STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Randomized, Observer-Blind, Antigen and Adjuvant Dose-Ranging Clinical Study to Evaluate Safety and Immunogenicity of Different Formulations of MF59-Adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine (aQIVc) in Older Adults ≥50 Years of Age
Study Number:	V201_01
Protocol Version and Date:	2, 22 JAN 2021
Phase of Development:	Phase 2
Plan Prepared by:	[redacted], [redacted]
Version and Date:	Version 2.0: 26 AUG 2021
Approvers:	[redacted], [redacted], [redacted], [redacted]

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Approvals

[redacted], [redacted]

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CSR	Clinical Study Report
DMC	Data Monitoring Committee
FAS	Full Analysis Set
GMR	Geometric Mean Ratios
GMT	Geometric Mean Titers
HI	Hemagglutination Inhibition
ICH	International Council for Harmonisation
IRT	Interactive Response Technology
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intention-to-Treat
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SP	Statistical Programmer
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables, Figures and Listings
TOC	Table of Content

1. BACKGROUND AND RATIONALE

Vaccination is the primary method for preventing influenza and its potentially severe complications. Efficacy of the conventional influenza vaccines in the adult population is demonstrated to be high. In contrast, the efficacy in elderly individuals is significantly lower due to the aging of the immune system (i.e. immunosenescence) and underlying medical conditions that can both increase the risk of influenza complications as well as interfere with immune responses (Sasaki and Sullivan 2011). In view of the limitations of conventional influenza vaccines in older adults, there continues to be an unmet need for a new generation of influenza vaccines that provides more consistent and broader coverage against all seasonal virus subtypes and variants (Wong and Webby 2013; Reber et al. 2012). The investigational vaccines in this study are seven different formulations of the adjuvanted quadrivalent cell-based (aQIVc) vaccine, including different amount of antigen and different dose of the adjuvant MF-59. The primary aim of this study is to assess immunogenicity and safety of the seven different formulations of the aQIVc vaccine versus the non-adjuvanted quadrivalent cell-based influenza (QIVc) vaccine. The results are to be used to select the optimal formulation to study in Phase 3 study.

For further details please refer to Section 1.0 of the protocol.

This plan describes all details related to the statistical analysis of the data collected in the study V201_01 and is based on protocol version 2, 22 Jan 2021.

This analysis plan is compliant with ICH Harmonized Tripartite Guideline, 5 February 1998, Statistical Principles for Clinical Trials, E9; World Health Organization, WHO Technical Report, Series No. 924. 2004, Annex 1: Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations; and FDA Center for Biologics Evaluation and Research (CBER) Guidance for Industry, May 2007, Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines.

2. OBJECTIVES

2.1 Primary Objective

2.1.1 Primary Immunogenicity Objective

1. To assess the immunogenicity of the different aQIVc formulations in comparison with the non-adjuvanted QIVc vaccine as measured by hemagglutination inhibition (HI) assay* at 28 days after vaccination.

* *In case of lack of agglutination for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by microneutralization (MN) assay as an acceptable alternative.*

2.1.2 Primary Safety Objective

1. To assess the reactogenicity of all aQIVc formulations and the comparator, QIVc, for 7 days after vaccination.

2. To assess the safety of all aQIVc formulations and the comparator, QIVc, for 28 days after vaccination.

2.2 Secondary Objectives

2.2.1 Secondary Immunogenicity Objective(s)

1. To assess the immunogenicity of the different aQIVc formulations in comparison with the QIVc vaccine as measured by HI assay* at 180 days after vaccination.
2. To assess the immunogenicity of the different aQIVc formulations in comparison with the QIVc vaccine as measured by MN assay at 28 and 180 days after vaccination.

* *In case of lack of agglutination for a specific strain, immunogenicity for that strain will be assessed as measured by MN assay as an acceptable alternative.*

2.2.2 Secondary Safety Objectives

1. To assess the safety of all aQIVc formulations and the comparator, QIVc for 180 days after vaccination.

2.3 Exploratory Objectives

2.3.1 Exploratory Immunogenicity Objectives

1. To assess the immunogenicity of the different aQIVc formulations in comparison with the QIVc vaccine as measured by MN assay using heterologous target viruses at 28 days after vaccination in a subset of collected samples.
2. Additional exploratory immunogenicity analyses may be conducted to further characterize the immune response of the study vaccines.

The results of these exploratory analyses may be presented in an addendum to the Clinical Study Report (CSR).

3. STUDY DESIGN

3.1 Overview of Study Design

Experimental design: This is a Phase 2, randomized, stratified, observer-blind, antigen and adjuvant dose-ranging clinical study in approximately 800 male and female adults aged 50 years and older (approximately equally split between two age groups; ≥50-64 and ≥65 years of age) who are healthy or have co-morbidities which increase their risk of complications from influenza infection.

Duration of the study: The study duration is approximately 6 months for each subject. The study will be conducted in one single influenza season.

Vaccination schedule: Single vaccination (Day 1).

Investigational Vaccine: The study will use 7 investigational formulations of aQIVc (see Table 1)

Comparator Vaccine: The study will use 1 comparator vaccine (see Table 1)

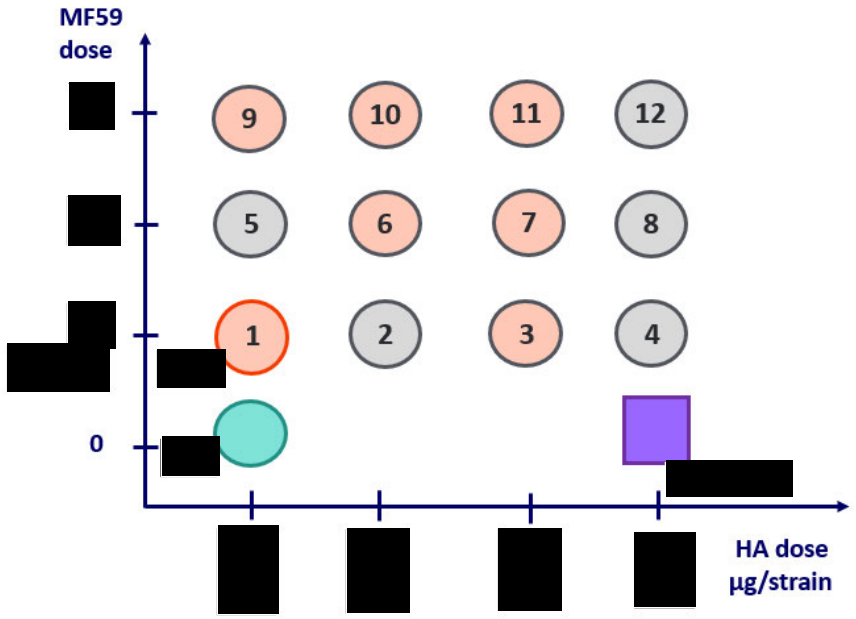
Treatment groups: All treatment groups will include approximately 100 subjects aged ≥50 years of age (see Table 1). All subjects will receive one dose of study vaccine at Day 1. The aQIVc formulation numbers correspond to the design space as presented in Figure 3-1. Not all formulations within the design space will be directly evaluated in this study, but the study results will make it possible to model the effect of the non-tested formulations within the design space.

