STATISTICAL ANALYSIS PLAN
PHASE 2B

DATE OF PLAN:

Final Version 2.0, 01Jan2020

BASED ON:

Protocol Final Version 3.0, dated 20May2019

eCRF, dated 27Mar2019

STUDY DRUG:

MVA-NP+M1

PROTOCOL NUMBER:

FLU009

STUDY TITLE:

A Phase 2b Study to Determine the Efficacy of Candidate Influenza Vaccine MVA-NP+M1 in Adults aged 18 years and over

SPONSOR:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
CNS	Clinical Network Services Pty Ltd
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ELIspot	IFN-γ Enzyme Linked Immunospot
GMC	Geometric Mean Concentration
ICH	International Conference on Harmonization
ICS	Intracellular Cytokine Staining
ILI	Influenza-like Illness
ISR	Injection Site Reactions
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NCS	Not Clinically Significant
PFU	Plaque Forming Units
PT	Preferred Term
QIV	Quadrivalent Influenza Vaccines
RR	Relative Risk
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Term
SD	Standard Deviation
SFU	Spot Forming Units
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
VE	Vaccine Efficacy
WHO-DD	World Health Organization Drug Dictionary

2. SUMMARY OF UPDATES FROM SAP FINAL VERSION 1 (21NOV2019)

- Futility analysis at interim analysis has been updated by following a non-binding conditional power approach.
- Sample size re-estimation at interim analysis will be conducted as proposed by protocol.
- Other editorial changes to clarify the text.

3. INTRODUCTION

This Statistical Analysis Plan (SAP) is an adjunct to the Vaccitech Ltd Protocol FLU009. This SAP outlines the FLU009 study and describes the methods for the analysis of the data arising from this clinical trial. This document is mainly based on the statistical section of the study protocol (Final Version 3.0, 20May2019). Therefore some sections are described briefly, and references are made to the related sections in the protocol. The analyses outlined in this document, if different from the protocol, will supersede those specified in the protocol.

The structure and content of this SAP aim to provide sufficient detail to meet the requirements described by CNS Standard Operating Procedure CNSSOPBMT002_V001: Statistical Analysis Plan, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.

This is a Phase 2b, multicentre, randomised, single-blind study in up to 6000 adults to compare the efficacy, safety and immunogenicity of MVA-NP+M1 when given as an adjunct to a standard, licensed adult dose of Quadrivalent Influenza Vaccines (QIV).

4. STUDY OBJECTIVE(S) AND ENDPOINT(S)

4.1. Study Objective(s)

4.1.1. Primary Objective

The primary objective of the study is:

- To assess the effect of MVA-NP+M1 on the reduction of laboratory confirmed influenza when given as an adjunct to licensed QIV in adults

4.1.2. Secondary Objectives

The secondary objectives of the study are:

- To assess the impact of MVA-NP+M1 on incidence and severity of influenza-like symptoms in adults aged 18 years and over when given as an adjunct to licensed QIV
- To assess the safety of MVA-NP+M1 or placebo when given as an adjunct to licensed QIV in adults aged 18 years and over
- To assess the immunogenicity of MVA-NP+M1 when given as an adjunct to licensed QIV in adults aged 18 years and over

4.2. Study Endpoint(s)

4.2.1. Primary Endpoint

The primary endpoint of the study is:

- Incidence rate of laboratory confirmed influenza using reverse transcription polymerase chain reaction (RT-PCR) on deep nasal/mid-turbinate swab samples

4.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- Incidence and severity of influenza-like illness (ILI)
- Duration of ILI
- Occurrence of solicited local and systemic reactogenicity signs and symptoms for 7 days following vaccination
- Occurrence of SAEs during the whole study duration
- Frequency of influenza-specific T-cells measured by IFN-γ/granzyme B ELISpot
- Geometric mean titre of influenza-specific neutralising antibodies

5. STUDY DESIGN

5.1. Design Information

As mentioned above, this is a Phase 2b, multicentre, randomised, single-blind study in up to 6000 adults to compare the efficacy, safety and immunogenicity of MVA-NP+M1 when given as an adjunct to a standard, licensed adult dose of QIV. The study will be conducted on an outpatient basis and will run over two consecutive influenza seasons. It is aimed to recruit approximately 2200 participants in Season 1 and 2800-3800 participants in Season 2.

The study will consist of a screening/vaccination visit and a follow-up period:

- Screening/Vaccination visit: In this visit, potential participants will be identified for study eligibility. Following screening and confirmation of eligibility on Day 0, all participants will be randomised in a 1:1 ratio to receive MVA-NP+M1 or placebo, which will be administered by intramuscular injection.
- Follow-up period: This period is from Day 1 to the end of the influenza season. In the follow-up period, participants will:
    - record oral temperature and any solicited adverse events for 7 days post-vaccination
    - record unsolicited adverse events for 28 days post-vaccination
    - record respiratory illness and / or ILI every week during the influenza season, starting on 01 May and ending on or before 15 October in line with official Australian influenza season.
    - receive two nasal swabs, within 72 and 96 hours of respiratory/ILI symptom onset, for laboratory to confirm influenza using RT-PCR

The majority of participants will participate in the main cohort of the study. Approximately 50 participants will participate in an immunogenicity cohort; it is anticipated this will be at one centre only. In addition to the visits and procedures for the main cohort, the immunogenicity cohort will attend three additional clinic visits on Days 7 (+3 days) and 28 (±7 days) and Week 26 (±1 week) (approximate end of the influenza season).

For both main and immunogenicity cohorts, to accommodate the timing of vaccination in the influenza season, slightly different follow-up procedures are outlined for:

- participants who are vaccinated early in the influenza season and have completed Day 28 assessments prior to the start of the ILI reporting period on 01 May: Not required to complete the eDiary in the period after Day 28 until 01 May, otherwise as normal.

- participants who are vaccinated later in the influenza season and have Day 28 just prior to, or after, the start of the ILI reporting period on 01 May: required to complete the eDiary for the study period as normal.

The treatment groups and number of study participants are as follows:

	Group 1	**Group 2**
Study treatments	MVA-NP+M1	Placebo
Dose	1.5 x 10^8 pfu	None
Volume	0.5 mL	0.5 mL
Route of administration	Intramuscular injection	Intramuscular injection
Vaccination days	Day 0	Day 0
Number of participants; *Main cohort* *Immunogenicity cohort*	2500-3000 *2475* *25*	2500-3000 *2475* *25*

Data Monitoring Committee

The study will be subject to oversight by a Data Monitoring Committee (DMC). The DMC will review the study safety data and make recommendations concerning the continuation, modification, or termination of the study. According to protocol, a DMC will hold following meetings:

- Kick off meeting before the first participant is enrolled
- A meeting at the end of the first influenza season to review safety and efficacy data and perform a futility analysis (with re-powering if required),
- Perform unscheduled review of data if one of the study pausing or holding rules is met.

This study is not a group sequential design, with no formal stopping rules set up for efficacy. The futility analysis is informal and is for information only. It should not impact the overall type I error control at the final analysis.

