core Body Date: 01Jul2024

Protocol Version Number: v3.0

The SAP Code Body should be used in conjunction with the study protocol and the SAP TLF.

Version History

Previous Version	Date	Comments
1.0	11 December 2023	Initial version based on protocol v1.0
2.0	28 June 2024	Version based on protocol v3.0 + Precision in section 3.5 for interim analysis + An analysis added in Section 3.4.5

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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	Parallel, with dose-escalation for sentinel cohort, multi-center
Phase	I / II
Control method	Active-controlled (control = QIV-SD; QIV-HD [adults ≥ 65 years of age only]; RIV4)
Study population	Adults 18 years of age and older
Level and method of blinding	Modified double-blind (sentinel and main cohorts) (Participants; Sites except for those preparing/administering study intervention; Sponsor's except Sponsor unblinded internal safety review committee)
Investigational intervention assignment method	Randomization
Number of participants	Up to 1002 participants (471 participants 18-64 years of age and 531 participants ≥ 65 years of age)
Intervention groups	Sentinel safety cohort 1: up to 147 participants (up to 70 participants aged 18-64 years and up to 77 participants aged 65 years and above) Sentinel safety cohort 2: up to 119 participants (up to 56 participants aged 18-64 years and up to 63 participants aged 65 years and above) The enrollment of participants will be performed in a stepwise manner, based on the successful early safety data reviews (ESDR) performed by an internal Sponsor core Safety Management Team (SMT). Further details on the sequential enrollment of cohorts and ESDRs are presented in Section 8.4.9 of the protocol. Main cohort: up to 736 participants (up to 345 participants aged 18-64 years and up to 391 participants aged 65 years and above)
Total duration of study participation	Approximately 12 months
Countries	US, Puerto Rico, Honduras
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	Independent Data Monitoring Committee: No Sponsor's internal safety management team (SMT): Yes External cardiac adjudication committee (CAC): Yes

Table 1.2: Sentinel safety cohort - Planned sample size

Cohort	Group	Group Name	Total quantity of mRNA (µg) per dose	Number of participants (n) (N = 266)		Total number of participants
				18-64 years	≥ 65 years	
Sentinel safety cohort 1	1	QIV mRNA / [redacted] MRT5421)	192	-	-	147
	2	QIV mRNA [redacted] MRT5429)	30	14	14	
	3	QIV mRNA [redacted] MRT5429)	96	14	14	
	4	QIV mRNA / [redacted] MRT5429)	132	14	14	
	5	QIV mRNA / [redacted] MRT5429)	192	-	-	
	6	QIV mRNA / [redacted] (MRT5424)	96	14	14	
	7	QIV mRNA / [redacted] (MRT5424)	192	-	-	
	8	QIV-SD	-	7	7	
	9	QIV-HD	-	-	7	
	10	RIV4	-	7	7	
Sentinel safety cohort 2	1	QIV mRNA / [redacted] (MRT5421)	192	14	14	119
	2	QIV mRNA [redacted] MRT5429)	30	-	-	
	3	QIV mRNA [redacted] MRT5429)	96	-	-	
	4	QIV mRNA / [redacted] (MRT5429)	132	-	-	
	5	QIV mRNA / [redacted] (MRT5429)	192	14	14	
	6	QIV mRNA / [redacted] (MRT5424)	96	-	-	
	7	QIV mRNA / [redacted] (MRT5424)	192	14	14	
	8	QIV-SD	-	7	7	
	9	QIV-HD	-	-	7	
	10	RIV4	-	7	7	
Total number of participants:				**126**	**140**	

Table 1.3: Main cohort - Planned sample size

Cohort	Group	Group Name	Total quantity of mRNA (µg) per dose	Number of participants (n) (N = 736)	
				18-64 years	≥ 65 years
Main	1	QIV mRNA / [redacted] (MRT5421)	192	23	23
	2	QIV mRNA [redacted] MRT5429)	30	-	-
	3	QIV mRNA [redacted] MRT5429)	96	46	46
	4	QIV mRNA / [redacted] (MRT5429)	132	46	46
	5	QIV mRNA / [redacted] (MRT5429)	192	46	46
	6	QIV mRNA / [redacted] (MRT5424)	96	46	46
	7	QIV mRNA / [redacted] (MRT5424)	192	46	46
	8	QIV-SD	-	46	46
	9	QIV-HD	-	-	46
	10	RIV4	-	46	46
Total number of participants:				**345**	**391**