Table 1: Overview of study vaccines

Group	Vaccine	Type of vaccine	HA antigen content/ strain (µg)	MF59 squalene content (mg)	Total injected volume (mL)	Number of randomized subjects
A	aQIVc 1	Investigational	[redacted]	[redacted]	[redacted]	100
B	aQIVc 3	Investigational	[redacted]	[redacted]	[redacted]	100
C	aQIVc 6	Investigational	[redacted]	[redacted]	[redacted]	100
D	aQIVc 7	Investigational	[redacted]	[redacted]	[redacted]	100
E	aQIVc 9	Investigational	[redacted]	[redacted]	[redacted]	100
F	aQIVc 10	Investigational	[redacted]	[redacted]	[redacted]	100
G	aQIVc 11	Investigational	[redacted]	[redacted]	[redacted]	100
H	QIVc	Comparator	15	0	0.5	100

The treatments for Groups B, C, D, E, F and G will be obtained by 'bed-side' mixing of QIVc, standard dose of aQIVc (formulation aQIVc 1) and MF59 solution. Mixing is not required for Groups A and H.

Figure 3-1: Design Space



Randomization: An Interactive Response Technology (IRT) will be used in the study with stratification factors for age (≥50-64 and ≥65 years of age) and history of any influenza

vaccination within 3 previous years (yes/no) to randomly assign each subject to one of the 8 treatments.

Blinding: Observer-blind study.

Blood sample schedule: A blood sample will be collected from all subjects on Day 1 (prior to vaccination), Day 29 and Day 181.

Data collection: electronic Case Reporting Form (eCRF) and electronic Diary (eDiary).

Study periods: The study has a treatment period (Day 1 to Day 29) and a follow-up period (Day 30 to Day 181).

Study clinic visits: Three clinic visits for each subject: at Day 1, Day 29 and Day 181.

Safety phone call: Two safety phone calls (Day 7 and Day 91) will be conducted: on Day 7 to review the eDiary as well as to collect any unsolicited AEs, and their related medications and any vaccinations, and on Day 91 to collect only SAEs, medically attended adverse events (MAAEs), AEs leading to withdrawal, and AESIs, and their related medications and any vaccinations.

Reactogenicity data collection: Solicited AEs, occurring at the day of study vaccination and the following 6 days (Day 1 through Day 7, or longer if the events are not resolved), will be recorded daily using an eDiary as completed by the subject. The qualified healthcare professional will separately evaluate the solicited systemic events and injection site pain during the Day 7 safety phone call.

Safety data collection: All unsolicited AEs will be collected for 28 days after vaccination. During the follow-up period (from 29 days after vaccination onwards), only unsolicited AEs will be collected that are SAEs, MAAEs, AEs leading to study withdrawal, and/or AESIs. These data will be captured by interviewing the subject during the clinic visits and safety phone calls and by review of available medical records. Subjects will be instructed to call the site in the event of any AE which they perceive as being of concern during the entire study period.

Serological assays:

- HI assay for homologous vaccine strains, using cell-derived target virus, will be performed in all subjects on serum samples collected on Days 1, 29 and 181.

- MN assay for homologous vaccine strains, using cell-derived target virus, will be performed in all subjects on serum samples collected on Days 1, 29 and 181.
- HI assay for heterologous vaccine strains, using cell-derived target virus, will be performed in a subset of collected samples from serum samples collected on Days 1 and 29.

For further details please refer to Section 3.0 of the protocol.

Table 2 Time and Event Schedule

	Visit Type	Clinic Visit	Safety Phone Call	Clinic Visit*	Safety Phone Call	Clinic Visit*
	Study Day	**1**	**7**	**29**	**91**	**181**
	Visit Window (Days)	**n/a**	**+3 day**	**-7/+3 days**	**+/-7 days**	**+/-14 days**
	Visit Number	**1**	**2**	**3**	**4**	**5**
Study Event	**References**					
Screening and Randomization						
Informed Consent[a]	Section 5.1.1	X				
Medical History[b]	Section 5.1.2	X				
Physical Exam	Section 5.1.2	X				
Targeted Physical Exam[c]	Section 5.4.1			X		X
Measuring body temperature	Section 5.1.2	X				
Pregnancy test[d]	Section 5.1.2	X				
Exclusion/Inclusion Criteria	Section 4	X				
Randomization	Section 5.1.4	X				
Study Treatment						
Vaccination	Section 5.2	X				
Safety						
30 Minutes Post Injection Assessment	Section 5.3	X				
Train and Dispense Subject eDiary	Section 5.3	X				
Review of eDiary data and compliance	Section 3.6.2	Ongoing during eDiary use				
Assess unsolicited AEs	Section 7.1.2	X	X	X		
Assess SAEs	Section 7.1.4	X	X	X	X	X

	Visit Type	Clinic Visit	Safety Phone Call	Clinic Visit*	Safety Phone Call	Clinic Visit*
	Study Day	**1**	**7**	**29**	**91**	**181**
	Visit Window (Days)	**n/a**	**+3 day**	**-7/+3 days**	**+/-7 days**	**+/-14 days**
	Visit Number	**1**	**2**	**3**	**4**	**5**
Study Event	**References**					
Assess for AEs leading to withdrawal, medically attended AEs and AESIs	Section 7.1.4.1	X	X	X	X	X
Assess relevant medications and vaccinations	Section 6.5	X	X	X	X	X
Immunogenicity						
Serology blood draw	Section 5.1.5	X[e]		X		X
Study End						
Study Completion/termination	Section 5.6					X[f]

* In the exceptional situation in which a clinic visit is not possible, such as in the case when a site is not able to see study subjects at the clinic due to local regulations related to the coronavirus pandemic, a home visit may be considered.