5.2. Definition of Study Drugs

MVA-NP+M1 is the investigational study vaccine. On day 0, each participant will receive a single dose of

- 1.5 x 10^8 plaque forming units (pfu) MVA-NP+M1 or
- 0.5 mL 0.9% saline placebo

5.3. Sample Size Considerations

5.3.1. Sample Size Justifications

Various disease incidence rates in the control arm, relative vaccine efficacy in the MVA-NP+M1 arm, and alpha levels (two-sided) were assumed for the sample size calculation. Sample sizes based on various scenarios are provided as follows:

Rate of Influenza in Control Arm	Relative Vaccine Efficacy	Total Sample Size Required		
		α=0.10	α=0.15	α=0.20
2%	30%	11478	9658	8360
	35%	8188	6890	5964
	40%	6082	5118	4430
	50%	3652	3074	2660
3%	30%	7586	6382	5524
	35%	5412	4554	3,942
	40%	4022	3384	2930
	50%	2416	2034	1760
4%	30%	5640	4746	4108
	35%	4026	3386	2932
	40%	2992	2516	2178
	50%	1798	1512	1310

All calculations assumed 80% power. Given this is a proof of concept study, an alpha of 0.1 (two-sided test) was chosen for powering analyses. Based on the projected range of incidence rates in the control arm, a total sample size of approximately 5000 to 6000 participants over two influenza seasons is expected to provide approximately 80% power to detect a meaningful vaccine efficacy (approximately 35%) in the MVA-NP+M1 arm.

5.3.2. Sample Size Re-estimation

After the first influenza season, which will enrol approximately 2,200 participants, a sample size recalculation will be performed on the basis of the observed relative vaccine efficacy of MVA-NP+M1 during the first influenza season, as well as the observed rates of influenza within each treatment group

5.4. Randomization

Eligible participants will be randomised to the study based on a randomisation schedule managed by IBM Clinical Development. The randomisation schedule will be prepared by an independent statistician not involved in the study. Participants will be randomised on Day 0 after informed consent has been provided and eligibility confirmed.

Participants in the main cohort will be stratified by age <65 years and ≥65 years at the time of randomisation. Investigators will aim to enrol approximately 70% of participants in the <65 years old strata. Participants recruited into the immunogenicity cohort will be randomised separately from the main cohort with no stratification.

All participants will be randomised in a 1:1 ratio to one of two treatment groups:

- Group 1: 1.5 x 10^8 pfu MVA-NP+M1
- Group 2: 0.5 mL 0.9% saline placebo

Discontinued participants will not be replaced.

This study is single blind. The participant will be blinded to which study vaccine (MVA-NP+M1 or placebo) they are administered. The Investigator and all study staff acting to determine or record safety, as well as all laboratory staff will also remain blinded ("observer blind"). The pharmacist and any study staff administering the study vaccine will not be blinded.

6. PLANNED ANALYSES

6.1. Interim Analyses

FLU009 was not designed as a group sequential trial. Therefore, no formal interim stopping boundaries for efficacy have been established. However, a DMC will be appointed to review the study data and make recommendations concerning the continuation, modification, or termination of the study.

The DMC will review cumulative safety and efficacy data from the first influenza season. This review of safety and efficacy data will also include a futility analysis, as well as a sample size recalculation based on the observed relative vaccine efficacy in the MVA-NP+M1 vaccine group. Plans for the futility analysis and sample size recalculation will be established a priori (prior to any unblinding of study data) and are described below. . The study will not be stopped for efficacy at the interim analysis because no stopping rule was set up for this purpose.

All unblinded-by-group summaries will be prepared for the DMC by an independent unblinded statistician not associated with the study conduct or development of the SAP for the final analysis. All procedures associated with this review, including objectives, data handling, and elements to be included for review will be documented in the DMC charter.

Futility Analysis

The futility analysis will be conducted using a Conditional Power (CP) approach, with various assumptions of the final sample size to be recruited at the end of study. A final sample size of 6000, 6500, 7000, or a final sample size based on sample size recalculation will be assumed for the purpose of conditional power calculation.

Given the first influenza season resulted in a relatively high number of virologically-confirmed cases of influenza, investigators anticipate the second influenza season will be somewhat milder than the first. Therefore, various assumptions for vaccine effect in the next influenza season will be made under each of the final sample size assumptions. CP will be calculated for the following scenarios:

a. CPT – Conditional power under the current trend (i.e., observed relative VE following season 1)
b. CPD – Conditional power under the original design (i.e., influenza incidence for MVA-NP+M1: 1.56%, and for placebo: 2.4%)
c. CPN – Conditional power under the null hypothesis (i.e., influenza incidence for MVA-NP+M1: 2.4%, and for placebo: 2.4%)
d. CP80LB – Conditional power under the lower bound of the 80% CI of the current trend

e. CPHF – Conditional power under influenza case accrual in the second season being approximately half of that observed in the first influenza season (i.e., pooled influenza incidence during Season 2 is approximately 0.8%). Other influenza incidence rates in the second season for both groups could be assumed as well.

The calculation of CP will follow the approach proposed by Jennison and Turnbull (2000). CP is a predictive power, and is used as a non-binding guide to stop the study for futility. When the final decision of DMC is made, CP and the totality of data for efficacy and safety at IA need to be considered.

Refer to the DMC charter for guidelines relating to the interpretation of these calculations and the resulting recommendations to the Sponsor.

Sample Size Recalculation

A sample size recalculation will be performed on the basis of the observed relative vaccine efficacy and the observed incidence rates of influenza within each treatment arm following the first influenza season. This calculation will be based on an alpha of 0.10 significance level (two-sided test) and 80% power, and the results will be shared with the DMC at the time of the interim analysis.

Refer to the DMC charter for guidelines relating to the interpretation of these calculations and the resulting recommendations to the Sponsor.

6.2. Final Analysis

The final analysis of the study will be conducted once all participants have completed the study, the clinical database has been locked, and randomisation has been unblinded. All planned analyses to be conducted at the final analysis will be included within the SAP, which will be finalized prior to database lock.

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

7.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings will be prepared according to ICH Guideline E3 (as appropriate for a phase II study).

In general, summary tables will be organized with respect to the vaccination groups. The summary tables will clearly indicate the number of participants to which the data apply and unknown or not performed are distinguished from missing data. Summary tables for any concomitant medications will be coded according to the latest available version of World Health Organization Drug Dictionary (WHO-DDE). Adverse event preferred terms and body/organ systems and medical history conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) dictionary version 20.1 (or higher). The WHO-DDE and MedDRA version numbers used for coding will be reported in the outputs.

Listings will also be sorted by vaccination group, subject number and visit date/time.

In general, missing data will not be imputed unless otherwise specified. Any imputed or derived data will be flagged in the individual participant data listings. Imputed data will not be incorporated into any raw or primary datasets. These data will be retained in derived analysis datasets.

7.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

The tables, figures and listings will be numbered using a decimal system to reflect main levels of tables and listings (e.g., Table XX.YY.ZZ. …).