[redacted]

Table 1.4: Summary of schedule of activities

Phase I / II Study, 5 Visits, 1 Phone Call, 1 Vaccination, 4 or 5 Blood Samples, 12 Months' Duration

Visit/Contact	***Collection of information in the eCRF***	**V01**	**V02**	**V03**	**V04**	**V05** [a]	**12-month follow-up phone call** [a]
Study timelines (days)		D01	D03	D09	D29	D181	D366
Time interval days			V01 + 2 days	V01 + 8 days	V01 + 28 days	V01 + 180 days	V01 + 365 days
Time windows (days)		NA	NA	[+2 D]	[+7 D]	[+14 D]	[+14 D]
Visit procedures:							
Contact IRT system for randomization, participant number and treatment allocation	X	X					
Blood sampling (BL)	X	X pre-vac	X	X	X	X[b]	
Safety laboratory parameters [c]	X	X [d]	X [d]	X [e]			
Serum for antibodies (HAI, SN)		X			X	X	
Potential retesting and future research		X	X	X	X		
Vaccination (vac)	X	X					

[a] If any participants discontinue the study early (except the lost to follow-up), they are still to be followed up for safety and are to be contacted at D181 and D366 safety telephone call to identify the occurrence of any pregnancies, SAEs, and AESIs that had not yet been reported.

[b] Blood sampling will only be performed for participants who did not receive a licensed seasonal influenza vaccine during study conduct.

[c] Safety laboratory assessments will include clinical chemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin, C-reactive protein [CRP], and creatinine), and hematology (white blood cell [WBC] count with differential, hemoglobin, platelet count, and red blood cell [RBC] count). In case of abnormal safety laboratory results, unscheduled visits or additional laboratory assessments or procedures may occur based on Investigator's judgment to ensure the participant's safety.

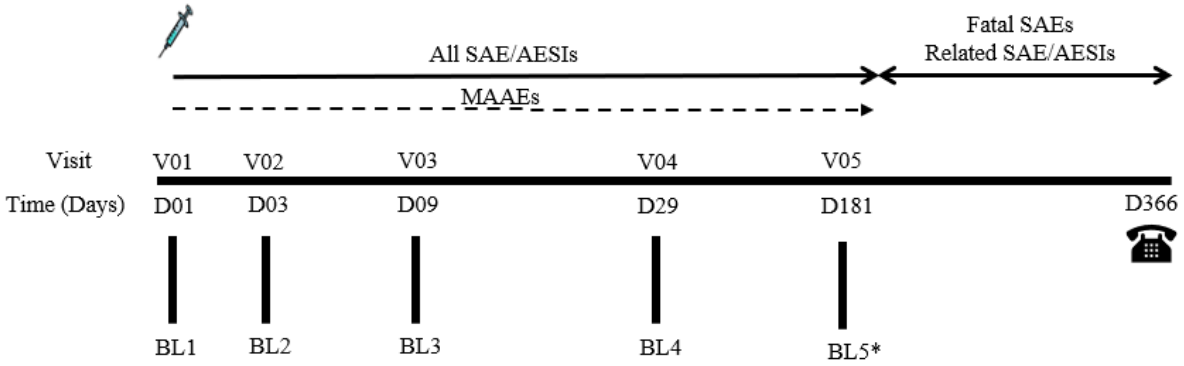
[d] In addition to safety laboratory assessment performed at D01 and D03, troponin I testing will also be performed for screening for potential myocarditis cases.

[e] Troponin I will not be tested systematically at D09. Troponin I could be tested at D09 in case of abnormal values in previous samples.