Notes: [a] Consent form(s) should be signed prior to performing any procedures. The informed consent process may be conducted earlier, but within 10 days prior to Day 1. [b] Medical history includes existing comorbidities. [c] Based on specific complaints as indicated by the subject. [d] A pregnancy test should be done for females of childbearing potential in order to rule out any pregnancy. [e] Blood draw to be done prior to vaccination. [f] Subjects who terminate the study early will be requested to complete all safety-related Study Completion procedures. Abbreviations: AE = adverse event; AESI = adverse event of special interest; n/a = not applicable; SAE = serious adverse event.

4. RANDOMIZATION AND BLINDING

4.1 Method of Group Assignment and Randomization

Enrolled subjects will be randomized to one of the eight treatment groups in equal ratios (Groups A-H, see Table 1). Subjects will be stratified based on age (≥50 to 64 years and ≥65 years) and History of any influenza vaccination within 3 previous influenza seasons (yes/no) and site.

The subject will be randomized in the IRT/ Randomization and Trial Supply Management (RTSM) system. The subject will receive a unique Subject ID that will be used for all eCRFs and associated study documentation for the duration of the study. After randomization, the Screening Number ceases to be used and remains in the Screening and Enrolment Log only. The list of randomization assignments is produced by the IRT service provider and approved by the Sponsor according to the applicable Sponsor's Standard Operating Procedure (SOP). The randomization list is generated using permutated blocks assigned by site and strata.

4.1.1 Definition of Randomization/Vaccination Errors

The list below provides categories for errors that may occur during vaccination.

Randomization errors:

- Administered wrong kit (subject was vaccinated with a vaccine different from the one assigned at randomization).

Vaccination errors:

The list below provides some examples of potential errors that may occur during vaccination:

- Administered only part of the study vaccine.
- Administered an incorrect dose Incorrect vaccine location.
- Administered expired vaccine.
- Administered temperature deviated vaccine.

Stratification error:

- Subject randomized in the wrong stratification stratum.

Randomization and vaccination errors are considered as major (CSR-reportable) protocol deviations. Stratification errors will not be considered as CSR-reportable PDs as there will be no impact on the actual dose administered. Subjects will be included in analysis according to actual age subgroup and previous vaccination history.

4.1.2 Forced Randomization

Not applicable.

4.2 Blinding and Unblinding

The study is designed as an observer-blind study. Unblinded teams will be used for preparation of the safety reports for the Independent Safety Team (IST) and Data Monitoring Committee (DMC).

If a subject is unblinded during the study, it is to be documented as a CSR-reportable PD, except for subjects unblinded by Pharmacovigilance due to suspected unexpected serious adverse reactions (SUSAR). The unblinding will be documented appropriately. The unblinded subject(s) are excluded from the PPS. Unblinded subjects will be included in the FAS and safety sets.

A final analysis on the primary and the secondary objectives including all immunogenicity and safety data collected up to and including the Day 29 Visit will be conducted on cleaned and locked data. Access to information about study groups will be limited to biostatisticians and programmers in charge of statistical analysis. No individual listings and unblinding data will be generated at this stage until the completion of the study.

5. SAMPLE SIZE AND POWER CONSIDERATIONS

This study is an exploratory Phase 2 study without any formal hypothesis testing. The total sample size of 800 subjects has been determined based on feasibility and to provide information for further development. The power calculations are provided to illustrate what differences can be detected.

Anticipating 5% of the subjects will be non-evaluable over the course of the study (due to being lost to follow-up, having insufficient samples, incomplete laboratory results, or protocol violations, etc.), approximately 95 evaluable older adult subjects for each vaccine group will be included in the statistical analysis. Based on data from Seqirus study V133_01EXP (Otten et al. 2020), it is assumed that the within group standard deviations for the log10 HI titers for all strains are about 0.7 or lower.

Assuming a standard deviation (SD) of 0.7 for the log 10 HI titer at Day 29, a comparison between dose groups with n=95 per group has at least 80% power with a two-sided α=0.05 if the GMT ratio between the two groups is at least 1.93, and at least 90% power if the ratio is at least 2.14.

Table 3 below describes the statistical power to detect that the GMT ratio of an aQIVc formulation versus QIVc is significantly higher than 1 or higher than 1.5 at a two-sided 5% level of significance assuming 95 evaluable subjects per formulation and a standard deviation of 0.7 for the log10 titers.

Table 3 Power Calculations

	Power % to detect	
Actual GMT ratio	**Lower limit of the 95% CI of GMT ratio above 1**	**Lower limit of the 95% CI of GMT ratio above 1.5**
2.00	83.86	23.08
2.50	97.37	58.44
3.00	99.67	83.86
3.50	99.96	95.00
4.00	100	98.65

N=95 per group and two-sided alpha = 0.05

6. DETERMINATION OF PROTOCOL DEVIATIONS

6.1 Definition of Protocol Deviations

CSR reportable PDs are defined in accordance with International Conference on Harmonization (ICH) E3 as important PDs related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment resulting in the potential to jeopardize the safety or rights of the trial subjects or the scientific value of the trial. Protocol deviations will be classified as CSR-reportable and non-CSR-reportable.

Seqirus's standard Protocol Deviation Specification Document lists all the pre-specified observable and programmable PDs, including their classification, categories, sub categories and impact on the analysis.

CSR reportable PDs may lead to exclusion of the subject or part of the subject's data from at least the PP analysis set.

The number of subjects in any and by PD category will be summarized by study treatment and overall. Individual subject listings will be provided sorted by subject and by PD category.

Prior to unblinding, all reportable PDs will be evaluated, and designated study staff will develop a memo that describes the PDs that led to exclusions from analysis sets. This memo will be signed off by at least the Lead Biostatistician, Lead Data manager, Global Clinical Operations Lead and the Clinical Scientist and will be included in the trial master file.

6.2 Determination of Protocol Deviations

The source/method of identification can be either observable or programmable. Programmable PDs are those which can be programmed from the data recorded in the clinical database. Observable PDs are identified by CRAs during monitoring or other team members.

A set of listings will be programmed following the Protocol Deviation Specification List to determine and categorize the protocol deviations. These listings will be provided for review on an ongoing basis during the study.

This review will also include protocol deviations reported in monitoring reports. After the review, the Clinical Scientist and the Global Clinical Operation Lead will provide the Biostatistician with:

- An assessment of CSR reportable PDs based on blinded clinical data review.

