Efficacy of MVA-NP+M1 in the Influenza H3N2 Human Challenge Model

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Efficacy of MVA-NP+M1 in the influenza H3N2 Human Challenge model

Product	MVA-NP+M1
Protocol Number	FLU010
EudraCT Number	2018-004015-49
OR IND Number	018827
Clinical Phase	2
Clinical Indication	Protection against influenza disease
Issue Date (Version)	10-July-2019 (Version 5.0)

Sponsor	Vaccitech Ltd.
Sponsor Representative	Tom Evans, MD [redacted]
EU Legal Representative*	Venn Life Sciences
Contact	[redacted]

* Vaccitech is the EU Legal Representative until Brexit date

SIGNATURES

Signature of Sponsor Representative

Title: **CEO**

Name: Tom Evans, MD
Company: Vaccitech Ltd

'This Clinical Study Protocol has been reviewed and approved by the Sponsor in order to ensure compliance with Good Clinical Practice.'

Signature: Tom Evans MD

Date: 11 JUL 2019

Signature of Sponsor Statistician

Title: **Statistician**

Name: Kathryn Rutkowski
Company: Vaccitech Ltd.

'This Clinical Study Protocol has been reviewed and approved by the study statistician in order to ensure that the protocol and any amendments cover all relevant statistical matters clearly and accurately, using technical terminology as appropriate.'

Signature: [redacted]

Date: 10 JUL 2019

Signature of Investigator

Title: **Principal Investigator**

Name: Robin Rogiers, MD

Company: SGS Life Sciences, Clinical Pharmacology Unit (CPU)

Address: Lange Beeldekensstraat 267, 2060 Antwerpen, Belgium

'I have read this Clinical Study Protocol and agree that it contains all information necessary for proper conduct of the study. I will carry out the study as outlined herein and will complete the study within the designated time.'

Signature:

Date: 11 JUL 2019

PROTOCOL HISTORY

Protocol History
VACCITECH - CLINICAL STUDY PROTOCOL – FLU010

Document	Issue Date	Amendment Type	Comments
Initial Clinical Study Protocol – v1.0	19-Dec-2018	NA	
Clinical Study Protocol - v2.0	27-Feb-2019	Contraception requirements as per EC's request i.e. 6 months prior vaccination and 6 months post-challenge Contraception methods have been changed to highly effective methods as per FAMHP's request	Following sections have been impacted by this amendment: • Eligibility Criteria / Inclusion Criteria, Bullet point 4b, page 10, • Section 4.1 Inclusion Criteria, Bullet point 4b, page 28
		Vaccination start date has been changed from March 1, 2019 to April 2, 2019	Following sections have been impacted by this amendment: • Protocol synopsis: Study/treatment duration, page 12, • Section 3.1, page 27.
		Blood volumes removed from protocol; they are detailed in the laboratory manuals	Following sections have been impacted by this amendment: • Time and Events Schedule, Period 1, page 14, • Section 7.1.5, page 36, • Section 7.2.3, page 39.
		Clarification regarding samples collection pre-vaccination (PBMC, Serum & whole blood in Trizol)	Time and Events Schedule, Period 1, page 14.
		Randomization list to Bioanalytical Laboratory was removed	Section 5.5, page 32.
		Serum/ urine pregnancy test was clarified. Serum pregnancy test is to be performed at screening visit only for female subjects' eligibility in the study. Urine test is to be performed in all subsequent visits	Following sections have been impacted by this amendment: • Section 7.1.2.1, page 35, • Section 7.2.3, page 39.

Protocol History
VACCITECH - CLINICAL STUDY PROTOCOL – FLU010

Document	Issue Date	Amendment Type	Comments
		Reference to Plasma samples was removed everywhere in the protocol	Following sections have been impacted by this amendment: • Section 7.1.5, page 36, • Section 7.1.6, page 37.
Clinical Study Protocol – v3.0	02-Apr-2019	Exclusion criteria reorganised: - #10 & 18 moved to Exclusion (Challenge Period Only) where they are respectively numbered # 4 & 6. - #19 deleted as already present in the challenge exclusion list. - #3 & 5 in the challenge exclusion list have been added to ensure participants safety Exclusion criterion #3 clarified	• Synopsis – Sections Exclusion Criteria & Exclusion (Challenge Period Only) respectively pages 13 & 14 Sections 4.2 & 4.3 respectively pages 32 & 33
		Endpoints section: **Secondary endpoints:** clarified (deletion of "regardless of take rate" in endpoint 2 & 4 and "consecutive" in endpoint 6) **Exploratory endpoints:** - qPCR and culture results were added - Transcriptomic analysis, initially part of the protocol, but omitted in the endpoints, has been added - Epigenetic response of T-Cells has been added	Synopsis – pages 14 & 15 Sections 2.2 & 2.3 page 29 Section 7.1.6 – page 40 Section 9.1.2.3. page 48
		- Statistical Methods: removal of participants with virologically confirmed influenza in the symptom severity total AUC - IDMC analysis and timing were removed in section 9.1 - Section 9.1.2 reorganised for better understanding. Subsections 9.1.2.1, 9.1.2.2 & 9.1.2.3 have been created. The information	Synopsis - Section Efficacy – page 15 Section 9.1.2.2 page 47 Section 9.1 page 46 Section 9.1.2 and its subsections – pages 47 & 48

Protocol History
VACCITECH - CLINICAL STUDY PROTOCOL – FLU010

Document	Issue Date	Amendment Type	Comments
		initially under section 9.1.2 has been placed accordingly in appropriate new subsections.	
		Time and Events Schedules (Periods 1 & 2) have been clarified: - footnotes have been added or amended - Month 6 post-vaccination follow-up call was moved from the challenge period to Period 1 - Hep B was removed as redundant; HBsAg is being measured - Trizol samples have been renamed with the appropriate test name i.e. transcriptomics - PBMC, serum and transcriptomics have been split into 2 rows for better clarity - Transcriptomics timepoints in Period 2 have been added on Days 2, 5 and 8. - The blood tests in Period 2 have been combined to allow the site to withdraw blood on Day -2 or Day -1 - NP swabs sample line in Period 2 has been deleted as repeated - Clarification that MNT can be tested at screening visit 1 or screening visit 2	Section Periods 1 & 2 – pages 16 to 19
		New members of the team have been added: - Vaccitech new Head of Clinical Operations, Elizabeth Eagling-Vose (replacing Chris Ellis) - Approved EU Legal Representative, Venn Life Sciences	Section: Study Administrative Structure and Investigators – pages 1 & 22
		Randomization and Blinding section has been amended to describe the process put in place to maintain the study double blind	Section 3.2 – page 30
		- The number of MVA-NP+M1 vials number per box has been changed in the Packaging and labelling section. “50 or 10 vials” has been replaced by “25 vials”.	Section 5.3 – page 34 Section 5.4 – pages 34 & 35

Protocol History
VACCITECH - CLINICAL STUDY PROTOCOL – FLU010

Document	Issue Date	Amendment Type	Comments
		- The study drug accountability process has been clarified	
		HRT added to the Permitted Concomitant Therapies section	Section 6.1 – page 36 & 37
		Solicited symptoms have been updated in the Assessments section Clarification of MNT performed at screening visit 1 or screening visit 2 A subsection relating to Transcriptomics was added under section 7 Transcriptomics initially referred to as Trizol was already part of the protocol	Section 7 – page 37 Section 7.1.1 - pages 37 & 38 Section 7.1.7 – page 40
		Sodium and potassium tests were added to the biochemistry assessment in Period 2	Section 7.2.3 – pages 42 & 43
		The Stopping Rules or Discontinuation Criteria section has been renamed "Stopping Rules or Non-Vaccination Criteria". This section has been slightly reworded to provide clarity. Temperature has been changed to be consistent with the toxicity grading scale in Appendix 2. The stopping rules have been amended by removing the time limit in the solicited and unsolicited AEs	Section 8.3 – pages 45 & 46
		A causality assessment has been added "Not Related"	Section 10.3 – page 51
		A number of changes implemented for clarification, consistency and typo corrections with no substantial amendment to previous protocol version	Throughout the protocol
		The period between vaccination and challenge has been changed from "**2 months post vaccination and no later than 6 months"** to "**6 weeks post vaccination and not later than 6 months"**	Throughout the protocol - added to improve recruitment rates with no major change in overall window