Visit/Contact	***Collection of information in the eCRF***	**V01**	**V02**	**V03**	**V04**	**V05** [a]	**12-month follow-up phone call** [a]
Study timelines (days)		D01	D03	D09	D29	D181	D366
Time interval days			V01 + 2 days	V01 + 8 days	V01 + 28 days	V01 + 180 days	V01 + 365 days
Time windows (days)		NA	NA	[+2 D]	[+7 D]	[+14 D]	[+14 D]
Immediate surveillance (30 minutes)	X	X					
Collection of unsolicited AEs	X	For 28 days after vaccination					
Collection of MAAEs	X	For 180 days after vaccination					
Collection of SAEs (including AESIs)	X	All SAEs and AESIs				Fatal SAEs, and related SAE/AESIs	
Collection of End of Study Intervention Phase [f]	X				X		
Collection of Immunogenicity (for participants included into the Ab persistence) and collection of Safety Follow-up Phase (for all participants)	X					X	
Collection of 12-Month Follow-up – End of study	X						X

[f] In case of participant discontinuation at a visit, the entire visit will be completed.

Figure 1.1 - Graphical study design



*BL5 is taken only if participants did not receive a licensed seasonal influenza vaccine since V01

Abbreviations: AESI, adverse event of special interest; BL, Blood sample; D, day; MAAE, medically attended adverse event; SAE, serious adverse event; V, visit

2 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 2.1.

Table 2.1: Objectives and endpoints

Objectives	Endpoints
Primary	
Safety objective • To describe the safety profile of each QIV mRNA compared to each other and to QIV-SD, RIV4, or QIV-HD* in all participants and in each age group	***Safety endpoints*** • Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after injection • Presence of solicited injection site reactions (ie, pre-listed in the participant diary and in the case report form [CRF]) occurring up to 7 days after injection • Presence of solicited systemic reactions (ie, pre-listed in the participant diary and in the CRF) occurring up to 7 days after injection • Presence of unsolicited AEs reported up to 28 days after injection • Presence of medically attended adverse events (MAAEs) reported up to 180 days after injection • Presence of SAEs and AESIs throughout the study • Presence of out-of-range biological test results (including shift from baseline values) up to 8 days after injection[†]

Immunogenicity objective
• To describe the HAI immune response induced by each QIV mRNA compared to each other and to QIV-SD, RIV4, or QIV-HD* in all participants and in each age group
	Immunogenicity endpoints
	• HAI antibody (Ab) response to each homologous strain at Day (D)29:
	  • HAI titers at D01 and D29
	  • Detectable HAI titer (HAI titer ≥ 10 [1/dil]) at D01 and D29
	  • Individual HAI Ab titer ratio D29/D01
	  • Seroconversion (HAI Ab titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold increase in titer [1/dil] at D29)
	  • HAI Ab titer ≥ 40 (1/dil) at D29
	  • 2-fold and 4-fold rise in HAI titers from D01 to D29

Secondary	

• To describe the neutralizing Ab immune response induced by each QIV mRNA compared to each other and to QIV-SD, RIV4, or QIV-HD* in all participants and in each age group	• Neutralizing Ab response to each homologous strain at D29
	  • Neutralizing Ab titers at D01 and D29
	  • Individual neutralizing antibodies titer ratio D29/D01
	  • 2-fold and 4-fold increase in neutralizing titers from D01 to D29

Exploratory	
[redacted]	[redacted]

[redacted]

† Safety laboratory assessments will include serum chemistries (liver enzymes including aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin, C-reactive protein [CRP], creatinine); hematology (white blood count [WBC] with differential, hemoglobin, platelet count, and red blood cell [RBC] count); and troponin I (for screening for potential myocarditis cases, systematically tested at D01 and D03, and at D09 only in case of abnormal values in previous samples).

3 Statistical Considerations

3.1 Statistical Hypotheses

No statistical hypotheses will be tested. Statistics will be descriptive.

3.2 Sample Size Determination

A total of up to 1002 participants is planned to be randomized, with 266 participants in the sentinel safety cohorts and 736 participants in the main cohort. The study will target recruitment of racial and ethnic diversity that will be representative of the countries in which the study will be conducted.