7. ANALYSIS SET

7.1 All Enrolled Set

All screened subjects who provide informed consent, receive a subject ID, and provide demographic and/or baseline screening assessments, and are randomized in the study.

Demography and baseline characteristics tables as well as subject listings will be produced on the All Enrolled Set.

7.2 Exposed Set

All subjects in the All Enrolled Set who are randomized and received study vaccination.

7.3 Full Analysis Set (FAS) Immunogenicity Set

All subjects in the Exposed Set who are randomized, received study vaccination and provided immunogenicity data on Day 1 and Day 29 assessment.

In case of vaccination error, subjects in the FAS sets will be analyzed "as-treated" (i.e., according to the vaccine the subject received).

If a subject is unblinded before the completion of the Day 29 visit, he/she will be included in the FAS, but excluded from the Per Protocol.Set.

7.4 Per Protocol Set (PPS) Immunogenicity

All subjects in the FAS Immunogenicity who:

- Correctly receive the vaccine (i.e., receive the vaccine to which the subject is randomized within the defined window).
- Have immunogenicity assessments within the window of - -7 to +21 days around the Day 29 visit, and Day 1 sample taken
- Have no protocol deviations leading to exclusion as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defined prior to unblinding or analysis.

If a subject receives a vaccine, labelled for another subject but the same as the one the subject was randomized to, the subject will not be removed from the PPS. If a subject is unblinded during the study (except for SUSAR), he/she will be excluded from the PPS.

7.5 Safety Set

Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

Solicited Safety Set

All subjects in the Exposed Set with any solicited adverse event data including body temperature measurements or use of analgesics/antipyretics recorded by the subject in the eDiary.

The investigator assessment of the solicited adverse event will be based on the subjects with non-missing data recorded on the investigator assessment. In case, there are subjects without any eDiary data recorded (so not part of the solicited safety set) but with an investigator assessment an extra set will be defined for the investigator evaluation – **Solicited Safety Set, per investigator**.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set for whom safety has been assessed after vaccination (including 30-minute post-vaccination assessment).

Overall Safety Set

All subjects who are in the Solicited Safety Set and/or in the Unsolicited Safety Set.

7.5.1 Restricted Safety Set

Not applicable.

7.6 Other Analysis Set

For the analysis of the immunogenicity data collected at Day 181 assessment, revised sets of the FAS and PPS, Day 181 immunogenicity will be used. For the FAS, Day 181, subjects will be

only included if there were Day 1 and Day 181 immunogenicity data collected. The PPS, Day 181 will be a subset of the FAS, Day 181 with a sample visit within +/- 4 weeks around the target Day 181 and excluding protocol deviations related to the subjects and no disallowed concomitant medication impacting the results was used.

8. GENERAL ISSUES FOR STATISTICAL ANALYSES

8.1 Adjustment for Covariates

The log-transformed antibody titers at Day 29 and Day 181 will be analyzed using an Analysis of Covariance (ANCOVA) model which includes the log-transformed pre-vaccination antibody titer, age subgroup stratification (≥50 – 64, ≥65 years) and previous vaccination history stratification (no in previous 3 years, yes). Summary tables will show both adjusted and unadjusted GMTs for each vaccine group and adjusted and unadjusted GMT ratio for the different aQIVc investigational vaccines versus QIVc vaccine.

Instead of Vaccine group as categorical variable, levels of antigen and the amount of MF-59 will be included as covariates to model the antibody titers at Day 29 as function of the level of antigen and the amount of MF-59.

The main analysis of binary immunogenicity endpoints ((i.e., percentages of subjects with seroconversion and with titer ≥1:40) will not be adjusted for any of the covariates. Binary data will be summarized for each group using unadjusted estimates and will be reported together with two-sided exact 95% CIs. Additional adjusted analysis may be done including the stratification factors age and previous vaccination history as covariates in a generalized linear model.

8.2 Handling of Dropouts, Missing Data

The distribution of subjects with reasons for missing immunogenicity values will be described by vaccine group. Key baseline characteristics, such as age and previous vaccination history, will be compared between the subjects with immunogenicity values and those who have missing data. For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative.

Therefore, the immunogenicity analysis will comprise a complete case analysis only, without introducing any bias.

Solicited adverse events are collected using electronic diaries from Day 1 to Day 7 post-vaccination. If no data have been recorded for all 7 days, the assessment is considered missing and excluded from the safety analysis. In case, at least one day is filled in but other days are missing the presence or absence of the event will be based on the available data. If more than 5% of the subjects have incomplete diary data, additional tables for solicited adverse events will be created based on complete diary card data. The number of days and number of subjects with missing data will be tabulated by treatment group.

8.3 Multicenter Studies

Stratification is used on two important factors related to the immunogenicity endpoints: age and previous vaccination history. These factors will be included in the statistical model.
Centers will not be included in the statistical analysis, but countries will be considered in the sub-group analyses.

8.4 Multiple Comparisons and Multiplicity

This a phase 2, exploratory study and no adjustment will be applied for multiple endpoints and multiple comparisons.

8.5 Immunogenicity/Safety/Other Subsets

Not applicable.

8.6 Subgroups

All analyses (safety and immunogenicity) will be done by the age subgroups ≥50-64 years or ≥65 years.
Unadjusted and adjusted immunogenicity analysis of the GMTs will be performed by the following subgroups:

- Influenza vaccination history previous 3 years as yes and no, where we excluding this factor in the analysis model;
- Comorbidity risk (yes/no) defined as the Comorbidity Risk Score (by Hak et al.) < 50 (comorbidity risk = no) or ≥50 (comorbidity risk = yes);
- Sex;
- Country;
- Pre-vaccination status HI or MN < 1:10 (or LLOQ) and HI or MN ≥ 1:10 (or LLOQ)..

The adjusted GMT subgroup analysis will not be conducted if , the number of subjects in a subgroup category is less than 10% of the total population.

Exploratory interaction analyses may be conducted to support consistency or lack of consistency of the results among the subgroups.

8.7 Data Transformation

Distributions of antibodies are generally skewed to the right and approximately log-normally distributed. Therefore, prior to any statistical analysis that assumes normally distributed observations, antibody titers will be $\log_{10}$-transformed. GMTs and their 95% CIs will be then computed by exponentiating (base 10) the means and 95% CIs of the $\log_{10}$ transformed titers.