1. The first level number will be consistent with the corresponding Clinical Study Report (CSR) appendix in which the tables or listings will appear. For example, the post text tables will appear in Appendix 14 (and will be numbered 14.XX.YY) and the individual participant data listings will appear in Appendix 16 (and will be numbered 16.XX.YY). The participant disposition table will be first in the first section of the report and will be numbered Table 14.1. The supportive participant data listing will be Listing 16.1. Any subset table will have the number Table 14.1.2, etc.
2. Table numbering will follow ICH E3 for CSRs. Participant disposition, baseline characteristics and demography, and prior and concomitant medications tables should appear as the second level number (Table 14.1 series). Efficacy tables will occupy the next sub-level (Table 14.2 series). Safety tables will follow next (Table 14.3 series). Similar conventions will be applied to the participant data listings.

3. Each table and listing title will be complete, accurate and concise. The last line of the title will provide the analysis group being summarised (e.g., Safety Population, etc.).
4. If possible, variables being summarised and statistics reported will appear in the left most column of a table. The next columns for vaccination groups should report the data from left to right for the vaccination group (MVA-NP+M1 and Placebo) respectively.

7.3. Data Management

All data will be recorded by the site in individual source documents. An electronic Case Report Form (eCRF) will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

Data storage, data transfer and data cleaning will be conducted according to the relevant CNS Standard Operating Procedures (SOPs).

7.4. Data Presentation Conventions

Continuous safety variables (e.g., clinical laboratory values and vital signs) will be reported to the same precision as the source data. Derived variables will be reported using the same precision as the value(s) from which they were derived. For the reporting of descriptive statistics, the mean and median will be reported to 1 decimal place more than the source data; the minimum and the maximum values will be presented to the same precision as the source data and standard deviations (SD) will be reported to 2 decimal places more than the source data.

For categorical/discrete variables, the frequency count and the percentage (of available data) for each class of the variable will be presented and will be displayed in the form XX (XX.X%) where the percentage is in the parentheses. When there is no data for a category, the result will be presented as 0.

Date variables will be formatted as DDMMMYYYY for presentation. Time will be formatted in military time as HH:MM for presentation.

Extra measurements (such as unscheduled or repeat assessments) will not generally be included in summary tables but will be included in participant listings. They may be used if a scheduled measurement is missing and the timing of the extra measurement is deemed suitable. They will be used in summary tables which are not ‘time specific’, for example, summaries of maximum post vaccination values. In the data listings and summary tables presented as part of the CSR,

scheduled assessments will be identified by the protocol specified nominal visit day and scheduled time point.

The table, figures and listing shells as part of this SAP provide the expected layout and titles of the tables, figures and listings. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

Minor modifications may be necessary to the planned design of tables, listings and figures to accommodate data collected during the actual study conduct. Any major deviations from the final approved SAP (e.g., change in the population used, change from statistical method/assumption listed, transformation of data type [e.g., continuous data transformed to categorical], exclusion of planned analysis, etc.) or additional unplanned analyses will be documented (with justification) in the CSR.

7.5. Analysis Populations

Four different analysis populations will be defined: Safety Analysis Set, Efficacy Analysis Set Immunology Analysis Set, and All Randomised Analysis Set. Participant inclusion into each population will be determined after database lock and prior to the randomisation unblinding.

7.5.1. Safety Analysis Set

The Safety Analysis Set will consist of all randomised participants who received at least one vaccination (according to the vaccination actually received). The safety population will be used for all safety endpoint analysis.

7.5.2. Efficacy Analysis Set

The Efficacy Analysis Set will consist of all randomised participants who received the study vaccine according to the randomised treatment group (i.e. intent-to-treat). The Efficacy Analysis Set will be used for the analyses of demographics, baseline, prior and concomitant medications, and all efficacy endpoints. This is the main analysis population for efficacy endpoints.

7.5.3. Per Protocol Analysis Set

The Per Protocol Analysis Set will consist of all randomised participants who received the study vaccine, had follow-up for respiratory illness and/or influenza-like illness (ILI) during the influenza season, and did not have major protocol violation/deviation. The Per Protocol Analysis Set will be used for the analyses of all efficacy endpoints, and results based on Per Protocol Analysis Set will be used as supportive evidence to Efficacy Analysis Set.

7.5.4. Immunology Analysis Set

The Immunology Analysis Set will consist of all randomised participants according to their randomised treatment group who received the study vaccine, provided the pre-vaccination and at least one post-vaccination blood sample evaluable for immunological analysis and did not have any major protocol deviations that would impact on the results of the immunological analysis. The Immunology Analysis Set will be used for the analysis of all immunogenicity endpoints.

7.5.5. All Randomised Analysis Set

The All Randomised Analysis Set will consist of all randomised participants regardless of whether the participant received the study vaccine or not. The All Randomised Analysis Set will be used for the analysis of participant disposition.

7.6. Baseline Definition

Baseline will be defined as the last available, non-missing observation prior to the vaccination, unless specifically mentioned otherwise.

In general, Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered when calculating baseline observations. However, valid categorical observations will be considered for baseline calculations. In addition, non-missing results from unscheduled assessments prior to the vaccination may also be considered in the calculation of baseline observations.

7.7. General Derived and Transformed Data

7.7.1. Age

Age, in completed years, at screening will be defined as:

Age (years) = integer value ((Date Signed Informed Consent – Date of Birth + 1) / 365.25)

7.7.2. Study Day

Study day will be calculated using the vaccination date as the reference date. If the date of interest occurs on or after the vaccination date, then study day will be calculated as (date of interest – date of vaccination). If the date of interest occurs prior to the vaccination date, then study day will be calculated as (date of interest – date of vaccination). The day of vaccination will be identified as Study Day 0 in data analysis according to protocol. In CDISC standard, however this is Study Day 1, which will not be followed.

Data listings will present study days in addition to assessment dates, where applicable.

7.7.3. Change from Baseline

Actual change from baseline will be calculated as (post-baseline result – baseline result).

Percent change from baseline will be calculated as (actual change from baseline/baseline result)* 100.

7.7.4. Other Derivations

Body Mass Index (kg/m^2, to one decimal place) = Body Weight (kg) / (Height^2 (m)).

Treatment emergent adverse events (TEAEs) will be defined as AEs which commence on or after the time of start of vaccination. AEs without an onset date or time will be defined as treatment emergent except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to start of vaccination or if the AE stop date indicates that the event started and/or stopped prior to start of vaccination.

Duration of AE (in hours, to one decimal place) = (AE Resolution Date/Time) - (AE Onset Date/ Time).

8. TREATMENT COMPARISONS

8.1. Data Display Treatment and Other Sub-Group Descriptors

For data listings, Main and Immunogenicity cohorts will be listed separately for clarity. For the summary tables of efficacy and safety analyses, where applicable, data from both cohorts will be pooled together for the summary.

The following labels for vaccination groups will be used on all listings, in the following order:

- MVA-NP+M1/Main
- Placebo/Main
- MVA-NP+M1/Immunogenicity
- Placebo/ Immunogenicity

The following labels for vaccination groups will be used on all tabulations and plots, in the following order:

- MVA-NP+M1
- Placebo

.

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The listings, figures and summary tables for the disposition, safety, efficacy and immunogenicity data will be the responsibility of the study Biostatistician at CNS.