[redacted]

See also Table 1.2: Sentinel safety cohort - Planned sample size and Table 1.3: Main cohort - Planned sample size.

3.3 Populations for Analysis Sets

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

Participant Analysis Set	Description
Modified Full analysis Set (mFAS)	Participants who have received the study vaccine. Participants will be analyzed according to the intervention they received
Ab Persistence Set	Participants included in the mFAS and who did not receive a licensed seasonal influenza vaccine before visit V05 (D181).

To be noted: Data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

3.4 Statistical Analyses

This SAP is finalized prior to database lock and it includes a technical and detailed description of the statistical analyses. A SAP TLF is also available. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® (Enterprise Guide) version 8.3 or later.

3.4.1 General Considerations

All analyses will be descriptive.

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 is also possible)
	Continuous data	Mean, standard deviation, quartiles, 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% confidence interval [CI] for main endpoints) of participants Unsolicited: Number and percentage (95% CI for main endpoints) of participants and number of events
Biological safety results	**Categorical data**	Number and percentage (95% CI for main endpoints) of participants
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum
Immunogenicity results	**Categorical data**	Number and percentage (95% CI for main endpoints) of participants
	Continuous data	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), ie, 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

Safety

The safety parameters, including frequencies of immediate reactions, solicited reactions, unsolicited AEs, MAAEs, SAEs, and AESIs will be described by study group with the 95% confidence interval (CIs) for main endpoints of point estimates calculated using the exact binomial distribution (Clopper-Pearson method) for proportions. In addition, biological safety will be analyzed, counting the presence of out-of-range biological test results (including shift from baseline values for some parameters) and also according to severity grades. The mFAS will be used for the safety analyses.

Immunogenicity

Immunogenicity endpoints will be summarized by study group with 95% CIs for main endpoints. The 95% CIs for the geometric mean titers (GMTs) and GMT ratios (GMTRs) will be calculated using a normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method.

The ratios of GMTs (Group X / Group Y[1]) will be obtained between groups with the 95% CIs calculated using a normal approximation of log-transformed titers. In addition, the ratios of GMTs (Group X / Group Y) will be obtained between groups with the 95% CIs after adjustment on baseline, through linear model for log post-vaccination HAI titers, including group as an independent factor and log pre-vaccination HAI titers as a covariate. This will be performed by age group and for pooled age groups, adding age group as another independent factor.

The differences in frequencies between groups (Group X - Group Y) will be computed along with the 2-sided 95% CIs by the Wilson-Score method without continuity correction. Additional parameters may be displayed as appropriate. Additionally, the effect of dose level on the immune response on [redacted] may be explored through linear model for log post-vaccination HAI titers (or SN), including dose level as an independent factor and log pre-vaccination HAI titers (or SN) as a covariate. This will be performed by age group and/or for pooled age groups, adding age group as another independent factor.

Reverse cumulative distribution curves (RCDCs) against each strain will be performed for baseline (D01) and at D29. The mFAS will be used for the primary immunogenicity analyses.

[1] In term of groups, each QIV mRNA will be compared to each other and to QIV-SD or RIV4 or QIV-HD (as applicable) in all participants and in each age group

3.4.3 Secondary Endpoints

Immunogenicity

Immunogenicity endpoints will be summarized by study group with 95% CIs for main endpoints. The 95% CIs for the GMTs and GMTRs will be calculated using a normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The mFAS will be used for the secondary immunogenicity analyses.

3.4.4 Exploratory Endpoints

[redacted]

3.4.5 Other Analysis

In addition to analysis splitting by class of age (18-64 years and ≥ 65 years), a similar descriptive analysis will be conducted for demography, safety, and immunogenicity with a split of age by: 18-49 years and ≥ 50 years. The analyses will be displayed in Appendix 15 of the CSR.

3.4.6 Handling of Missing Data and Outliers

3.4.6.1 Safety

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

3.4.6.1.1 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.

3.4.6.1.2 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 the 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 at the time of analysis
- The missing relationship to study procedures for SAEs will not be imputed

3.4.6.1.3 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.

3.4.6.1.4 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.