8.8 Derived and Computed Variables

Demographics

In the case that Age and/or Body Mass Index must be recomputed by standard software

Age will be calculated in years using the following formula:

Integer [(Date of Visit 1 – Date of Birth + 1) / 365.25]

Body Mass Index (kg/m^2) will be calculated using the following formula:

Mass (kg) / Height^2 (m^2)

The total Comorbidity Risk Score will be derived by the sum of all scores (see protocol appendix 1). The total Comorbidity Risk Score will be categorized as a score < 50 or ≥ 50.

Immunogenicity

Values below the lower limit of quantification will be set to half that limit. Values above the upper limit of quantification will be set to the value of this upper limit.

Seroconversion based on **HI** antibodies is defined as binary variable for subjects with non-missing values pre-vaccination- and post-vaccination as:

= 1, if seroconverted (defined as a ≥ 4-fold increase in titer post-vaccination in those with pre-vaccination titer above the LLOQ (1:10), or a post-vaccination titer ≥ 1:40 for subjects with pre-vaccination titer below the LLOQ (1:10))

= 0, otherwise

Seroconversion based on **MN** antibodies is defined as binary variable for subjects with non-missing values pre-vaccination- and post-vaccination as:

= 1, if seroconverted (defined as a ≥ 4-fold increase in titer post-vaccination in those with pre-vaccination titer above the LLOQ, or a post-vaccination titer ≥ 4 times the LLOQ for subjects with pre-vaccination titer below the LLOQ

= 0, otherwise

Fold increase is defined as the post-vaccination titer divided by the pre-vaccination titer.

Geometric Mean Titer

The GMT will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers. The 95% confidence intervals for GMT will be calculated as $10^{\{M-t_{0.975,n-1}SE)\}}$, $10^{\{M+t_{0.975,n-1}SE)\}}$; where M and SE are the means and standard error of logarithm base 10-transformed titers, respectively.

Solicited Adverse Events

For details see Section 13.2.

Unsolicited Adverse Events

All adverse events will be characterized according to the date of occurrence related to the vaccination. If the start date is before the date of injection of study vaccine or indicated as on injection day but before injection, these events will not be considered as unsolicited adverse events and mapped to the medical history.

Note: If an adverse event start date is missing or unknown and no indication is provided on the timing, the adverse event will be considered as unsolicited adverse event.

When start and/or end dates of an adverse event are only partially known, adverse events will be categorized as unsolicited adverse event unless the partial end date is before the vaccination date.

All unsolicited adverse events emergent will be categorized as occurring during the treatment period of 28 days following vaccination (period Day 1 to Day 29) based on the start date. If start date is missing, events will be counted as yes during the period of 28 days following vaccination.

The **maximum event severity** is the greatest severity associated with a preferred term (PT) for a reported adverse event according to the following order: Mild < Moderate < Severe.

Vaccination-related Adverse Events are those for which the cause has been evaluated by the investigator, and recorded as possibly related, probably related or unknown/ missing.

Prior and Concomitant Medications

All medications will be characterized according to the start and end date of occurrence related to the vaccination as follows:

- **Pre-vaccination**: start date before the date of injection of study vaccine.
- **Concomitant:** start date before vaccination but continued after vaccination or start date after vaccination. Concomitant medication during the period Day 1- 29 will be labeled if in addition, the start date is on or before the Day 29. If start date and/or stop date is missing or incomplete, medication is considered concomitant unless the information on the stop date is unambiguous before the vaccination date.

Previous vaccination will be categorized by the previous year the latest influenza vaccination was done within the three years prior to the study vaccination. The categories year since last vaccination will be 1 year (if 2020 is the last year), 2 years (if 2019 is the last one) or 3 years (if 2018 is the last one).

8.9 Treatment groups

The different treatment groups will be labeled as shown in the table below. The HA antigen content and the MF59 content will be used as co-variates in selected statistical analyses.

Table 4: Overview of treatment groups

Group	Vaccine	Vaccine description	HA antigen content/ strain (µg)	MF59 squalene content (mg)	Total injected volume (mL)	Sorting Order
A	aQIVc 1	[redacted] and [redacted]	[redacted]	[redacted]	[redacted]	2
B	aQIVc 3	[redacted] and [redacted]	[redacted]	[redacted]	[redacted]	6
C	aQIVc 6	[redacted] and [redacted]	[redacted]	[redacted]	[redacted]	4
D	aQIVc 7	[redacted] and [redacted]	[redacted]	[redacted]	[redacted]	7
E	aQIVc 9	[redacted] and [redacted]	[redacted]	[redacted]	[redacted]	3

F	aQIVc 10	[redacted] and [redacted]	[redacted]	[redacted]	[redacted]	5
G	aQIVc 11	[redacted] and [redacted]	[redacted]	[redacted]	[redacted]	8F
H	QIVc	15 mcg	15	0	0.5	1

8.10 Analysis Software

All analyses will be performed using SAS Software version 9.4 or higher.

9. STUDY SUBJECTS

9.1 Disposition of Subjects and Withdrawals

All randomized subjects will be accounted for in this study. The numbers and percentages of subjects in each analysis set, study withdrawals, subgroups, and major protocol deviations will be presented. Number of subjects per country and site will be presented by vaccine group and overall for All Enrolled Set.

The time in days (i.e. date of last assessment minus date of vaccination plus 1) the subjects are under observation for safety will be summarized by vaccine group and overall using summary statistics (mean, Standard Deviation, minimum, median, maximum).

All subjects who are randomized will be accounted for in this study. The frequencies and percentages of subjects in each analysis set, study withdrawals, subgroups, and major protocol deviations will also be presented.

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

In general, all tables related to baseline characteristics should include a Total column across vaccine groups.

10.1 Demographics

Age, height, weight, body mass index and Comorbidity Risk Score will be summarized by reporting the mean, standard deviation, median and range, and will be calculated by vaccine group and overall.

In addition, the frequencies of age categories will be reported as 50 – 64 and ≥ 65 years old (age as a randomization stratum) and 50-64, 65-74, and 75-84, and ≥ 85 years old. The number and percentages of subjects by sex, ethnic origin, race, previous vaccination history (in past 3 years), country and Comorbidity Risk Score (<50 and ≥50) will be presented by vaccine group and overall.

Demographic data will be tabulated for the All Enrolled, FAS, PPS and Safety sets.

The distribution across all stratification factors (age subgroup * previous vaccination history) will be presented by vaccine group and overall. This table will be presented based on the IRT data and – if different – also for the actual eCRF data.

10.2 Medical History

The numbers and percentages of subjects with medical history will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by vaccine group and overall. Medical history data will be tabulated for the All Enrolled, FAS, PPS and Safety Sets.