The currently supported version (9.4 or higher) of SAS software will be used to perform all data analyses. The actual SAS version used will be presented in the Clinical Study Report.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by vaccination group, participant number and assessment date/time.

Unless otherwise stated, continuous variables will be summarised using descriptive statistics including number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum values. Categorical variables will be summarised with frequency counts and percentages. The population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Percentages will be rounded to one decimal place, with the denominator being the number of participants in the relevant population, unless otherwise stated.

Only data from nominal protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the figures and listings.

All statistical tests, if conducted, will be two-sided and statistical significance will be determined at the 0.05 level, unless otherwise stated.

9.1. Multicentre Studies

Vaccine efficacy by study sites will be assessed separately as a subgroup analysis.

9.2. Other Strata and Covariates

Not applicable for this study.

9.3. Examination of Subgroups

Vaccine efficacy for age<65 years and age ≥65 years will be assessed separately as subgroup analysis.

9.4. Multiple Comparisons and Multiplicity

No multiplicity adjustment will be performed unless otherwise stated.

9.5. Data Handling Conventions

9.5.1. Premature Withdrawal and Missing Data

For participants who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

There will be no imputation for missing data, unless otherwise stated. Adverse events with missing or partial dates will be handled such that in the absence of contradictory information an AE is treatment emergent.

9.5.2. Handling of Dropouts

All data collected prior to drop out will be listed and included in data summaries.

9.5.3. Additional/Unscheduled Assessments

Extra measurements (such as unscheduled or repeat assessments) will not generally be included in summary tables but will be included in participant listings. They may be used if a scheduled measurement is missing and the timing of the extra measurement is deemed suitable. They will be used in summary tables which are not 'time specific'; for example, summaries of maximum post dosing values.

The original data will always be presented in the listings.

9.5.4. Assessment Windows

No derived visit windows will be applied to assessments. All assessments will be included in the listings. Protocol specified nominal visit names will be used for the analyses. For vaccine efficacy, all clinical events happened during the influenza season, starting on 01 May and ending on or before 15 October in line with official Australian influenza season, will be included for the analysis.

9.6. Derived and Transformed Data

The required endpoints and variables will be derived by the Statistical Programmers at CNS using the derivations specified in Section 7.7 of this SAP.

10. STUDY POPULATION

All disposition analyses will be conducted on the All Randomised Analysis Set. Baseline and demographic analyses will be conducted on the Efficacy Analysis Set. All summaries will be presented by vaccination group and overall.

10.1. Disposition of Subjects

A disposition listing will present date of informed consent, randomization, study completion or withdrawal, the reason for withdrawal, if applicable, and whether included in each analysis population, for each participant.

A listing of whether or not all inclusion and exclusion criteria were met and if not, which criteria were not met, by participant, will also be presented.

The following will be summarised, by vaccination group and for all participants:

- The number of participants randomised overall and by study site
- The number of participants followed during the influenza season overall and by study site
- Number of participants completed the study
- Number of participants withdrawn and primary reason for withdrawal
- Number of participants in each analysis population

10.2. Protocol Deviations

Participant data will be examined for evidence of protocol deviations in order to assess how well the protocol was followed. These will be assessed prior to the unblinding of the study.

Participants with major protocol deviations may be summarised if these CRF data are available. The sponsor will review all protocol deviations that are recorded and will identify those that are deemed to be major protocol deviations.

All protocol deviations will be detailed in listings.

10.3. Demographic and Baseline Characteristics

All baseline and demographic data recorded at Screening/Vaccination visit and prior to the vaccination will be listed.

Participant demographic and baseline variables (age, sex, childbearing potential, post menopausal status, ethnicity, race, height, body weight, BMI and body temperature) will be summarised by vaccination group.

Medical history at Screening/Vaccination visit will be listed only.

10.4. Vaccine Administration

All vaccine administration data will be listed based on available data reported from CRF.

10.5. Prior and Concomitant Medications

The start dates of non-investigational medications will be used to assign medications into different categories.

- Prior medication: Any medication which started and ended before the time of vaccine administration. If the start date of the medication is not complete or missing, it will be treated as prior medication.
- Concomitant medication: Any medication which ended on or after the time of vaccine administration or still ongoing at the final visit or at the premature study withdrawal.

Medications will be classified as a prior medication or a concomitant medication. There is no overlapping between these two. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it ended before or after the time of vaccine administration, it will be considered as prior medication.

Prior and concomitant medications will be coded by WHO-DDE latest available version. Data will be summarised by Anatomical Therapeutic Chemical (ATC) system (Level 2) and drug preferred name. The summary tables will show the number and percentage of participants taking each medication by ATC Level 2 and preferred name.

For the summaries of prior and concomitant medications, participants who take the same medication (in terms of the ATC Level 2 and preferred name) more than once will only be counted once for that medication.

In the summary tables, prior medication and concomitant medications will be presented by decreasing frequency of total medications overall within each ATC class and then similarly by decreasing frequency of total medications overall within each preferred name. In cases of ATC classes or preferred names with equal frequencies, medications will be sorted alphabetically.

Prior medication and concomitant medications will be listed and summarised, separately, by vaccination group.

11. EFFICACY ANALYSES

The primary efficacy endpoint is the incidence rate of laboratory confirmed influenza using reverse transcription polymerase chain reaction (RT-PCR) on deep nasal/mid-turbinate swab samples. The secondary efficacy endpoints are:

- Incidence and severity of influenza-like illness (ILI)
- Duration of ILI

All efficacy analyses will be conducted on the Efficacy and Per Protocol Analysis Sets, and all efficacy data will be listed. Efficacy data will be analysed separately for overall participants, age <65 years and age ≥65 years, and by study site.

Incidence rate of laboratory confirmed influenza using RT-PCR

Participants will be asked to record whether or not they have a respiratory illness and / or ILI every week during the influenza season, starting on 01 May and ending on or before 15 October in line with official Australian influenza season. If participants experience any influenza symptom(s), participants should attend the clinic on two occasions, the first as soon as possible within 72 hours of the onset of symptoms for deep nasal/mid-turbinate swabs to be taken. Both swabs must be taken within 96 hours of symptom onset. Participants with laboratory confirmed influenza using RT-PCR will be defined as the influenza positive cases, otherwise they will be defined as influenza negative cases. Some participants might have confirmed RT-PCR data from hospital or general practitioner visits within the influenza season. These data, if available, will be included in the analysis.

The incidence rate of laboratory confirmed influenza using RT-PCR will be estimated for each vaccine group. The 95% CI for the incidence rate will be estimated by mid-p exact method. The 90% CI and 85% CI will be estimated as well based on the same method. The difference in incidence rate between vaccine groups will be compared by Fisher's exact method.

Vaccine efficacy (VE) will be estimated as:

VE (%) =100*(1-RR), where RR is the relative risk of confirmed influenza between MVA-NP+M1 and placebo. The RR and its 95% CI (90% CI and 85% CI as well) will be estimated from a log binomial regression model. The log-binomial model might be less numerically stable than the logistic model or might fail to converge. For comparison purpose, the RR and its 95% CI (90% CI and 85% CI as well) will also be estimated from a Poisson regression with robust variance, which provides adequate correction for overestimation of standard error when binomial data are applied to Poisson regression.