3.4.6.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.4.6.2 Immunogenicity

For immunogenicity objectives, lower level of quantitation (LLOQ) and ≥ upper level of quantitation (ULOQ) will be performed as described in Section°4.2.4. No test or search for outliers will be performed.

No replacement will be done for missing values.

3.4.6.3 Efficacy

Not applicable.

3.5 Interim Analyses

The following sequence analysis will be done:

- Beside the regular safety reviews performed by the Sponsor's unblinded internal safety review committee (see SMT/ESDR section of the protocol), interim analyses may be conducted in all or a subset of participants who completed V04 (D29) for business decisions. These analyses may contain all safety data up to D29 and partial HAI D01 and D29 data.

  Based on recent progress on the study and internal sponsor needs, the analysis will be conducted as follows. The blind will be broken for individual subjects for the sponsor members involved in statistical activities for this analysis. A first run on safety in July 2024, will be shared within sponsor using unblinding group analysis. Safety Information will be also shared for group [redacted] linked to an investigational brochure and another protocol. The laboratory in charge of HAI testing will remain blinded. Later in August 2024, the complementary analysis for HAI data D01 and D29 will be generated and shared within sponsor using unblinded results at group level. The immunogenicity data could contain all or partial HAI data. Overall, the unblind analyses will be done during July/August 2024 period and kept internally at sanofi level (the sites remain blinded). The analyses in July/August 2024 will focus especially on 18-49 years and ≥ 50 years age groups.

- An interim analysis may be conducted once the 6-month data (with or without immunogenicity data) have been collected.

- A final analysis will be conducted once all data have been collected, including 12 months safety data, and the final database lock has occurred.

No statistical adjustment will be applied as this is a learning study.

3.6 Data Monitoring Committee (DMC)

Not applicable.

To be noted: An adjudication committee will review cardiac cases (myocarditis/pericarditis) if any, but without impact on statistical 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 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).

To derive daily intensity of solicited reactions, the sequential steps will be applied as follows:

- For non-measurable solicited reactions, daily intensity will correspond to daily records as reported in the clinical database. For measurable solicited reactions, the daily measurements reported in the clinical database will be converted according to the intensity scales defined in the protocol; in which a reaction too large to measure will be assumed to be Grade 3 severity.
- In case of daily intensity assessments between the investigator and the participant are different, the investigator's assessment available for any given days will be used for those days. Otherwise, the participant's assessment will be used for any given days in which the investigator's assessment is not available.

For measurable solicited, the Grade 1 start when at least 38.0°C (100.4°F) as temperature and 25°mm for measurable injection site solicited, and values non-missing below are considered as None.

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.

The time period is displayed as D01-D04, D05-D08, and D09 or later.

4.2.1.1.4 Time of Onset

Time of onset is derived from the computed daily intensity 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.

In case of any missing intensity before this day, the time of onset is missing. If a reaction is not continuous (ie, a reaction occurs over 2 separate time periods intervened by at least 1 daily intensity of None or Missing), then the time of onset is the first day of the first presence.

Time of onset is categorized as D01-D04, D05-D08, or missing for solicited reactions as follows:

- D01-D04: any Grade 1, 2 or 3 in D01-D04 period
- D05-D08: any Grade 1, 2 or 3 in D05-D08 period while only grade 0 in D01-D04 period
- Missing otherwise

4.2.1.1.5 Number of Days of Presence

Number of days of presence over the period considered is derived from the computed daily intensity as described in Section°4.2.1.1.1. It corresponds to the number of days with a daily intensity of Grade 1, Grade 2, or Grade 3. Number of days of presence with a specified intensity may also be derived. If any daily intensity is missing in the considered period then the number of days of presence is set to missing.

In the solicited period, the Number of days of Presence is categorized as 1-3 days, 4-7 days, and 8 days post-vaccination. If any daily intensity is missing in the considered period, and if the number of days with a presence stays in the same range when adding the number of days with missing daily presence, then the number of days of presence range can be set to this category, and so is not be missing. Otherwise, the number of days of presence range is set to missing.

The same applies to the overall period, with the ranges 2-3 days, 4-7 days, and 8 days or more.