Protocol History
VACCITECH - CLINICAL STUDY PROTOCOL – FLU010

Document	Issue Date	Amendment Type	Comments
Clinical Study Protocol – v4.0	14-May-2019	The challenge virus atomiser Teleflex VaxINator™ kit has been replaced by Teleflex MAD301 and MAD130.	Section 3.1 – page 30 Sections 5.2.2 & 5.4 – page 34
Clinical Study Protocol – v5.0	10-Jul-2019	MNT increase from ≤10 to <20	Synopsis – Inclusion Criteria – page 15 Section 1.1 – page 28 Section 3.1 – page 32 Section 3.2 – page 33 Section 4.1 – page 34
		Attack rate change from 90% to 83%	Synopsis – Statistical Methods – page 17 Section 9.1.2.3 – page 49
		A clarification added the challenge risk section	Section 7.2.1 – page 44

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PROTOCOL AMENDMENT: SUMMARY OF CHANGES

Overall Reason for Amending the Protocol:

Version 2.0 dated 27-Feb-2019:

Further to Belgian Ethics Committee request dated 13-Feb-2019 the contraception period has been extended to 6 months pre-vaccination and 6 months post-challenge.

FAMHP's request dated 26-Feb-2019 was implemented; i.e. highly effective contraception methods.

Additional changes were made to provide clarity in the protocol and correct some discrepancies that will impact vaccination period.

Version 3.0 dated 02-Apr-2019:

This substantial amendment includes:

- Additional timepoints in the challenge period to measure transcriptonics. The Time and Events Schedule has been reshuffled to allow clarity regarding the assessments to be performed. Sodium and potassium tests have been added to the biochemistry test in the challenge period.
- The exclusion criteria have been split in two categories i.e. study entry and challenge period entry.
- The process that maintains the double blind throughout the study has been amended to provide a robust procedure.

Further clarifications have been made throughout the protocol. These are considered minor.

Version 4.0 dated 14-May-2019:

This amendment is to specify that the Teleflex MAD301 and MAD130 are being used in the study, rather than the Teleflex VaxINator^{TM}.

Version 5.0 dated 10-Jul-2019:

This amendment is to increase MNT value at study entry. The rate of seronegativity in the screened population as defined by an MNT $\leq$ 10 units has declined since previous studies, but in general a twofold dilution is within the assay variability and should have a minor effect of take rates. As a value below 20 represents the geometric mean of one duplicate

sample reading 10 and one reading 20, this value should not impact the take rate after challenge but will increase the pool of potentially eligible participants.

PROTOCOL SYNOPSIS

Study Title	Efficacy of MVA-NP+M1 in the influenza H3N2 Human Challenge model		
Product	MVA-NP+M1	**Clinical Phase**	2
Protocol Number	FLU010	**Indication**	Prevention of influenza-related disease
EudraCT Number	2018-004015-49		
IND Number	018827		

Sponsor	Vaccitech Ltd
Sponsor Representative	Tom Evans, MD
Clinical Centre	SGS Antwerp Clinical Challenge Unit

Objectives:

The primary objective of this study is to show that MVA-NP+M1 decreases the viral shedding of influenza virus, as measured by the cumulative area under the curve, following human challenge.

Secondary objectives are to show safety, the effect on the incidence of laboratory-confirmed influenza-like illness (ILI), total and individual symptom scores, and mucous production (measured by tissue weight). Immune T cell responses and correlation of these responses with efficacy will also be investigated.

Overview of Study Design:

This is a single centre, randomized, double blind study. The study consists of an outpatient vaccination phase, and at least 6 weeks later an inpatient challenge phase. 155 participants will be randomized 93:62 to receive either MVA-NP+M1 or Placebo. Up to 20 participants will be challenged over several 3-week blocks, and the remainder at the final 3-week block for a total of 80 MVA-NP+M1 and 54 Placebo recipients challenged.

Study Population:

Healthy adult volunteers ages 18-55, male and female.

155 participants will be enrolled and vaccinated, and 134 will be challenged at least 6 weeks later.

Eligibility Criteria:

Inclusion Criteria:

1. Healthy males and females aged ≥18 and ≤55 years of age at the point of enrolment.
2. Non-smokers or those who stopped smoking ≥ 3 months prior to screening 1 visit.
3. Willingness to remain in isolation for the duration of the study.
4. A female participant is eligible for this study if she is not pregnant or breast feeding and 1 of the following:
    a. Of non-childbearing potential (i.e., women who have had a hysterectomy or tubal ligation or are postmenopausal, as defined by no menses in greater than or equal to 1 year).
    b. Of childbearing potential but has been, and agrees to continue practicing, highly effective contraception or abstinence (if this is the preferred and usual lifestyle of the participant) from 6 months prior to vaccination to 6 months after administration of the influenza challenge virus. Highly effective methods of contraception include 1 or more of the following:
        i. male partner who is sterile (vasectomised) prior to the female participants entry into the study and is the sole sexual partner for the female participant;
        ii. hormonal (oral, intravaginal, transdermal, implantable or injectable);
        iii. an intrauterine hormone-releasing system (IUS);
        iv. an intrauterine device (IUD) with a documented failure rate of < 1%;

v. bilateral tubal occlusion.

5. Pre-challenge serum microneutralization (MNT) against A/Belgium/4217/2015 (H3N2) challenge strain <20.

Exclusion Criteria:

1. Body Mass Index (BMI) < 19 and > 32.
2. Presence of any significant acute or chronic, uncontrolled medical (or psychiatric) illness including a history of chronic respiratory illness.
3. History of seasonal hay fever or clinically significant seasonal allergic rhinitis (SAR), including the use of symptomatic prescription only medication and non-prescription medication.
4. History or evidence of autoimmune disease or known immunodeficiency of any cause - with the exception of atopic dermatitis/eczema and atopic rhinitis.
5. Any history of anaphylaxis in reaction to vaccination or history of allergic reactions likely to be exacerbated by any component of the vaccine.
6. History of lung disease (Asthma, COPD).
7. Current smokers or those who stopped smoking < 3months prior to screening 1 visit.
8. Positive diagnostic tests for HIV, Hepatitis B or Hepatitis C indicating active infection.
9. Evidence of drug abuse or a positive urine drug screen or alcohol breath test.
10. Chronic use of any medication or other product (prescription or over-the-counter), for symptoms of rhinitis or nasal congestion or for any chronic nasopharyngeal complaint, or chronic use of any intranasal medication for any indication that has not cessed within 30 days prior to screening 1.
11. Receipt of any investigational drug within 3 months prior to vaccination, or prior participation in a clinical trial of any influenza vaccine, or any investigational vaccine or experimental influenza viral challenge delivered directly to the respiratory tract within 1 year prior to challenge.
12. Receipt of the 2018/2019 seasonal flu vaccine.
13. Receipt of any live vaccines within the 4 weeks prior to vaccination.
14. Any laboratory test which is abnormal and which is deemed by the Investigator(s) to be clinically significant.
15. Receipt of any systemic chemotherapy agent at any time.
16. Physician reported influenza or a syndrome consistent with influenza (as judged by the investigator) in the previous 6 months.
17. Known allergy to treatments for influenza (including but not limited to oseltamivir).
18. History of frequent epistaxis (nose bleeds).
19. Any nasal or sinus surgery within 6 months of Viral Challenge or any significant abnormality, either of which results in alteration of the anatomy of the nose or nasopharynx (including significant nasal polyps).
20. Volunteers with household contacts who are at risk for serious or severe complications of influenza disease including, but not limited to: persons ≥ 65 years; presence of significant chronic cardiopulmonary, metabolic, renal, or neurological conditions; immunosuppression due to any condition or therapies; BMI >40.
21. Participants that are an employee or family member of the Investigator or study site personnel may not be enrolled.
22. Any other finding that, in the opinion of the Investigator, deems the participant unsuitable for the study.