The RR can also be approximated based on the hazard ratio between MVA-NP+M1 and placebo. Survival analysis will be used for the analysis of time to confirmed influenza as well. The time to confirmed influenza is defined as the duration (days) from vaccination to first confirmed influenza using RT-PCR during the influenza season. For the calculation of time to the first confirmed influenza, the time of the first confirmed influenza swab will be used for the calculation (end date). Participants without confirmed influenza throughout the entire influenza season will be censored at the last day recorded with the ILI dairy.

The survival function will be summarized for 25th percentile, median, and 75th percentile and their 95% CIs. The plot of Kaplan-Meier estimates for the two vaccine groups will be presented. The hazard (chance) of confirmed influenza will be compared between MVA-NP+M1 and placebo by a Cox regression. The hazard ratio and its 95% CI (90% CI and 85% CI as well) will be estimated.

Incidence and severity of influenza-like illness (ILI)

ILI is defined as feeling feverish or having a fever (feeling feverish or having a fever (temperature ≥37.8 C)) and at least one of the following symptoms: cough, sore throat. ILI positive cases will be derived from daily ILI diary.

Similar analysis methods, as above for the incidence of laboratory confirmed influenza, will be used to estimate ILI incidence rate and 95% CI for each vaccine group. Rate difference between MVA-NP+M1 and placebo will be compared by Fisher's exact method. The relative risk and its 95% CI will be estimated from a log-binomial model and a Poisson regression model with robust variance.

The following symptoms will be recorded on daily ILI diary

- Feeling hot
- Temperature (use direct reading for AUC calculation)
- Cough
- Sore throat
- Blocked nose
- Chest pain
- Muscle aches
- Shortness of breath

with their severities (score) recorded as

- Not Present (0)

- Mild (1)
- Moderate (2)
- Severe (3)

For each symptom, the severity score as above will be used to calculate the area under the curve (AUC), along with the calendar day, for the entire influenza season (01 May to 15 October) by following trapezoidal rule. All the ILI diary records during the influenza season will be used for the analysis. If 'Have you experienced any Influenza Like Symptoms today?' is answered as 'No', then all the above symptoms will be treated as 'Not Present (0)' and body temperature treated as 37°C for AUC calculation purpose. Participants could be followed for varying days in the influenza season, therefore the AUC will be time weighted to 168 days:

Time weighted AUC=((raw AUC [time in days])/(number of days used for analysis)) * 168

The nonparametric comparison method of Wilcoxon rank-sum test (also named as Mann-Whitney U test) will be used to compare the time weighted AUC between MVA-NP+M1 and placebo. The time weighted AUC will also be logarithm transformed, and the logarithm transformed time weighted AUC will be compared between MVA-NP+M1 and placebo by using an Analysis of Variance (ANOVA) model. The estimated least squares means from ANOVA will be anti-log transformed to obtain the geometric mean, and the geometric mean ratio of the time weighted AUC and its 95% CI will also be estimated between MVA-NP+M1 and placebo.

Duration of ILI

ILI duration analysis is only applicable for ILI positive participants. The duration of ILI is defined as the duration (days) from the first day ILI criteria met (as defined above) until the first day afterwards ILI criteria not met (event, ILI recovery). ILI positive participants with ILI criteria met throughout the entire influenza season will be censored at the last day recorded with the ILI dairy.

Survival analysis will be used for the analysis of duration of ILI. The survival function for duration of ILI will be estimated by the Kaplan-Meier method. The survival function will be summarized for 25th percentile, median, and 75th percentile and their 95% CIs. The plot of Kaplan-Meier estimates for the two vaccine groups will be presented. The hazard (chance) of ILI recovery (ILI criteria not met) will be compared between MVA-NP+M1 and placebo by a Cox regression. The hazard ratio and its 95% CI will be estimated.

12. SAFETY ANALYSES

All safety analyses will be conducted on the Safety Analysis Set.

All safety summaries will be provided by vaccination group. Data for AEs, SAEs, clinical laboratory parameters, and physical examinations will be presented by participant listings (including assessments of abnormality and clinical significance, where applicable). Summaries will be prepared for key variables (detailed below) by protocol specified time-point (where applicable).

No inferential statistical testing will be performed for safety variables.

12.1. Adverse Events

Adverse events include unsolicited adverse events and solicited adverse events. Unsolicited adverse events are events meeting the criteria for adverse events apart from those the participant is specifically asked about. Solicited adverse events are events the participant is specifically asked about. These adverse events are commonly observed soon after receipt of vaccines and relate to local and systemic signs and symptoms. The solicited local injection site reactions (ISR) include ***pain, induration, warmth, and erythema (redness)***. The solicited systemic reactions include ***feverishness, chills, myalgia, fatigue, headache, nausea, arthralgia, and malaise***. These solicited AEs are sourced from '7 Day Diary' CRF pages.

Unsolicited non-serious adverse events will be collected for 28 days post-vaccination. Hospitalisations, other serious adverse events and or adverse events of special interest will be collected for the duration of the influenza season. Solicited adverse events, including solicited local injection site reactions (ISR) and solicited systemic reactions, will be collected for 7 days post-vaccination. These will be recorded daily in the eDiary for all participants.

Adverse events will be coded using MedDRA® (latest available version). Adverse events will be grouped by system organ class (SOC) and preferred term (PT), and summarised by actual vaccination group at time of onset of the AE. The summary tables will present the frequency and percentage of total participants and number of events, by system organ class and by preferred term. For the summaries of AEs, participants who experience the same AE (in terms of the MedDRA PT) more than once will only be counted once for that event in the number of participants, but all occurrences of the same event will be counted in the number of events.

All AE summaries will be restricted to TEAEs only. Treatment emergent events are defined as AEs which commence on or after the time of vaccine administration through to the end of the study. AEs without an onset date or time will be defined as treatment emergent except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to start of vaccine administration or if the AE stop date indicates that the event started and/or stopped prior to start of vaccine administration.

For any AEs with a missing or unknown severity, relationship to vaccination or outcome, a worst-case scenario will be implemented. Any AEs with a missing or unknown severity will be considered as severe in the summary tables. Similarly, any AEs with a missing or unknown relationship to vaccination will be considered related to vaccine in the summary tables. Further, any AEs with a missing or unknown outcome will be considered as fatal in the summary tables.

Incidence of AEs as well as the duration, severity, relationship to vaccination, outcome and action taken will be listed for each participant. In addition, listings of solicited local injection site reactions (ISR) and solicited systemic reactions, AEs leading to discontinuation of the study, SAEs and deaths, will be provided if applicable.