11. IMMUNOGENICITY ANALYSIS

The immunogenicity analysis will be descriptive in nature and focus on the estimation of the treatment effects of the seven different aQIVc formulations versus QIVc. All immunogenicity analyses will be evaluated based on the PPS Immunogenicity. In the case that there is >5% difference in the total number of subjects between the PPS and the FAS Immunogenicity, additional analysis based on the FAS Immunogenicity will be conducted.

11.1 Blood samples

The frequencies and percentages of subjects with blood draws will be summarized overall and by vaccine group. Data will be tabulated for the All Enrolled Set.

11.2 Primary Objectives Analysis

The primary endpoints in terms of HI antibody response against homologous vaccine strains are defined as:

- Geometric Mean Titer (GMT): Geometric mean of HI antibodies at Day 1 and Day 29.
- Geometric Mean Fold Increase (GMFI): The Geometric mean of the fold increase in serum HI titer post-vaccination (Day 29) compared to pre-vaccination (Day 1).
- Percentages of subjects with HI titers ≥ 1:40 at Day 1 and Day 29.
- Percentage of subjects with seroconversion (defined as a ≥4-fold increase in titer post-vaccination in those with pre-vaccination titer above the LLOQ (1:10), or a post-vaccination titer ≥1:40 for subjects with baseline titer below the LLOQ (1:10) for HI antibodies at Day 29).

Note that the HI assay could be replaced by the MN assay in case of a lack of agglutination.

In addition, reverse cumulative distribution plots will be generated to display the distribution of the antibody responses at Day1 and Day 29 for each of the vaccine groups. The x-axis represents the immunogenicity values, and the scale of the axis is logarithmic. The y-axis represents the

percentage of subjects having at least that immunogenicity value. Due to the discrete values of antibody response, the plot will show a step-wise function. The figures begin at 100%, and then descends to the lowest point on the curve, which is the percentage of subjects having an immunogenicity value equal to the highest observed value.

All statistical analyses will be descriptive in nature. No hypothesis testing will be applied.

Geometric Mean Titer

Summary statistics (geometric mean, 95% confidence interval of GMT, minimum, median, maximum) of the titers will be presented by strain, assessment (Day 1 or Day 29) and vaccine group.

The analysis model used for the comparison of the HI (or MN) GMT between each of the seven aQIVc formulations and QIVc will be done using a general linear model on log-transformed (base 10) Day 29 titers as the outcome variable and as covariates: treatment groups as categories (aQIVc1, aQIVc3, aQIVc6, aQIVc7, aQIVc9, aQIVc10, aQIVc11 and QIVc), log-transformed pre-vaccination titer, age subgroup and previous vaccination history. From this model, adjusted differences in the least square means (on the log scale) will be produced with 95% confidence limits for aQIVc1 versus QIVc, for aQIVc3 versus QIVc, for aQIVc6 versus QIVc, for aQIVc7 versus QIVc, for aQIVc9 versus QIVc, for aQIVc10 versus QIVc, and for aQIVc11 versus QIVc. The estimated difference and the confidence limits will be back-transformed to obtain an *adjusted GMT ratio* with 95% confidence limits. Each of the four strains will be analyzed separately.

In addition, a second analysis model will be applied – similar as the model described above but using the amount of antigen and MF-59 dose as factors instead of the treatment groups as category, but with the same covariates age group, previous vaccination history and log-transformed pre-vaccination titer. Model fit will be assessed, and alternative models may be considered.

Potential interaction between age subgroup and treatment effect will be examined by including an interaction term in the model and present all adjusted GMT ratios with 95% confidence intervals for each age subgroup.

Unadjusted GMT ratio will be based on a simple ANOVA model on the log-transformed titers and the treatment group.

Geometric Mean Fold Increase

Summary statistics (geometric mean, 95% confidence interval of GMT, minimum, median, maximum) of the relative increase in titers will be presented by assessment (Day 29), strain and vaccine group.

The analysis model for the fold increase in titers will be done using the same models as mentioned above on log-transformed (base 10) (Day 29 titers/Day 1 titers) as the outcome variable but excluding the log-transformed pre-vaccination titer.

Analysis of binary endpoints

The number and proportion of subjects achieving the binary endpoints (seroconversion or HI titer >=1:40) will be summarized by assessment (Day 29), strain and vaccine group.

For each of the influenza vaccine strains and for each of the vaccine groups, summaries will include the associated two-sided 95% confidence intervals according to Clopper-Pearson.

The binary endpoints (i.e. seroconversion or titer ≥1:40) will be compared between each aQIVc formulation and QIVc using the Miettinen and Nurminen method without adjustment for the age subgroup. The results will be presented as the difference in the percentage of subjects with 95% confidence intervals.

Additional supportive analyses may be done using generalized linear models with factors for vaccine group, age subgroup, pre-vaccination titer as well as previous vaccination history. Adjusted differences between vaccine groups with 2-sided 95% CI will be calculated based on the model and potential interaction effects will be examined.

11.3 Secondary Objectives Analysis

The secondary endpoints in terms of HI antibody response against homologous cell-derived vaccine strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria) at Day 181, are:

- GMT: Geometric mean of HI antibodies at Day 181;
- GMFI: The Geometric mean of the fold increase in serum HI GMTs post-vaccination (Day 181) compared to pre-vaccination (Day 1);
- Percentages of subjects with HI titers ≥ 1:40 on Day 181.

In addition, the humoral immune response in terms of MN antibody response against homologous cell-derived vaccine strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria) at Days 1, 29 and 181:

- GMT: Geometric mean of MN antibodies at Days 29 and 181;
- GMFI: The Geometric mean of the fold increase in serum MN GMTs post-vaccination (Day 29 and Day 181) compared to pre-vaccination (Day 1);

- Percentages of subjects with seroconversion (defined as ≥ 4-fold increase for subjects with pre-vaccination MN titers ≥ Lower Limit of Quantitation (LLOQ) or as ≥ 4*LLOQ for subjects with pre-vaccination MN titer <LLOQ) at Day 29.

The analysis of the secondary immunogenicity endpoints will be conducted in the same way as described for the primary immunogenicity endpoints.

11.4 Exploratory Objectives Analysis

Additional analyses may be done on the immunogenicity endpoints as measured on Day 29 by HI or MN assay using cell-derived target viruses or cell-derived heterologous target viruses. Details on this exploratory analysis will be included in a separate statistical analysis plan. The results may be presented in an addendum to the CSR.