Exclusion (Challenge Period only)

1. Abnormal spirometry assessed to be clinically significant.
2. Known close contact with anyone known to have influenza in the past 7 days at the time of quarantine.
3. ILI symptoms as assessed at the admission to clinic on Day -2 prior to challenge.

4. Presence of fever, defined as participant presenting with a temperature reading of > 38.0°C on admission to quarantine.
5. Qualitative PCR results positive for viral infection. However, participants may be re-tested and included into later challenge cohort, if they later test negative for viral infection.
6. Acute use of any medication or other product, prescription or over-the-counter, for symptoms of rhinitis or nasal congestion within 7 days prior to challenge. This includes any oral corticosteroid or beta agonist containing nasal spray.

Test Product, Dose, Mode of Administration:

Vaccination (one dose):

Single dose of MVA-NP+M1 at 1.5 x 10^8 pfu, 0.5mL given intramuscularly in the deltoid

Challenge Virus:

A/Belgium/4217/2015 [H3N2] will be used as the challenge virus at 1.0 x 10^6 $TCID_{50}$/mL given by intranasal spray, 0.25 mL per nostril

Reference Product, Dose, Mode of Administration:

Vaccination (one dose):

Saline Placebo (0.5 mL given intramuscularly) in the deltoid

Study/Treatment Duration:

The study consists of a screening phase, followed by vaccination of 155 participants starting in April 2019. In the challenge phase, cohorts up to 20 participants will begin inoculations and will remain in quarantine for 13 days. A new cohort of up to 20 participants is then challenged every 3 weeks thereafter until all 134 participants are enrolled. The total study length is approximately 8 months, excluding an initial screening phase.

Criteria for Evaluation:

Elicited local and systemic symptoms following vaccination will be collected for 7 days by diary card. Unsolicited adverse events (AEs) are collected throughout the study from consent form signature. Immune response will be measured using both T cell-related (ELISpot, ICS) and antibody (Hemagglutination Inhibition (HI) and MNT) assays. Samples will also be stored for potential future correlate of protection analysis.

Nasal swabs for influenza virus are collected twice a day (at least 8 hours apart) from Day 2 to Day 10 following intranasal challenge, which are tested for influenza PCR and culture. Symptoms of influenza-related infection will be collected from Day 1 to Day 11 of challenge, as will total nasal tissue weight.

Efficacy: Total viral area under the curve (vAUC) for virologic shedding as measured by quantitative PCR (qPCR) for MVA-NP+M1 vs. Placebo groups.

Secondary endpoints include:

- Incidence in each group (MVA-NP+M1 and saline Placebo) of laboratory-confirmed ILI (qPCR or culture)
- Total AUC for total symptom score for MVA vs. Placebo
- Total days of fever for MVA-NP+M1 vs. Placebo
- Total mucus weight for MVA vs. Placebo
- Correlation of T cell responses (as defined by ELISpot assay) to the primary endpoint, symptom scores, and influenza incidence
- The attack rate, defined as percentage of inoculated participants with at least two positive swabs as determined by qPCR

Exploratory endpoints

- Time to start; time to peak and duration of qPCR and quantitative culture results
- Time to start, time to peak, and duration for total symptoms for MVA vs. Placebo
- Severity of individual symptoms for MVA-NP+M1 vs. Placebo

- Correlation of antigen specific T cell phenotypes to the primary endpoint, symptom scores, and influenza incidence
- Effect of vaccination on the antibody responses to influenza following the intranasal challenge
- Transcriptional response to vaccination and viral challenge assessed by deep sequencing of RNA
- Potential assessment of epigenetic responses of T-Cells during the study.

Safety

- Frequency and severity of participant-recorded local and systemic adverse events recorded for the 7 days following vaccination
- Frequency and severity of non-solicited adverse events captured throughout the study after vaccination
- Frequency and types of serious adverse events
- Severity of adverse events in each study group following intranasal challenge with H3N2

Statistical Methods:

Sample size: determined by the challenge cohort of N=134

Immune response:

Primary immune endpoint will be the T cell response measured by ELISpot and recorded as the mean spot forming units per million peripheral blood mononuclear cells (PBMCs) in the peptide-stimulated wells minus the mean dimethyl sulfoxide (DMSO) control wells for the given sample.

Efficacy:

The primary endpoint upon which the powering analysis is performed using the vAUC from the qPCR for all collected samples, compared between groups using a Mann-Whitney U Test (Wilcoxon rank sum). The assumptions are based on the Placebo data from two prior challenge studies with this H3N2 virus. The study is powered to detect as low as a 20% efficacy of the vaccine using this endpoint at a power of 80%, and approximately 25% efficacy at a 90% power. This allows for up to 20% drop out without prejudicing the goal of the study.

Secondary endpoints include the rate of virologically confirmed ILI (symptoms of either an upper or lower respiratory illness along with two positive PCR or culture) measured between groups. Another key secondary endpoint of relevance to the biologic effect of this vaccine will be the comparison of the symptom severity as a total Area Under the Curve (AUC). This endpoint takes into account both the severity and the duration of symptoms. Mucosal secretions will be collected, and the weight of the sample tissues compared between groups.

Importantly, with a 83% attack rate and 30% efficacy, approximately 20 of the 80 vaccinated participants will have a zero AUC, and these participants can be compared to those with the highest vAUC in correlate of protection analyses.

Safety will be reported using standard frequency and severity tables.

At the protocol sample size, there is a 93% chance that a Serious Adverse Event (SAE) with a 3% incidence will be observed in at least one participant.

TIME AND EVENTS SCHEDULE

Period 1- Screening and Vaccination Schedule

Period 1	Screening 1	Screening 2	Baseline Vaccination	Out patient Clinic Visit	Phone[8]	Out patient Clinic Visit	Out patient Clinic Visit	Phone[8]	Unscheduled visit[7]	See Challenge Day -2	Phone
	Days -42 to -2	Day -21 to -1	Day 1	Day 2	Day 4	Day 8 ±1 (Week 1 Visit)	Day 28 ±3	Day 56 ±3			Month 6 (180 ±14 days)[9]
Informed Consent	x[1]	x[1]									
Inclusion/Exclusion	x[2]	x[2]									
Randomization			x								
Medical History/Demography		x									
Physical Examination		x[2a]				x	x		x		
Vital Signs		x				x	x		x		
Supine 12-lead ECG		x									
Haematology		x							x		
Biochemistry[2b]		x							x		
Microneutralization (MNT)[1]	x	x[1]									
Urinalysis		x							x		
HIV,, Hep C, HBsAg		x									
Urine Drug Screen		x	x						x		
Alcohol breath test		x	x						x		
Serum/Urine Pregnancy[3]		x	x						x		
Blood sample for cellular immunogenicity assays PBMCs[4], and Serum			x[4a]			x	x				
Transcriptomics - whole blood collection (PAXgene® RNA)			x[4a]	x[4b]		x	x				
Vaccination			x								
Dispense/Remind/Collect Diary Cards			x[6a]		x[5]	x[6b]					
AEs/Con-meds	x	x	x	x	x	x	x	x	x		x[9]