The following AE summaries will be provided:

- Overall summary of TEAEs
  - Any solicited local injection site reaction
  - Any severe solicited local injection site reaction
  - Any solicited systemic reaction
  - Any severe solicited systemic reaction
  - Any TEAE
  - Any severe TEAE
  - Any TEAE considered as related to vaccination (evaluated by the investigator as related to vaccination)
  - Any serious TEAE
  - Any TEAE leading to vaccine withdrawal
  - Any TEAE leading to discontinuation from study
  - Any TEAE leading to death
- Solicited local injection site reactions (ISR)
- Solicited local injection site reactions (ISR) by severity
- Solicited systemic reactions
- Solicited systemic reactions by severity
- TEAEs overall by SOC and PT
- TEAEs overall by severity and by SOC and PT
- TEAEs overall by relationship to vaccine and by SOC and PT
- Treatment-related TEAEs overall by severity and by SOC and PT

- Serious TEAEs overall by SOC and PT
- TEAEs overall leading to discontinuation from study by SOC and PT
- TEAEs overall leading to death

In the summary tables, AEs will be presented by decreasing frequency of total events overall within each SOC and then similarly by decreasing frequency of total events overall within each PT. SOCs or PTs with equal frequencies will be sorted alphabetically.

12.2. Deaths and Serious Adverse Events

Incidence of SAE's as well as the duration, severity, relationship to vaccination, outcome and action taken will be listed for each participant and summarised by vaccination group with frequency counts by SOC and PT.

Deaths, if any, will be listed with primary cause of death.

12.3. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study

Incidence of AE's leading to vaccine withdrawal or discontinuation from study, as well as the duration, severity, relationship to vaccination, outcome and action taken will be listed for each participant and summarised by vaccination group with frequency counts by SOC and PT.

12.4. Clinical Laboratory Evaluations

Laboratory safety tests will be performed for participants in the **immunogenicity cohort** only at pre-vaccination Day 0, Day 7 and Day 28.

All individual clinical laboratory results (haematology and biochemistry) will be presented in data listings. Values outside the laboratory reference range will be flagged (low-L, high-H).

Actual values and actual change from baseline for clinical laboratory data will be summarised at each protocol scheduled time point, by vaccination group. Box plots will be generated as well to present the observed and change from baseline values for each laboratory parameter. Frequency tabulations of the number of normal and abnormal (low and high) records, as well as the number of clinically significant (CS) and not clinically significant (NCS) (if data available) will also be summarised at each protocol scheduled time point, by vaccination group. Shift table of laboratory data from baseline to protocol defined post dosing visits will be summarised as well.

Haematology data to be collected are: full blood count, haemoglobin, haematocrit, erythrocytes, mean cell volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets.

Biochemistry data to be collected are: sodium, potassium, urea, creatinine, albumin and liver function tests (alanine transaminase, alkaline phosphatase and bilirubin).

12.5. eDiary Data

eDiary is used to collect solicited adverse events over the first 7 days post-vaccination and influenza symptoms and medications over the duration of the influenza season (between 01 May and 15 October). Unsolicited adverse events (all adverse events up to Day 28; hospitalisations and other SAEs only thereafter) and concomitant medications will also be collected through the eDiary. All participant diary data will be presented in data listings.

Diary reported ISRs will be summarised at each protocol scheduled time point, by vaccination group, using descriptive statistics. ISR by severity will be summarised as well. If a participant reported multiple injection sites at one scheduled time point, then any positive finding from any injection sites will be used for the frequency summary. The maximum redness (mm) and maximum skin thickening (mm) of all injection sites will be used for the summary analysis.

12.6. Other Safety Measures

All pregnancy test data and physical examination data will be listed.

13. IMMUNOGENICITY ANALYSES

Samples for immunogenicity analysis will only be taken from participants in the **immunogenicity cohort** at Day 0, Day 28 and Week 26. Immunological and immunogenicity parameters include:

- IFN-γ and GzmB enzyme linked immunospot (ELIspot) assay
- Immune response determined by Intracellular Cytokine Staining (ICS) assay

All immunogenicity analyses will be conducted on the Immunology Analysis Set. All Immunological and immunogenicity data will be listed.

In ELIspot, adjusted Spot Forming Units (SFU) per million (10^6) PBMCs (peripheral blood mononuclear cells) after background (dimethyl sulfoxide, DMSO) subtraction will be counted. For ICS assay, DMSO-subtracted cytokine response, as well as DMSO cytokine response will be collected. The cytokine response will be counted as the percentage CD4+ and CD8+ T cell response. The actual parameters depend on the final data reported from laboratory.

ELISpot Assay

ELISpot results will be evaluated in various ways to comprehensively understand the nature of cell-mediated immune responses following vaccination with MVA-NP+M1:

- Descriptive summaries (univariate statistics) of response magnitudes
- Assessing responder status
- Evaluating magnitude of immune response with baseline response as a covariate

With PBMC samples being evaluated using a double-color enzymatic (DCE) ELISpot assay, the analyses described below will be performed on both interferon-gamma (IFN-γ) and granzyme-B (GzmB) responses, with IFN-γ responses being the primary focus.

Descriptive Summaries

Univariate statistics (n, mean, SD, median, Q1, Q3, min, max) at each timepoint and changes from baseline, including 95% CI for the median based on order statistics, will be summarized for NP- and M1-specific DMSO-subtracted responses, Total (NP+M1) DMSO-subtracted responses, and DMSO (negative control) responses. Descriptive statistics for each stimulation antigen (NP, M1, NP+M1, and DMSO) will be calculated according to the average number of SFU per million PBMCs across all applicable wells. If the ELIspot data are reported in the unit of 250,000 PBMCc/well, the number for SFU needs to be converted to the unit of per million (10^6) PBMCs by multiplying 4.

Dot plots of participant-level, NP-specific DMSO-subtracted responses, M1-specific DMSO-subtracted responses, Total (NP+M1) DMSO-subtracted responses, and DMSO responses will be displayed graphically by timepoint. Results associated with a positive responder (definition in below section), a non-responder, and an unevaluable responder will be denoted by different symbols. Median responses and their associated 95% CI will also be plotted by study visit.

Responder Status

To determine a participant's responder status at a given timepoint, ELISpot responses will be evaluated using the Permutation-based Resampling (PR) method (Hudgens et al., 2004). This approach can only provide statistically significant results when there is an adequate number of permuted outcomes. Therefore, in instances where results from only one negative control well (instead of two as planned) are available, responder status cannot be determined.

A step-down permutation algorithm (Westfall and Young, 1993) is used by PR method to control the family wise error rate (FWER) when significant SFU difference between antigen and background is tested in order to identify responders. Briefly in a single step permutation, SFU for NP and M1 will be compared with SFU for DMSO (background) by using a t-test, and an actual unadjusted p-value will be calculated for each antigen (NP and M1). Then a permutation sample (re-randomisation sample) across all samples (NP, M1, and DMSO) will be formed. A pseudo p-value will be calculated for each antigen in the same way as above based on the permutation sample. The minimal p-value of the pseudo p-values (p-values for NP vs DMSO and for M1 vs DMSO) will be taken as the minimal pseudo p-value. The permutation will be conducted for 20,000 times. For each antigen, the permutation adjusted p-value is then computed as the proportion of times that the actual unadjusted p-value is greater than or equal to the minimal pseudo p-values. The above procedures are further adjusted by the step-down method to calculate the step-down permutation adjusted p-value to improve testing power while maintaining strong control of type I error. A participant is regarded as a responder for an antigen if the step-down permutation adjusted p-value is <0.05. The multiplicity adjustment by the step-down permutation algorithm is only used to control the type I error when the responder is identified for one endpoint at one timepoint. The multiplicity between endpoint (IFN-γ and GzmB) and between visits (Day 28 and Week 26) is not further adjusted. PR method is not applicable for Total (NP+M1) response because the assumptions of permutation test such as exchangeability and subset pivotality might not meet when samples are added and permuted with the original data (NP, M1 and DMSO).