12. EFFICACY ANALYSIS

Not applicable.

13. SAFETY ANALYSIS

The analysis of safety assessments in this study will include summaries of the following categories of safety data collected for each subject:

- Vaccine exposure;
- Solicited local and systemic adverse events as recorded by the subject;
- Solicited systemic events and injection site pain assessed using the investigator evaluation;
- Unsolicited adverse events;
- Serious AEs, MAAEs, AESIs and AEs leading to withdrawal from study.

13.1 Analysis of Extent of Exposure

The frequencies of subjects with vaccinations will be summarized overall and by vaccine group and by age group. Data will be tabulated for the All Exposed Set.

13.1.1 Safety Completeness

Analysis Solicited Adverse Events

The safety completeness analysis on solicited adverse events aims to identify subjects who completed the electronic diaries. The analysis will show the number of subjects with valid results by solicited adverse event and day.

Three summaries will be produced:

1. The frequencies of subjects who provided any data on the electronic diary cards by vaccine group.
2. For each solicited adverse event – including analgesic use, the frequencies of subjects with data will be presented by vaccine group and day
3. For each solicited adverse event – including analgesic use, frequency of the number of days with data on the eDiary by vaccine group.

For the corresponding percentages, the denominator will be the respective number of subjects vaccinated (All Exposed Set).

All analyses will be based on the 'as treated' analysis set.

13.2 Solicited Local and Systemic Adverse Events

Each solicited AE is to be assessed by the subject for Day 1 to Day 7 according to a defined severity grading scale; see specifics of the solicited event and grading system below in Table 3.

Table 5 Severity Grading for Solicited Local and Systemic Adverse Events

		Any Event		
Type	**Solicited Event**	**Grade 1/Mild**	**Grade 2/Moderate**	**Grade 3/Severe**
Local	Injection site pain	No interference with daily activity	Interferes with daily activity	Prevents daily activity
	Erythema	25-50 mm	51-100 mm	> 100 mm
	Induration	25-50 mm	51-100 mm	> 100 mm
Systemic	Loss of appetite	Eating less than usual with no effect on normal activity	Eating less than usual /interfered with normal activity	Not eating at all

		Any Event		
Type	**Solicited Event**	**Grade 1/Mild**	**Grade 2/Moderate**	**Grade 3/Severe**
	Nausea	No interference with daily activity	Interferes with daily activity	Prevents daily activity
	Fatigue	No interference with daily activity	Interferes with daily activity	Prevents daily activity
	Myalgia	No interference with daily activity	Interferes with daily activity	Prevents daily activity
	Arthralgia	No interference with daily activity	Interferes with daily activity	Prevents daily activity
	Headache	No interference with daily activity	Interferes with daily activity	Prevents daily activity
	Chills	No interference with daily activity	Interferes with daily activity	Prevents daily activity
	Fever	38.0 - 38.4 °C 100.4 – 101.1 °F	38.5 – 38.9 °C 101.2 – 102.0 °F	≥39.0 °C ≥102.1 °F

Note: presence of an event on a day is defined as grade 1, 2 or 3; absence is defined as non-missing and not present. Erythema and Induration: grading will be derived from the actual measurements in mm; Fever will be derived from the actual temperature.

Other Indicators of Reactogenicity

The use of analgesics/antipyretics will be captured as "absent" or "present" separately by reason "for treatment" or "for prevention".

The analyses will be based on the solicited safety set and encompass various summaries of the data by vaccine group, overall and by age subgroup.

1. Overall summary of subjects with solicited adverse events
2. Local Solicited adverse events, maximum event severity by event and time interval (i.e. Day 1-7, Day 1-3, Day 4-7)
3. Systemic Solicited adverse events, maximum event severity by event and time interval (i.e. Day 1-7, Day 1-3, Day 4-7)
4. Number of days of solicited adverse events, including ongoing AE after Day 7
5. Daily reports of subjects with solicited adverse events.
6. Day of first onset of solicited adverse events

7. Ongoing adverse events at Day 7
8. Distribution of maximum temperature
9. Other use of analgesics/antipyretics.
10. Exploratory analyses to investigate the effect of amount of antigen and MF-59 levels.

For each of the time points or time intervals presented in the summaries, only subjects with at least one valid observation (i.e., any non-missing values) for the solicited adverse events in the interval of interest will be considered. Subjects without valid data will be removed from the denominator to prevent a downward bias (towards zero).
All tables are run by vaccine group, overall and by age subgroup.

Overall summary of subjects with solicited adverse events.
Any solicited adverse event presence is defined as at least one day recorded a presence of a local or a systemic adverse event. No solicited adverse event is defined as for all days 'No' for all pre-defined solicited adverse events.
Note that, where applicable, missing values for all days for all events will be excluded from % calculations.
The use of analgesics/antipyretics will be considered in this summary as a separate category under "other", however will be considered as part of reactogenicity.

Local Solicited adverse events, maximum event severity by event and time interval
The **maximum event severity** will be defined if there is at least one non- missing observation within this time interval. Each subject's data will be aggregated across the time points of the interval and summarized according to the maximal severity observed for each local adverse event, followed by a summary across subjects for each vaccine. Subjects with missing values at each of the requested time points, will be excluded.
The time intervals will be Day 1 to Day 7, Day 1 to Day 3 and Day 4 to Day 7. A summary table will be created with the frequency using only any local solicited AE and severe local solicited events.

Systemic adverse events, maximum event severity by event and interval
The analysis on the maximum severity of the systemic adverse events will be done along the same methods as for the local adverse events.

Number of days with solicited adverse events
The number of days with the adverse event is defined irrespective of severity. If a solicited adverse event continues beyond day 7 the period after day 7 is added.

The frequency distribution of the number of days (including mean and median values) will be provided in a summary table by vaccine and by adverse event. As reference the number of missing days will be presented in a frequency table.

Daily reports of solicited adverse event

For each of the time points only subjects with at least one non-missing observation for the solicited adverse event in the interval of interest will be considered. Subjects with missing values will be removed from the denominator to prevent a downward bias (towards zero). Data collected will be summarized (frequencies and percentages of subjects) by vaccine group, solicited adverse event, and time point (i.e. by day).

Time of first onset of solicited adverse events

The **time of first onset** is defined, for each subject, for each solicited adverse event, as the day at which the respective solicited adverse event first occurred. The summary will provide the frequencies and percentages of subjects with first onset of each solicited adverse events by vaccine group and by each time point, as well as mean and median day of onset.