[1] If MNT was completed for another study within 6 weeks prior to vaccination then this test does not need to be completed for this study. Informed Consent Form (ICF) signature will be performed at Screening visit prior any study procedures take place. Also, to ensure a sufficient number of participants are vaccinated in a given group, MNT may be performed at Screening 2 at the same time as Screening 2 assessments

[2] Some inclusion/exclusion criteria [refer to section 7.1.1.] will be checked at Screening 1 visit to ensure participants are potentially eligible prior to MNT test

[2a] Physical examination at screening will include height and weight measurements

[2b] Biochemistry test includes creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamylaminotransferase (GGT), C-reactive protein (CRP), and bilirubin

[3] Serum sample will be used for pregnancy test at screening and urine pregnancy test will be used in subsequent visits

[4] PBMCs to be sent to Viroclinics for processing

[4a] PBMC, Serum and Transcriptomics samples at Day 1 are to be collected pre-vaccination

[4b] Transcriptomics sample on Day 2 is to be collected 24 hours (± 3 hours) post-vaccination

[5] Phone call to participants to remind them to complete Diary Card

[6a] Distribute Diary Cards to participants

[6b] Collect completed Diary Cards from participants (up to Day 8)

[7] Assessments during Unscheduled Visits are performed at the discretion of the Investigator

[8] During phone visits, AEs and ILIs will be collected and participants will be reminded about their potential next visits including the challenge period start

[9] Month 6 visit post-vaccination day (180 days ±14) will be performed for all vaccinated participants if it is later than Day 28 post-Challenge

Period 2 – Challenge Schedule

Period 2	In-Clinic Confinement													Unscheduled Visit[3]	Out-patient
	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11		Day 28[5] ±3
Screening/Administrative/Other Assessments															
Eligibility Criteria	x														
Medical and Medication History Review	x														
Ambulatory Visit															x
Admission to study unit / discharge	*Admission*[1]	*Confinement*											*Discharge*		
Full Days Residence		x	x	x	x	x	x	x	x	x	x	x			
Safety Assessments															
Physical Exam	x												x	x	x
Symptom-Directed Physical Examination		x	x	x	x	x	x	x	x	x	x	x		x	
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Spirometry		x										x		x	
Peak Flow		x	x	x	x	x	x	x	x	x	x	x		x	
Supine 12-lead ECG[6]		x				x							x	x	x
Pulse oximetry		x	x	x	x	x	x	x	x	x	x	x			
Drug / Alcohol Screen	x													x	
Urine Pregnancy Test	x													x	x
Biochemistry[4a]	x[1]			x						x				x	
Haematology	x[1]			x						x				x	
Symptom Score (Questionnaire) – b.i.d.			x	x	x	x	x	x	x	x	x	x	x[4]		
Concomitant therapy - AEs/ SAEs	x	x	x----------x											x	x
Study Agent Administration / Pharmacokinetic and Immunogenicity Assessments															
Viral Inoculation			x												
NP swabs samples for qualitative PCR testing - multiple viruses - (CPU Antwerp) [2]	x											x			
NP swabs sample for viral load by qPCR (culture done if positive) – b i.d. (after challenge)				x	x	x	x	x	x	x	x	x			
Tissue Collection for Mucus weights[7]			x	x	x	x	x	x	x	x	x	x	x		
Blood sample for humoral immunogenicity (MNT) and Hemagglutination Inhibition (HI) assays[8]	x[1]														x
Blood sample for cellular immunogenicity assays PBMCs[9]	x[1]														x

Period 2	In-Clinic Confinement													Unscheduled Visit[3]	Out-patient
	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11		Day 28[5] ±3
Transcriptomics - whole blood collection (PAXgene® RNA)	x[10]	x[10]		x			x			x					x

[1] Admission to clinic is possible on Day -1, in which case Day -2 assessments may be performed on Day -1. Pre-challenge assessments may be performed on Day -2 or Day -1.
[2] Multiplex PCR tests are to be performed to determine whether participants are incubating other viruses at the time of inoculation. Participants with positive results should not enter the challenge group and could be offered to be part of one of the subsequent groups if their infection is cleared.
[3] Assessments during Unscheduled Visits will be performed at the discretion of the Investigator
[4] Symptom Score Questionnaire to be administered b.i.d. from Day 1 to Day 10 but only once prior discharge on Day 11
[4a] During the challenge period the biochemistry test will include creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamylaminotransferase (GGT), C-reactive protein (CRP), bilirubin, sodium and potassium
[5] Month 6 visit post-vaccination day (180 days ±14) will be performed for all vaccinated participants if it is greater than Day 28 post-Challenge
[6] ECG performed on Day -1 pre-vaccination will be considered as study Baseline. Any change from Baseline considered significant by the Investigator is to be recorded as AE
[7] Tissue collection to start 12 hours post-Challenge
[8] Additional sera collected for future correlate work
[9] PBMCs to be sent to Viroclinics for processing
[10] Transcriptomics baseline samples are required on Day -2 and Day -1. For participants who replace challenge drop-outs, only Day -1 sample will be collected which is acceptable.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse Events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
b.i.d.	Bis in die; twice daily
BMI	Body mass index
CEF	Chicken Embryo Fibroblasts
CI	Confidence interval
CPU	Clinical Pharmacology Unit
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DMSO	Dimethyl sulfoxide
ECG	Electrocardiogram
ELISpot	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMT	Geometric mean titre
HBsAg	Hepatitis B surface antigen
HI	Hemagglutination Inhibition assay
HCV	Hepatitis C virus
HCT	Hematopoietic Cell Transplant
HIV	Human immunodeficiency virus
HLA-I	Human leukocyte antigen I
HLA-II	Human leukocyte antigen II
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
ILI	Influenza-like illness
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
LPLV	Last Participant Last Visit
MCH	mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration

MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-To-Treat
MNT	Microneutralization Test
NA	Not applicable
NP	Nasopharyngeal
PBMCs	Peripheral Blood Mononuclear Cells
PBS	Phosphate-buffered saline
PCR	Polymerase Chain Reaction
QC	Quality control
qPCR	Quantitative PCR (can be a reverse transcriptase PCR)
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard deviation
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$TCID_{50}$	50% Tissue culture Infective Dose
TMF	Trial Master File
vAUC	Viral area under the curve (as determined by qPCR)
WBC	White blood cell
WHO	World Health Organization

STUDY ADMINISTRATIVE STRUCTURE AND INVESTIGATORS

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1. INTRODUCTION

1.1 BACKGROUND INFORMATION

Influenza is an orthomyxovirus and encodes a segmented Ribonucleic acid (RNA) genome. Influenza is divided into 3 groups- A, B and C. Most seasonal influenza and all known pandemics are caused by Influenza A, whilst B causes seasonal influenza and influenza C infection is seen in sporadic outbreaks [1]. Influenza A is subdivided further on the basis of haemagglutinin (H or HA) and neuraminidase (N or NA) activity e.g., H1N1 subtype. There are at least 16 different types of HA and 9 of NA. These proteins are found as spiked surface projections on the Influenza A virus [2]. Other genes encode proteins vital for structure, reproduction and virulence including nucleoprotein (NP), Matrix 1 (M1), M2 (ion pore), NS1, NS2, PA, PB1, PB1-F2 and PB2, which are found in the virion core [1, 2].

Seasonal influenza has a significant annual global impact accounting for an estimated 1 billion illnesses and 290,000 – 650,000 deaths [3] with an estimated annual economic cost of $87.1 billion in the US alone [4]. Influenza pandemics also occur occasionally with significant health and economic burden [5]. In addition, the unpredictable risk of sporadic outbreaks of human infections with avian influenza (H5N1) could trigger a new pandemic if the virus acquires the ability to transmit from person to person [6] and make influenza a major global public health issue. The major demographic groups at highest risk of influenza infection, severe disease and death remain young children, older individuals, pregnant women and those with co-morbid conditions such as asthma, chronic respiratory disease, diabetes and immunosuppressive conditions.