For each timepoint, the proportion of participants within each treatment group who have a positive responder status will be compared using Fisher's Exact Test. Response rate (responder/non-responder) will be summarised at each protocol scheduled time point, by vaccination group, using frequency tabulations. Response rates will be calculated based on the number of participants with available data. The 95% CI for the response rate will be estimated by

mid-p exact method. A relative risk of response and its 95% CI will also be estimated between MVA-NP+M1 and placebo by a log binomial regression model.

ANCOVA

Many participants are expected to have baseline immune responses resulting from prior exposure to influenza. Therefore, a positive responder status at a post-baseline timepoint will not necessarily indicate the immune response came from vaccination with MVA-NP+M1; these immune responses will also need to be assessed in relation to the associated baseline response.

Day 28 and Week 26 ELISpot results (background subtracted NP, M1 and NP+M1) will each be analyzed independently using an ANCOVA model with treatment, Total (NP+M1) baseline ELISpot response (background subtracted), and treatment by baseline response interaction.

ICS Assay

The data and analysis for ICS assay will be exploratory. Depending on the ICS data available and final analysis decision, ICS assay might be analyzed in the same way as ELIspot assay. The final analysis of ICS assay might not happen at the same time for ELIsopt assay.

14. HEALTH OUTCOMES ANALYSES

Not applicable for this study.

15. CLINICAL PHARMACOLOGY DATA ANALYSES

Not applicable for this study.

16. BIOMARKER DATA ANALYSIS

Not applicable for this study.

17. PHARMACOGENETIC DATA ANALYSES

Not applicable for this study.

18. VIRAL GENOTYPING/PHENOTYPING

Not applicable for this study.

19. REFERENCES

- FLU009 Protocol: A Phase 2b Study to Determine the Efficacy of Candidate Influenza Vaccine MVA-NP+M1 in Adults aged 18 years and over. 20 May 2019; Version 3.0
- Hudgens, M.G., Self, S.G., Chiu, Y.L., Russell, N.D., Horton, H., McElrath, M.J., 2004. Statistical Considerations for the Design and Analysis of the ELISpot Assay in HIV-1 Vaccine Trials. J. Immunol. Methods 288 (1–2), 19 (May).
- Jennison, C., and Turnbull, B.W. 2000. Group Sequential Methods with Applications to Clinical Trials. Chapman & Hall/CRC. New York.

20. ATTACHMENTS

20.1. Table of Contents for Data Display Specifications

20.1.1. Planned Data Listings

The following listings are planned to be generated for the study (Note: Numbering is indicative only and may be updated based on CSR requirements):

Listing Number	Listing Title	Population	IA Outputs
16.2.1 Disposition			
Listing 16.2.1.1	Study Enrolment and Completion/ Discontinuation	All Randomised	
Listing 16.2.1.2	Visit Dates and Study Days	All Randomised	
Listing 16.2.1.3	Randomisation	All Randomised	
16.2.2 Protocol Deviations			
Listing 16.2.2	Protocol Deviations	Efficacy	Y
16.2.3 Subjects Excluded from Analyses			
Listing 16.2.3	Population Assignment and Reason for Exclusion	All Randomised	
16.2.4 Demographic and Other Baseline Data			
Listing 16.2.4.1	Demographics	Efficacy	
Listing 16.2.4.2	Eligibility	Efficacy	
Listing 16.2.4.3	Medical History	Efficacy	
Listing 16.2.4.4.1	Prior Medications	Efficacy	
Listing 16.2.4.4.2	Concomitant Medications	Efficacy	
16.2.5 Vaccine Administration Data			
Listing 16.2.5	Vaccine Administration	Efficacy	
16.2.6 Efficacy and Immunogenicity Data			
Listing 16.2.6.1	Nasal Swab Visit and Test	Efficacy	Y

Listing Number	Listing Title	Population	IA Outputs
	Result		
Listing 16.2.6.2	Daily Influenza-like Illness (ILI) Diary	Efficacy	Y
Listing 16.2.6.3	Intracellular Cytokine Staining (ICS) Assays	Immunology	Y
Listing 16.2.6.4	Enzyme Linked Immunospot (ELIspot) Assays	Immunology	Y
16.2.7 Adverse Event Data			
Listing 16.2.7.1	Adverse Events	Safety	
Listing 16.2.7.2	Solicited Local Injection Site Reactions (ISR)	Safety	
Listing 16.2.7.3	Solicited Systemic Reactions	Safety	
Listing 16.2.7.4	Serious Adverse Events	Safety	Y
Listing 16.2.7.5	Adverse Events Leading to Study Discontinuation	Safety	Y
Listing 16.2.7.6	Deaths	Safety	Y
Listing 16.2.7.7	Post-vaccination 28 Days Diary	Safety	
16.2.8 Laboratory Data			
Listing 16.2.8.1	Haematology	Immunology	
Listing 16.2.8.2	Biochemistry	Immunology	
16.4 Other Safety Data			
Listing 16.4.1	Pregnancy Test	Safety	
Listing 16.4.2	Physical Examination	Safety	
Listing 16.4.3	Comments	Safety	
Listing 16.4.4	Telephone Call	Safety	

20.2. Planned Summary Tables

The following tables are planned to be generated for the study (Note: Numbering is indicative only and may be updated based on CSR requirements). Sample size re-calculation will be provided at IA if needed.

Table Number	Table Title	Population	IA Outputs
14.1 Subject Data Summaries			
Table 14.1.1	Study Participation and Disposition	All Randomised	Y
Table 14.1.2	Demographics	Efficacy	Y
Table 14.1.3.1	Prior Medications	Efficacy	
Table 14.1.3.2	Concomitant Medications	Efficacy	
14.2 Efficacy and Immunogenicity Data Summaries			
Table 14.2.1.1.1	Incidence of Laboratory Confirmed Influenza using RT-PCR: Overall	Efficacy	Y
Table 14.2.1.1.2	Incidence of Laboratory Confirmed Influenza using RT-PCR: Overall	PP	
Table 14.2.1.1.3	Survival Analysis of Time to Confirmed Influenza using RT-PCR: Overall	Efficacy	Y
Table 14.2.1.1.4	Survival Analysis of Time to Confirmed Influenza using RT-PCR: Overall	PP	
Figure 14.2.1.1.5	Kaplan-Meier Plot of Time to Confirmed Influenza using RT-PCR: Overall	Efficacy	Y
Figure 14.2.1.1.6	Kaplan-Meier Plot of Time to Confirmed Influenza using RT-PCR: Overall	PP	
Table 14.2.1.2.1	Incidence of Laboratory Confirmed Influenza using RT-	Efficacy	Y