4.2.1.1.6 Number of Days of Presence During the Solicited Period

Number of days of presence over the period considered is derived from the daily intensities computed as described in Section°4.2.1.1.1. 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.

4.2.1.1.7 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.

4.2.1.1.8 Ongoing

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

- 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: Other exclusive conditions (ie, it is not included in the denominator of such analysis in safety tables)

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 analyses but are included in separate listings.

Unsolicited ARs (related) within 7 days coded as solicited could not be included in the safety analysis (and in separate listing).

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 (eg, swelling measurement > 0 mm but < 25 mm).

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 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 before the unsolicited AE + 1.

The start date will be used first. If the start date is at least partially missing, the variable "Appear after Visit V0x" ticked in the eCRF will be used to classify the participant in an adequate period (onset remaining missing).

In addition, the sub-periods of analyses are:

- Within 7 days, corresponds to unsolicited started between D01 and D08, or missing onset with variable "Appear after Visit V0x" corresponds to a visit lower or equal to V03 (or missing V0x).

  Note #1: The time of onset period is displayed as D01-D04, D05-D08, and Missing

  Note #2: Within 7 days is a subset of within 28 days

- Within 28 days, corresponds to unsolicited started between D01 and D29, or missing onset with variable "Appear after Visit V0x" corresponds to a visit lower or equal to V03 (or missing V0x)

  Note: The time of onset period is displayed as D01-D04, D05-D08, D09-D15, D16 or later, and Missing

- From D30 to D181, corresponds to unsolicited started between D30 and D181, or missing onset with variable "Appear after Visit V0x" ticked at V04

- D182 or after, corresponds to unsolicited (SAE/AESI) started after D181 or missing onset with variable "Appear after Visit V0x" ticked at V05

Additional considerations:

- After D29, any unsolicited non-MAAEs and non-serious and non-AESIs will be excluded from all analyses (but presented in a listing of Appendix 16 of the CSR).
- After D181, only SAE and AESI are planned to be collected. Any unsolicited non-serious and non-AESIs will be excluded from all analyses (but presented in a listing of Appendix 16 of the CSR).
- An AE which occurs before the vaccination will be excluded from all analyses (but presented in a listing of Appendix 16 of the CSR

4.2.1.2.4 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.

For analysis in the month after injection, duration period is displayed as 1-3 days, 4-7 days, 8-14 15 days or more, and missing. Other periods (for SAE and AESI) will be considered.

4.2.1.2.5 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 (collected up to V07).

4.2.1.2.6 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 throughout the study using the periods described in Section°4.2.1.2.3.

4.2.1.2.7 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 CRF.

AESIs will be analyzed throughout the study using the periods described in Section°4.2.1.2.3.

4.2.2 Biological Laboratory Data

Initial laboratory data are transformed into normalized results at the study data tabulation model (SDTM), via clinical data management tool. Attached to these normalized results, data could be converted into “within normal range” or “below/above normal range”. Normalized results will be also used for quantitative analyses. *Indirectly, it means also that original values with attached normal ranges are not used.*

In addition, intensity thresholds for laboratory abnormalities, as detailed in Table 16 of the protocol, will be derived. The derivation is based on normalized results.

Additional precisions:

- Baseline data correspond to Visit V01
- In case of value such as "<X" or "≤X", the value will be considered as X/2
- In case of value such as ">X" or "≥X", the value will be considered as X
- Bilirubin
  - For grading analysis, protocol Table 10.4 corresponds to total bilirubin (and not direct bilirubin)
  - At each timepoint, grades for bilirubin will be derived according to LFT grades at the same timepoint:
    - If ALT and AST are both grade 0, LFT is considered as “normal LFT”. And the corresponding rule is used for the derivation of the grades of bilirubin.
    - If ALT is grade 1-3 or AST is grade 1-3, then LFT is “any increase in LFT”. And the corresponding rule is used for the derivation of the grades of bilirubin.
    - if ALT or AST is grade 0 but the other is missing, then we consider this case as “any increase in LFT” and derive the grades of bilirubin with that rule.