Vaccination remains the most cost-effective strategy available to combat influenza. Current influenza vaccines work by inducing strain-specific antibodies against the highly polymorphic surface proteins (haemagglutinin, neuraminidase) of the influenza virus. Inactivated or live vaccines are made up of proteins from viruses or live viruses, respectively, covering four influenza virus strains (H1N1, H3N2 and two strains of influenza B). The composition of virus strains used in the production of vaccines is based on a prediction of strains likely to circulate in the population in the upcoming influenza season. As the circulating virus strains change, current vaccines need to be reformulated annually to match new strains arising through genetic drift in the surface proteins of these seasonal viruses. As these surface proteins to which vaccine-induced antibodies are targeted are highly polymorphic, there is little protection against strains of a new subtype and limited protection even across strains within the same subtype. Approximately one year in 20, vaccine efficacy is much lower than expected owing to antigenic drift away from the vaccine strain [7]. This need for constant redesign and remanufacture increases the vaccine cost, places limitations on supply [8] and critically delays vaccine production when new strains arise until the HA and NA sequences have been identified leaving large populations susceptible to infection and illness from the new strains. Furthermore, the efficacy of current vaccines is limited in the face of antigenic mismatch between circulating strains and those in the vaccine and it is also substantially reduced in older adults. Vaccination in older adults, who are a major target group for vaccination, prevents laboratory-confirmed influenza in only 30–40% compared to 70–90% in young adults [9]. Thus, there is a major demand for improved vaccination strategies that can provide protection against a broad spectrum of virus strains particularly for older groups.

In situations where individuals are exposed to a newly arisen influenza virus strain against which they lack protective neutralising antibodies, cross-reactive T-cells against conserved internal antigens of influenza have been shown to be associated with limiting viral shedding, reduced duration of symptoms and minimising severity of symptomatic illness [10, 11]. Thus, a vaccine against influenza that induced protective T cell responses against conserved internal antigens could provide lasting immunity against not only human seasonal influenza, but also

other subtypes currently found in avian species or swine which have the potential to cause a new pandemic. Since adults have been primed by prior exposure to influenza, a vaccine expressing conserved internal antigens of influenza such as NP and M1 could be used to boost cross-reactive T-cell responses to protective levels, providing durable broad immunity to all subtypes of influenza A.

The internal proteins of the influenza virus are more conserved compared to the external surface glycoproteins. There are two reasons for selecting NP and M1 as a target for T-cell inducing vaccines. First, there is very little polymorphism of NP and M1 between influenza A isolates. NP is 92% identical between H3N2 and H1N1 strains, and 91% identical between H3N2 and H5N1 strains. M1 is 95% identical between H3N2 and H1N1 strains, and 93% identical between H3N2 and H5N1 strains. This low level of variation appears to allow strong T cell cross-reactivity. In the local population more than 70% of individuals generate a T cell response to these two antigens [12]. Second, analysis of T-cell response to all the proteins of influenza have shown that the T-cell response to NP and M1 is the strongest and 80% of individuals have responses to these two proteins (Figure 1). Furthermore, recent studies have shown that T-cells specific to M1 and NP are associated with protecting individuals against influenza by limiting viral shedding, reduced duration of symptoms and minimising severity of symptomatic illness [10, 11].

Recombinant viral vectored vaccines have been used in humans to induce high frequencies of $CD4^+$ and $CD8^+$ T cell responses to a wide range of antigens. One such recombinant viral vector is Modified Vaccinia Ankara (MVA) which has been used to generate strong T-cell responses to a wide range of antigens, including antigens from plasmodium, tuberculosis, hepatitis C, HIV and influenza. We have constructed MVA-NP+M1 which is a recombinant, replication-deficient MVA vector expressing the influenza antigens NP and M1 as a fusion protein [13].

MVA is an attractive candidate orthopox vaccine vector for safety and immunogenicity reasons. The successful worldwide eradication of smallpox using vaccination with vaccinia virus highlighted vaccinia as a candidate vaccine vector. Although millions of humans have been vaccinated with conventional replication-competent vaccinia virus, its small but definite risk to both researchers and future patients led to the development of several attenuated strains of vaccinia during smallpox eradication. MVA was originally derived from the vaccinia strain Ankara by over 500 serial passages in primary chicken embryo fibroblasts (CEF cells). MVA has six major genomic deletions compared to the parental Ankara genome and is severely compromised in its ability to replicate in mammalian cells. No replication has been documented in non-transformed mammalian cells.

MVA has an excellent safety record. It was administered intradermally to approximately 120,000 people during the smallpox eradication campaign [14]. MVA is currently in development as a vector for multiple diseases including HIV-1[15, 16], tuberculosis[17], HCV [18], influenza [13] and melanoma [19]. MVA vectored vaccines developed at the University of Oxford have been administered to over 4500 individuals including infants, young children, elderly adults, HIV-infected adults and children and patients with cancer in Europe and Africa without any safety concerns. Clinical studies have shown intramuscular administration, as compared to intradermal, to be associated with fewer and short-lived local AEs and no reduction in immunogenicity [20].

Vaccination with MVA-NP+M1 results in a rapid increase in influenza-specific cross-reactive IFN-γ-secreting effector T cells which are maintained at protective levels over the course of a year [13]. In the older age groups, MVA-NP+M1 can boost pre-existing levels of influenza-specific T-cells and maintain them for up to 6 months post-vaccination [21]. MVA-NP+M1 in combination with licensed inactivated influenza vaccine induced influenza-specific T-cells and in addition, increase the magnitude and breadth of the antibody response induced by the inactivated influenza vaccine [22]. Furthermore, in a small Phase 2a challenge study of MVA-NP+M1 alone, MVA-NP+M1 vaccinated individuals experimentally challenged with live influenza virus trended to less severe symptoms and shorter duration of viral shedding compared to unvaccinated controls [23]. These studies demonstrated the safety of MVA-NP+M1 in older adults and in combination with seasonal influenza vaccine, the immunogenicity of MVA-NP+M1 in older adults and in combination with licensed inactivated seasonal

influenza vaccine and the potential efficacy of MVA-NP+M1 in limiting the severity of influenza illness in adults.

[H3N2] Challenge background

The A/Belgium [H3N2] challenge strain is a live, wild-type influenza A virus that was initially isolated from a nasopharyngeal swab from a paediatric patient in Antwerp, 2015. The first-in-human study was a non-controlled, open-label, single-centre, dose-escalation study to determine the safety, infectivity and immunology of the potential novel influenza virus H3N2 challenge strain. The primary objective was to determine the viral challenge strain dose that had an acceptable safety profile and an observed attack rate (on symptom and positive viral confirmation after day 2) of >60% (i.e. at least 8 out of 12 participants had to be infected). 36 participants were allocated to 3 cohorts. Each cohort consisted of 12 participants.