Adverse events ongoing at Day 7

For each of the solicited adverse events, the number and proportion of subjects in the solicited safety set reported the event ongoing at Day 7 will be summarized.

Distribution of maximum temperature

Body temperature will be summarized by 0.5 °C increments from 36.0 °C up to ≥40 °C by frequency tables.

Use of analgesics/antipyretics

The use of antipyretics and analgesics will be summarized as “other” by type of use (prophylactic versus treatment) as the number and percentage of subjects reporting use.

Exploratory analyses to investigate the effect of amount of antigen and MF-59 levels.

A logistic regression analysis will be applied with the binary response (presence of solicited adverse reaction or no reaction), to explore the relation with antigen and MF59 levels as factors as well as with age and previous vaccination history. This model will be applied for both reported solicited local or systemic adverse events (AEs) for 7 days following vaccination and reported severe solicited local or systemic AEs for 7 days following vaccination (Day 1 through Day 7).

13.3 Investigator assessment of Solicited Adverse Events

The solicited systemic events and injection site pain will also be assessed by the investigator. For each subject, the investigator will assess if the subject's solicited symptoms are consistent with the data reported in the e-diary. If no, the investigator will record the evaluation of the solicited systemic events and injection site pain for consistency with eDiary and if not presence or absence, and if present the maximum severity and start and stop date. If yes, the subject's eDiary data will be mapped to the investigator's assessment.

A frequency table will be presented on the consistency assessment of the investigator (yes/no) by vaccine group and total.
Furthermore, the overall occurrence during Day 1 to 7 after vaccination for each of the solicited systemic events and injection pain based on the investigator assessment will be tabulated by vaccine group for total and by age group. The same summaries will be presented by the maximum severity including the occurrence of severe events according to the investigator. All subjects for which an investigator assessment has been done will be included in these analyses.

13.4 Unsolicited Adverse Events

This analysis applies to all AE's occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in the AE eCRF.

The original verbatim terms used by investigators to identify adverse events in the eCRFs will be mapped to preferred terms using the MedDRA dictionary.

The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and the preferred term within system organ class. These summaries will be presented by vaccination group. When an AE occurs more than once for a subject, the maximum severity and strongest relationship to the vaccine group will be counted.

The assignment to safety follow-up time intervals will be done by day of onset and not by days ongoing/persisting.

The summaries will be presented by period of onset (Day 1 to Day 29, Day 30 to end of study or Day 1 to end of study). An overview summary will be created by time -period with number and % of subjects with the following categories:

- AE
- AE by maximum severity
- Related (i.e. at least possible) AE
- SAEs
- Related SAEs
- AESIs
- MAAEs
- AEs leading to withdrawal from study
- Deaths.

The following summaries will be produced by SOC and Preferred Term and by time-period (Day 1 to Day 29, Day 30 to end of study or Day 1 to end of study):

- AEs
- AEs by maximum severity
- AEs that are possibly or probably related to the vaccine
- SAEs
- SAEs that are possibly or probably related to the vaccine
- AESIs
- MAAEs
- AEs leading to withdrawal
- Deaths.

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

All tables will be produced overall and by age subgroup.

13.5 Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA. For clinicaltrials.gov posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and according to occurrence of each event based on the Overall Safety set.

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13.6 Clinical Safety Laboratory Investigations

Not applicable.

13.7 Concomitant Medication

Medications and vaccines taken prior or during the study are categorized as pre-trial and/or concomitant. In addition, a subset of concomitant medications is defined for the period Day 1 to 29 (see section 8.7 for definition).

Medications (generic drug name) will be coded using the WHODRUG dictionary.

The frequencies and percentages of subjects reporting pre-trial, concomitant medications (Day 1 – 29 and Day 1 to end of study) will be tabulated by vaccine group.

14. INTERIM ANALYSIS

There are no planned interim analyses for this study.
The statistical analyses will be performed stepwise in two parts, as follows:

1. A final analysis including all immunogenicity and safety data collected from Visit 1 to Visit 3 (Day 29) and associated primary and secondary objectives will be conducted on cleaned and locked data. No individual listings and unblinding data will be generated at this stage. Access to information about study groups will be limited by a biostatistician in charge of statistical analysis.

2. The analysis of immunogenicity and safety data collected between Visit 3 and Visit 5 will be performed after all data is available. The results of this analysis will cover the entire study duration. All results will be presented in the clinical study report and will include individual data listings and unblinded information.

15. DATA MONITORING COMMITTEES

An internal safety team (IST) – independent of the study team - will be installed to monitor the safety data collected during the enrollment of the subjects in the study. Details are included in the IST charter. In addition, upon request an independent DMC will be asked to review the safety data and make recommendations for the conduct of the trial. Further details are described in the DMC charter.

Alerting and pausing rules

A summary table will be created with number and % of subjects who met one of the criteria by treatment based on the solicited or unsolicited Safety set.

- Any SAE that cannot be reasonably attributed to a cause other than vaccination, according to the Investigator's assessment, within 7 days post-vaccination (i.e. probable).
- Severe systemic hypersensitivity such as anaphylaxis, within 24 hours after study vaccination.
- Any Grade 3 (severe) local solicited AE lasting ≥2 consecutive days, within 7 days postvaccination.
- Any Grade 3 (severe) systemic solicited AE lasting ≥2 consecutive days, within 7 days postvaccination.
- Any severe unsolicited AE that cannot be reasonably attributed to a cause other than vaccination (i.e. probable), within 7 days postvaccination.

16. CHANGES TO PLANNED ANALYSIS

Compared to the final protocol, an additional safety set may be defined for the investigator assessment of the solicited adverse events. This will only be applicable if there are subjects without any eDiary data, but with an investigator assessment of the solicited adverse events.

The SAP, version 1.0, 16 April 2021 has been amended with a few changes mainly related to the programming of data sets.

- The window around the Day 29 sample visit has been extended to -7 and + 21 days with respect to the Day 29 visit to be included in the PP analysis.
- The Day 181 FAS and PPS have been defined in more detail
- Last vaccination prior to study will be categorized as 1 year before, 2 years or 3 years before
- The investigator assessment will be derived both on the overall consistency as well as the particular symptom.

17. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The list of tables, listings and figures will be developed based on the final version 1.0 of this statistical analysis plan. This will be documented as part of the TLF shells.
Numbering will follow ICH E3 guideline on clinical study report.

18. REFERENCES

Clinical Study Protocol V201_01 FINAL VERSION 2.0: JAN 2021SEPT 2020

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