Table Number	Table Title	Population	IA Outputs
	PCR: Age<65 Years and Age ≥65 Years		
Table 14.2.1.2.2	Incidence of Laboratory Confirmed Influenza using RT-PCR: by Study Site	Efficacy	Y
Table 14.2.1.2.3	Survival Analysis of Time to Confirmed Influenza using RT-PCR: Age<65 Years and Age ≥65 Years	Efficacy	Y
Table 14.2.1.2.4	Survival Analysis of Time to Confirmed Influenza using RT-PCR: by Study Site	Efficacy	Y
Figure 14.2.1.2.5	Kaplan-Meier Plot of Time to Confirmed Influenza using RT-PCR: Age<65 Years and Age ≥65 Years	Efficacy	Y
Figure 14.2.1.2.6	Kaplan-Meier Plot of Time to Confirmed Influenza using RT-PCR: by Study Site	Efficacy	Y
Table 14.2.2.1.1	Incidence of Influenza-like Illness (ILI): Overall	Efficacy	Y
Table 14.2.2.1.2	Incidence of Influenza-like Illness (ILI): Overall	PP	
Table 14.2.2.2.1	Incidence of Influenza-like Illness (ILI): Age<65 Years and Age ≥65 Years	Efficacy	Y
Table 14.2.2.2.2	Incidence of Influenza-like Illness (ILI): by Study Site	Efficacy	Y
Table 14.2.3.1.1	Time Weight Area Under the Curve (AUC) for Symptoms of Influenza-like Illness (ILI): Overall	Efficacy	Y
Table 14.2.3.1.2	Time Weight Area Under the Curve (AUC) for Symptoms of Influenza-like Illness (ILI):	PP	

Table Number	Table Title	Population	IA Outputs
	Overall		
Table 14.2.3.2.1	Time Weight Area Under the Curve (AUC) for Symptoms of Influenza-like Illness (ILI): Age<65 Years and Age ≥65 Years	Efficacy	Y
Table 14.2.3.2.2	Time Weight Area Under the Curve (AUC) for Symptoms of Influenza-like Illness (ILI): by Study Site	Efficacy	Y
Table 14.2.4.1.1	Survival Analysis of Duration of Influenza-like Illness (ILI): Overall	Efficacy	Y
Table 14.2.4.1.2	Survival Analysis of Duration of Influenza-like Illness (ILI): Overall	PP	
Table 14.2.4.2.1	Survival Analysis of Duration of Influenza-like Illness (ILI)): Age<65 Years and Age ≥65 Years	Efficacy	Y
Table 14.2.4.2.2	Survival Analysis of Duration of Influenza-like Illness (ILI)): by Study Site	Efficacy	Y
Figure 14.2.5.1.1	Kaplan-Meier Plot of Duration of Influenza-like Illness (ILI): Overall	Efficacy	Y
Figure 14.2.5.1.2	Kaplan-Meier Plot of Duration of Influenza-like Illness (ILI): Overall	PP	
Figure 14.2.5.2.1	Kaplan-Meier Plot of Duration of Influenza-like Illness (ILI): Age<65 Years and Age ≥65 Years	Efficacy	Y
Figure 14.2.5.2.2	Kaplan-Meier Plot of Duration of Influenza-like Illness (ILI): by	Efficacy	Y

Table Number	Table Title	Population	IA Outputs
	Study Site		
Table 14.2.6.1	Intracellular Cytokine Staining (ICS) Assay: Response Level and Change from Baseline	Immunology	
Table 14.2.6.2	Intracellular Cytokine Staining (ICS) Assay: Responder Analysis	Immunology	
Table 14.2.6.3	Intracellular Cytokine Staining (ICS) Assay: ANCOVA Analysis	Immunology	
Figure 14.2.6.4	Dot Plot of Intracellular Cytokine Staining (ICS) Assay: Individual	Immunology	
Figure 14.2.6.5	Median of Intracellular Cytokine Staining (ICS) Assay by Study Visit	Immunology	
Table 14.2.7.1	Enzyme Linked Immunospot (ELIspot) Assay: Response Level and Change from Baseline	Immunology	
Table 14.2.7.2	Enzyme Linked Immunospot (ELIspot) Assay: Responder Analysis	Immunology	
Table 14.2.7.3	Enzyme Linked Immunospot (ELIspot) Assay: ANCOVA Analysis	Immunology	
Figure 14.2.7.4	Dot Plot of Enzyme Linked Immunospot (ELIspot) Assay: Individual	Immunology	
Figure 14.2.7.5	Median of Enzyme Linked Immunospot (ELIspot) Assay by Study Visit	Immunology	
14.3.1 Safety Data Summaries			
Table 14.3.1.1	Overall Summary of Treatment Emergent Adverse Events	Safety	Y
Table 14.3.1.2.1	Solicited Local Injection Site	Safety	Y

Table Number	Table Title	Population	IA Outputs
	Reactions (IRS)		
Table 14.3.1.2.2	Solicited Local Injection Site Reactions (IRS) by Severity	Safety	Y
Table 14.3.1.3.1	Solicited Systemic Reactions	Safety	Y
Table 14.3.1.3.2	Solicited Systemic Reactions by Severity	Safety	Y
Table 14.3.1.4	Treatment Emergent Adverse Events	Safety	Y
Table 14.3.1.5	Treatment Emergent Adverse Events by Severity	Safety	Y
Table 14.3.1.6	Treatment Emergent Adverse Events by Relationship to Vaccine	Safety	Y
Table 14.3.1.7	Treatment Related Treatment Emergent Adverse Events by Severity	Safety	Y
Table 14.3.1.8	Serious Treatment Emergent Adverse Events	Safety	Y
Table 14.3.1.9	Treatment Emergent Adverse Events Leading to Discontinuation from Study	Safety	Y
Table 14.3.1.10	Treatment Emergent Adverse Events Leading to Death	Safety	Y
14.3.4 Clinical Laboratory Data			
Table 14.3.4.1.1	Haematology	Immunology	
Table 14.3.4.1.2	Haematology Abnormalities	Immunology	
Table 14.3.4.1.3	Shift Table of Haematology	Immunology	Y
Figure 14.3.4.1.4	Boxplot of Haematology (Observed and Change from Baseline)	Immunology	Y

Table Number	Table Title	Population	IA Outputs
Table 14.3.4.2.1	Biochemistry	Immunology	
Table 14.3.4.2.2	Biochemistry Abnormalities	Immunology	
Table 14.3.4.2.3	Shift Table of Biochemistry	Immunology	Y
Figure 14.3.4.2.4	Boxplot of Biochemistry (Observed and Change from Baseline)	Immunology	Y
14.3.5 Other Safety Summaries			
Table 14.3.5.1	Diary Data – Injection Site Reactions (ISR)	Safety	
14.3.6 Other Summaries			
Table 14.3.6.1	Conditional Power at Interim Analysis	NA	Y
Table 14.3.6.2	Sample Size Re-estimation at Interim Analysis	NA	Y