Challenge agent dose levels increased per cohort and dosing started at a titre of approximately 10^5TCID$_{50}$ (50% tissue culture infective dose/mL). In vivo toxicity, as determined by the established ferret model for Influenza A pathogenesis, suggested that A/Belgium/4217/2015 (H3N2) could be used at similar dosing titres (starting from 10^5 TCID$_{50}$/mL to $6.76x10^6$ TCID$_{50}$/mL) as those previously used in human challenge trials. Based on international literature, comparing HI titres to MNT, a provisional cut-off for participant inclusion based on a MNT of ≤20 was chosen. Since the influence of low MNT (≥10) was unknown, volunteers with low MNT were equally distributed over the cohorts

While the lower bound of the required attack rate (>60%) was reached in all cohorts, none of the participants experienced an SAE or cytokine-related AE during the study even at the highest inoculation dose tested. The observed attack rate in all cohorts was well above the lower bound of the required attack rate. The signs and/or symptoms of Influenza infection similar to community acquired disease. Taken together, the data from the first in human dose escalation study show that A/Belgium/4217/2015 (H3N2) is a truly wild-type Influenza A H3N2 strain which, when used as challenge agent, results high attack rates and significant host changes with relatively low variation in virological, haematological, clinical laboratory and symptom efficacy parameters. The choice of challenge dose is dependent on several factors but an intermediate dose (10^6 TCID$_{50}$/mL) in volunteers with MNT ≤10 is adequate given the relatively low variation of essential efficacy parameters observed. Combining all data from further and ongoing studies, the attack rate for this dose with those participants with MNT ≤10 has been approximately 90%. Increasing this cut-off to <20 should have a minimal effect on the predicted attack rate based on previous evidence.

Non-Clinical Studies

MVA NP+M1 has been shown to be immunogenic in BALB/c mice. Biodistribution studies were not conducted with MVA-NP+M1. However, distribution studies in mice showed no evidence of replication of the virus or presence of disseminated infection 1 week after intradermal (ID) and intramuscular (IM) injections using similar MVA vaccines (MVA85A, MVA ME-TRAP, MVA AMA1 and MVA MSP1). A distribution study was therefore not thought to be necessary for MVA-NP+M1. Previous toxicology studies in mice showed no evidence of systemic MVA-related toxicity after administration (either intradermal or intramuscular). A low level of local irritation at the site of injection after intradermal administration is normally noted in these toxicology studies.

Single and repeat dose toxicology studies were performed on BALB/c mice using the MVA-NP+M1 produced in chicken embryo fibroblasts and revealed that repeated administration of MVA-NP+M1 had no effect on mortality, cage side observations or bodyweights. Mice gained weight and had normal food consumption during the study. Clinical observations, inoculation site reactogenicity, clinical chemistry, clinical haematology, gross

necropsy, organ weights and histopathology indicated no overt toxicity related vaccine administration (see the Investigator Brochure).

The MVA viral vector manufactured using the AGE1.CR.pIX avian cell line has been previously used with a different insert for an Ebola preventive vaccine (MVA-EBOZ). A GLP-compliant non-clinical toxicology study was conducted to evaluate the local and systemic toxicity of the MVA85A vaccine manufactured using the AGE1.CR.pIX® avian cell line. The MVA85A was used as a surrogate test article to support the use of MVA-EBOZ vaccine produced in the AGE1.CR.pIX® avian cell line and to demonstrate the safety of the vaccine for the first in human trial.

1.2 CLINICAL STUDIES

This is the third trial of MVA-NP+M1 produced using the AGE1.CR.pIX immortal avian cell line. To date 436 participants have received the product from a single batch manufacture run, including 430 participants age 65 or older. In addition, MVA-NP+M1 manufactured using chicken embryo fibroblasts (CEF) cells has been administered to 145 adults in 6 clinical trials (5 Phase 1 trials and 1 small Phase 2a challenge study). The vaccine has been shown to have a good safety profile with no vaccine related serious adverse events during these trials.

The vaccine was safe and boosted T-cell responses as expected when administered to healthy adults. A dose dependent increase in adverse events was observed in trials of CEF-produced MVA, and a dose of 1.5 $x10^8$ pfu was found to be the optimal balance between immunogenicity and reactogenicity [13]. It has also been given at the same time as the standard seasonal influenza vaccine (FLU003) and has been shown to have a good safety profile. In FLU002, fewer vaccinated volunteers developed influenza symptoms than the unvaccinated volunteers and there was a trend toward significant reduction in duration of virus shedding in vaccinated volunteers [23].

MVA-NP+M1 in CEF cells has been administered to 145 individuals across a range of doses and via both the intramuscular and intradermal routes, as shown in Table 1. Figure 1 demonstrates the immunogenicity (as determined by interferon-gamma ELISpot) of MVA-NP+M1 in older adults (aged 50+) receiving a dose of 1.5 $x10^8$ pfu.

Table 1. Previous MVA-NP+M1 trials

Country	Study	Vaccine	Age	Route	Dose of MVA-NP+M1	Number of volunteers
UK	FLU001	MVA-NP+M1	18-50	ID	5 $x10^7$ pfu	12
		MVA-NP+M1	18-50	IM	5 $x10^7$ pfu	8
		MVA-NP+M1	18-50	IM	2.5 $x10^8$ pfu	8
		MVA-NP+M1	50-59	IM	1.5 $x10^8$ pfu	10
		MVA-NP+M1	60-69	IM	1.5 $x10^8$ pfu	10
		MVA-NP+M1	70+	IM	1.5 $x10^8$ pfu	10
UK	FLU002	MVA-NP+M1	18-50	IM	1.5 $x10^8$ pfu	15
UK	FLU003	MVA-NP+M1 *(together with seasonal influenza vaccine)*	50+	IM	1.5 $x10^8$ pfu	9
UK	FLU004	ChAdOx1-NP+M1/MVA-NP+M1 *(7-14 weeks apart)*	18-50	IM	1.5 $x10^8$ pfu	3
UK	FLU005	ChAdOx1-NP+M1 / MVA-NP+M1 *(8 weeks apart)*	18-50	IM	1.5 $x10^8$ pfu	12

Country	Study	Vaccine	Age	Route	Dose of MVA-NP+M1	Number of volunteers
		ChAdOx1-NP+M1 / MVA-NP+M1 *(52 weeks apart)*	18-50	IM	1.5 x10^8 pfu	8
		MVA-NP+M1 / ChAdOx1-NP+M1 *(8 weeks apart)*	18-50	IM	1.5 x10^8 pfu	13
		MVA-NP+M1 / ChAdOx1-NP+M1 *(52 weeks apart)*	18-50	IM	1.5 x10^8 pfu	12
		ChAdOx1-NP+M1 / MVA-NP+M1 *(8 weeks apart)*	>50+	IM	1.5 x10^8 pfu	12
UK	FLU006	MVA-NP+M1 *(co- administered with seasonal influenza vaccine - Viroflu®)*	18-50	IM	1.5 x10^8 pfu	3

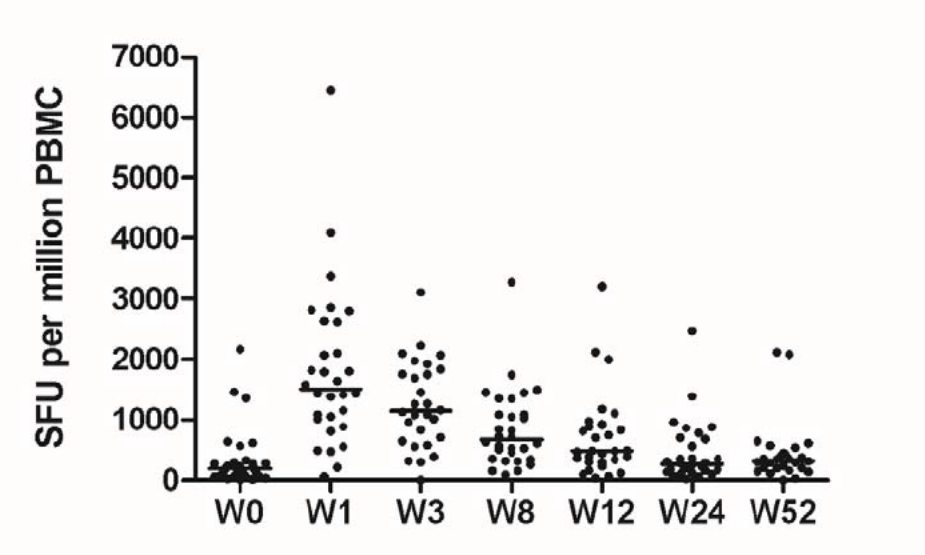

Figure 1: Immunogenicity of MVA-NP+M1 in older adults (FLU001)

A small Phase 1 study of the vaccine made in the AGE1.CR.pIX cell line was performed in 2017 in 6 healthy adult participants to ensure the product was safe, and elicited immune responses as good or better than that induced by the same vaccine made in CEF cells.