4.2.3 Other Safety Endpoints

4.2.3.1 Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

4.2.3.2 Action Taken

This information will be summarized as collected, including missing observations. 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, including missing observations. 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°3.4.6.1.2. 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 in order to identify AEs leading to discontinuation before the end of the study.

In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Study" form question "What was the participant's status?", has "Adverse Event" checked
- Safety overview table: A participant who either has "Adverse Event" checked for form question "What was the participant's status?" on the "Completion at End of Study" form; has "Caused Study Termination" checked and lists a solicited AE that is at least Grade 1; or has "Caused Study Discontinuation" checked and lists an unsolicited AE 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 Immunogenicity

Computed Values for Statistical Analysis

In order 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 and SN, homologous or heterologous:

- If a value is "< LLOQ" or "≤ LLOQ", then use the computed value LLOQ/2
- If a value is between "> LLOQ" and "< ULOQ" (ie, already numerical value), then use the value
- If a value is "> ULOQ" or "≥ ULOQ", then use the computed value ULOQ

If a duplicate record (per participant, antigen, and time) is applied for HAI, a geometric mean of duplicates is applied to obtain a unique value for statistical analysis.

Following management of LLOQ/ULOQ values and computation of the geometric mean of duplicate, if applicable for HAI records, other derivations are applied:

- Computation of a ratio post/D01 for HAI and NT. The ratios are D29/D01 and D181/D01.
- Seroconversion (HAI Ab titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold increase in titer [1/dil] at D29).
- Superiority (or inferiority) to a cut-off at a specific time. Typically, the cutoff HAI Ab titer ≥ 40 [1/dil] at D29. Nevertheless, additional cut-off will be presented in the tables as identified in the SAP TLF.
- 2-fold and 4-fold increase from D01 to D29 for HAI and NT.

4.2.5 Efficacy

Not applicable.

4.2.6 Derived Other Variables

4.2.6.1 Age for Demographics

The age corresponds to the calendar age in years as derived in the SDTM, at the time of screening. In case of randomization strata error, the true calendar age will be used, instead of the class of age available in participant identification.

The age is an integer. For example, "18 years" means from the day of the 18th birthday to the day before the 19th birthday.

4.2.6.2 Duration of a Participant in the Study

Duration is computed in days as follows for a participant: Latest period date - Earliest period date + 1.

4.2.6.3 Duration of the Study

The duration of the study is computed as follows (whatever the participant): Maximum (Termination date, Follow-up date) - V01 date + 1

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
ADaM	analysis data model
AE	adverse events
AESI	adverse events of special interest
Ag	antigen
ALT	alanine aminotransferase
AR	adverse reactions
AST	aspartate aminotransferase
BL	blood sample
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	Case Report Form
CRP	C-reactive protein
CSR	clinical study report
D	Day
eCRF	electronic case report form
ESDR	Early Safety Data Review
GBS	Guillain-Barré syndrome
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GPV	Global Pharmacovigilance
HA	hemagglutinin
HAI	hemagglutination inhibition
ICH	International Council for Harmonisation
Ig	immunoglobulin
[redacted]	
IMP	investigational medicinal product
IRT	interactive response technology
LLOQ	lower limit of quantitation

LLN	lower limit of normal
LLT	lowest level term
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MAAR	medically attended adverse reaction
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
mRNA	messenger ribonucleic acid
mRNA-LNP	mRNA encapsulated in a lipid nanoparticle
NA	neuraminidase
NIMP	non-investigational medicinal product
NOCMC	new-onset chronic medical condition
NSAID	non-steroidal anti-inflammatory drug
NT	neutralization test
PT	preferred term
RBC	red blood cell
RCDC	reverse cumulative distribution curve
rHA	recombinant hemagglutinin protein
SAE	serious adverse events
SAP	statistical analysis plan
SDTM	study data tabulation model
SMT	Safety Management Team
SOC	(primary) system organ class
SUSAR	suspected unexpected serious adverse reactions
TBD	to be determined
TLF	tables, listings and figures
ULN	upper limit of normal
VAC	vaccination (as in vaccination #)
WBC	white blood cell

7 References

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

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