This study was immediately followed by a Phase 2 study of participants aged 65 years or over who either received the licensed QIV vaccine followed by Placebo (N=430) or the QIV followed by MVA-NP+M1 (N=430). The expected short-lived local and systemic adverse events were seen, and no vaccine associated SAEs were recorded. The trial, which collected symptom endpoints but not virologic outcomes, is now unblinded and undergoing further analysis.

1.3 OVERALL RATIONALE FOR THE STUDY

Vaccination remains the most cost-effective strategy available to combat influenza. Current influenza vaccines work by inducing strain-specific antibodies against the highly polymorphic surface proteins of the influenza virus. The need for constant redesign and remanufacture increases the vaccine's cost, places limitations on supply and critically delays vaccine production when new strains arise. Thus, there is a major demand for improved vaccination strategies that can provide protection against a broad spectrum of virus strains.

Previous MVA-NP+M1 trials have shown satisfactory immunogenicity across different age groups with tolerable reactogenicity. A Phase 2a influenza challenge study has shown the MVA-NP+M1 may improve protection against viral shedding and reduce severity of influenza symptoms. Importantly, this trial will show that a T-cell inducing vaccine, when given alone, can ameliorate the degree of viral shedding and the total number and severity of symptoms following challenge with a replicating H3N2 influenza A virus. This MVA-NP+M1 produced in the novel immortalized duck retinal cell line AGE1.CR.pIX also addresses the scalability issues of CEF produced vaccines.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of the study is to determine the efficacy of MVA-NP+M1 vaccine administered in a human influenza challenge model to reduce the degree of nasopharyngeal viral shedding (recorded as viral AUC as determined by qPCR).

Hypothesis: The primary hypothesis tested in this study is that the induction of influenza-specific CD4+ and CD8+ T cells by MVA-NP+M1 will result in a decrease of the viral replication and symptoms associated with influenza following challenge with an H3N2 influenza A virus in healthy volunteers.

2.2 SECONDARY OBJECTIVES

Secondary objectives are to determine:

- The incidence in each group (MVA-NP+M1 and saline Placebo) of laboratory-confirmed influenza (qPCR or culture) (and time to start; time to peak and duration of qPCR and quantitative culture results)
- The attack rate, defined as percentage of inoculated participants with at least two positive swabs as determined by qPCR
- Total AUC for total symptom score for MVA-NP+M1 vs. Placebo
- Total days of fever for MVA-NP+M1 vs. Placebo
- Total mucus weight for MVA-NP+M1 vs. Placebo
- Correlation of T cell responses (as defined by ELISpot assay) to the primary endpoint, symptom scores, and influenza incidence
- Safety of MVA-NP+M1 vaccination
- Safety of H3N2 challenge in the setting of MVA-NP+M1 vaccination

2.3 EXPLORATORY OBJECTIVES

Exploratory objectives are to determine:

- Time to start; time to peak and duration of qPCR and quantitative culture results
- Severity of individual symptoms for MVA-NP+M1 vs. Placebo
- Time to start, time to peak, and duration for total symptom score for MVA-NP+M1 vs. Placebo
- Correlation of antigen specific T cell phenotypes with illness outcomes
- Effect of vaccination on the antibody responses to influenza following the intranasal challenge

- Transcriptional response to vaccination and viral challenge assessed by deep sequencing of RNA
- Determine epigenetic response of T-Cells during the study.

3. STUDY DESIGN

3.1 OVERVIEW OF STUDY DESIGN

This is a randomized, single-centre, double blind study. The study will screen healthy volunteers and only enrol those with MNT <20. The study consists of an outpatient vaccination phase, and at least 6 weeks later an inpatient challenge phase.

155 participants will be randomized 3:2 to receive either MVA (N=93) or Placebo (N=62) by intramuscular injection in the non-dominant arm deltoid. Vaccination-related local and systemic symptoms will be followed by participant-directed diary cards for 7 days, and unsolicited adverse events will be followed throughout the study from consent signature. The vaccinations will be administered starting in April 2019. Blood for immunogenicity and storage of samples for correlates of protection will be drawn at five time points: Days 1, 8, 28 post-vaccination, on entry to the quarantine facility for challenge (Day -1), and 27 days post-challenge (Day 28).

Up to 20 participants with no intercurrent ILI will be challenged during each of the challenge periods lasting three weeks (approximately 12 MVA-NP+M1 recipients and 8 Placebo recipients per three-week block), to achieve a total of 80 participants from the MVA-NP+M1 group and 54 from the saline Placebo group being challenged. Participants will enter the quarantine facility on Day -2 or Day -1 and be discharged the morning of Day 11. The grouping of participants undergoing challenge will be as consistent as possible with the grouping used during the randomization process; i.e., the first participants vaccinated will be the first quarantined and challenged, but in all cases at least 6 weeks will have passed between vaccination and challenge.

Participants will receive a single intranasal administration of the H3N2 challenge agent (A/Belgium/4217/2015) as a nasal spray via the Teleflex MAD301 and MAD130. The MAD301 hard plastic atomizer will be combined with the MAD130 syringe and vial adaptor to constitute components that are the most similar to the VaxINator^{TM} kit, used in previous studies for H3N2 inoculation.

Participants will be in a semi-recumbent (45°) position, lying in bed and will receive 0.25 mL of the challenge agent solution into each nostril.

After viral inoculation, participants are to remain in a supine position for 2 hours. Participants are not allowed to blow their noses during this period. All administrations will be performed by a member of the clinical site staff.

The assessments performed are summarized per visit in the Time and Events Schedule.

3.2 DISCUSSION OF STUDY DESIGN

Dose Selection

The dose of MVA-NP+M1 to be used in this study will be 1.5 x10^8 pfu (4.3 x10^8 $TCID_{50}$) 0.5 mL administered intramuscularly, based on previous Phase 1 and 2a clinical trials, which have shown the vaccine is safe and immunogenic at this dose (FLU001, FLU002, FLU003, FLU004 and FLU005). Participants received the proposed 1.5 x 10^8 pfu dose in FLU001 which was less reactogenic and better tolerated than the 2.5 x 10^8 pfu used in one group. The immune responses were not significantly different between the two doses. The 1.5 x 10^8 pfu dose was thus chosen to balance reactogenicity and immunogenicity.

Placebo Control

Placebo saline control given as 0.5 mL intramuscularly in the deltoid will be used to establish the frequency and magnitude of solicited and non-solicited adverse events, as well as to control for the laboratory and clinical assessments used as endpoints. All such recordings will be performed in a blinded fashion.

Dose of challenge agent

The choice of challenge dose is dependent on several factors but an intermediate dose (10^6 $TCID_{50}$/mL) in volunteers with MNT <20 is adequate given the relatively low variation of essential efficacy parameters observed. Combining all data from previous and ongoing studies, the attack rate for this dose with those participants with MNT <20 has been approximately 83%.

Randomization and Blinding

Randomization will be used to avoid bias in the assignment of participants to treatment, to increase the likelihood that known and unknown participant attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Participants are blinded to study allocation.

Since MVA-NP+M1 has a cloudy appearance compared to saline Placebo and regular transparent syringes will be used, a label will surround the syringes to maintain the blind. The syringes will be transported from the pharmacy to the vaccination room in opaque containers to keep the study treatment blinded from the site staff and the study participants. The dedicated unblinded dosing team will be assigned for the vaccine administration. The participant receiving the vaccine/placebo will be asked to look away from the injection site to keep the blind and will not be unblinded during the trial. After administration, the unblinded dosing team will lift the label to ensure the full dose has been given to the participant. The used syringes will then be returned to the pharmacy in the opaque transport containers. Detailed procedural instructions will be made in the study execution documents.

The pharmacist will confirm that the vaccine has been completely injected. Since the person administering the vaccine might become unblinded due to spillback of the solution from the skin outwards, only the assigned unblinded team will be responsible for the vaccination. Further instructions are provided in the pharmacy manual to ensure the syringes have no residue left when returned to the pharmacy and the study blinding during this procedure is preserved. All personnel that record adverse events throughout the study and all personnel involved in the challenge will remain blinded to treatment allocation. This will be assured to reduce potential bias during safety data collection and evaluation of clinical endpoints. All laboratory personnel conducting immunology assays will receive blinded samples and will report these values back to the data management and statistics group in a blinded fashion.

4. SELECTION OF STUDY POPULATION

Screening for eligible participants will be performed within approximately 1 month prior to randomization and the administration of either MVA-NP+M1 or saline Placebo.

Approximately 155 participants are planned to be enrolled into the vaccination phase. They will be randomized to one of 2 treatment groups, A or B, in a 93:62 ratio. 134 of these participants will be included in the challenge phase.

For details on the sample size calculation, please refer to Section 9.2.

4.1 INCLUSION CRITERIA

1. Healthy males and females aged ≥18 and ≤55 years of age at the point of enrolment.

2. Non-smokers or those who stopped smoking ≥ 3 months prior to screening 1 visit.
3. Willingness to remain in isolation for the duration of the study.
4. A female participant is eligible for this study if she is not pregnant or breast feeding and 1 of the following:
   a. Of non-childbearing potential (i.e., women who have had a hysterectomy or tubal ligation or are postmenopausal, as defined by no menses in greater than or equal to 1 year).
   b. Of childbearing potential but has been and agrees to continue practicing highly effective contraception or abstinence (if this is the preferred and usual lifestyle of the participant) from 6 months prior to vaccination to 6 months after administration of the influenza challenge virus. Highly effective methods of contraception include 1 or more of the following:
      i. male partner who is sterile (vasectomised) prior to the female participants entry into the study and is the sole sexual partner for the female participant;
      ii. hormonal (oral, intravaginal, transdermal, implantable or injectable);
      iii. an intrauterine hormone-releasing system (IUS);
      iv. an intrauterine device (IUD) with a documented failure rate of < 1%;
      v. bilateral tubal occlusion.
5. Pre-challenge serum MNT against A/Belgium/4217/2015 (H3N2) challenge strain <20.

4.2 EXCLUSION CRITERIA

1. BMI < 19 and > 32.
2. Presence of any significant acute or chronic, uncontrolled medical (or psychiatric) illness including a history of chronic respiratory illness.
3. History of seasonal hay fever or a clinically significant seasonal allergic rhinitis (SAR), including the use of symptomatic prescription only medication and non-prescription medication.
4. History or evidence of autoimmune disease or known immunodeficiency of any cause - with the exception of atopic dermatitis/eczema and atopic rhinitis.
5. Any history of anaphylaxis in reaction to vaccination or history of allergic reactions likely to be exacerbated by any component of the vaccine.
6. History of lung disease (Asthma, COPD).
7. Current smokers or those who stopped smoking < 3months prior to screening 1 visit.
8. Positive diagnostic tests for HIV, Hepatitis B or Hepatitis C indicating active infection.
9. Evidence of drug abuse or a positive urine drug screen or alcohol breath test.
10. Chronic use of any medication or other product (prescription or over-the-counter), for symptoms of rhinitis or nasal congestion or for any chronic nasopharyngeal complaint, or chronic use of any intranasal medication for any indication that has not cessed within 30 days prior to screening 1.
11. Receipt of any investigational drug within 3 months prior to vaccination, or prior participation in a clinical trial of any influenza vaccine, or any investigational vaccine or experimental influenza viral challenge delivered directly to the respiratory tract within 1 year prior to challenge.
12. Receipt of the 2018/2019 seasonal flu vaccine.
13. Receipt of any live vaccines within the 4 weeks prior to vaccination.
14. Any laboratory test which is abnormal and which is deemed by the Investigator(s) to be clinically significant.
15. Receipt of any systemic chemotherapy agent at any time.

16. Physician reported influenza or a syndrome consistent with influenza (as judged by the investigator) in the previous 6 months.
17. Known allergy to treatments for influenza (including but not limited to oseltamivir).
18. History of frequent epistaxis (nose bleeds).
19. Any nasal or sinus surgery within 6 months of Viral Challenge or any significant abnormality, either of which results in alteration of the anatomy of the nose or nasopharynx (including significant nasal polyps).
20. Volunteers with household contacts who are at risk for serious or severe complications of influenza disease including, but not limited to: persons ≥ 65 years; presence of significant chronic cardiopulmonary, metabolic, renal, or neurological conditions; immunosuppression due to any condition or therapies; BMI >40.
21. Participants that are an employee or family member of the Investigator or study site personnel may not be enrolled.
22. Any other finding that, in the opinion of the Investigator, deems the participant unsuitable for the study.

4.3 EXCLUSION (CHALLENGE PERIOD ONLY)

1. Abnormal spirometry assessed to be clinically significant.
2. Known close contact with anyone known to have influenza in the past 7 days at the time of quarantine.
3. ILI symptoms as assessed at the admission to clinic on Day -2 prior to challenge.
4. Presence of fever, defined as participant presenting with a temperature reading of > 38.0°C on admission to quarantine.
5. Qualitative PCR results positive for viral infection. However, participants may be included into later challenge cohort.
6. Acute use of any medication or other product, prescription or over-the-counter, for symptoms of rhinitis or nasal congestion within 7 days prior to challenge. This includes any oral corticosteroid or beta agonist containing nasal spray.

5. TREATMENT

5.1 PHYSICAL DESCRIPTION OF THE STUDY DRUG

MVA-NP+M1 is a Modified Vaccinia Ankara virus recombinant, replication-deficient, vector expressing the conserved influenza antigens nucleoprotein (NP) and matrix 1 (M1) (H3N2 2007/Panama) as a fusion protein. The dose of MVA-NP+M1 to be used in this study will be 1.5 x10^8 pfu. Each glass vial of MVA-NP+M1 contains 700 microlitres volume in formulation buffer containing 10% sucrose, 0.1% pluronic acid, 25 mM TRIS to a target final concentration of approximately 3 x 10^8 pfu/mL. The vaccine is not diluted prior to administering.

MVA-NP+M1 is manufactured in accordance with Good Manufacturing Practice (GMP) by Emergent BioSolutions, USA as required by the current Good Clinical Practice (GCP).

The vaccine has undergone UK and European Qualified Person release.

A copy of the certificate of analysis of the MVA-NP+M1 drug product will accompany the vials to the clinical site.

5.2 OTHER MEDICATION ADMINISTERED IN THE STUDY

5.2.1 *Placebo*

Participants who are allocated to the control group will receive a Placebo injection of 0.9% saline (sourced by Fisher Clinical Services) instead of MVA-NP+M1. The volume and site of injection will be the same as for group A and participants will be blinded as to which injection they are receiving. Each vial of saline will only be used for a single participant. A vaccine accountability log of the saline will be maintained at the trial site.

5.2.2 *Challenge Product [H3N2]*

A/Belgium/4217/2015 (H3N2) is a solution of $6.76x10^6$ $TCID_{50}$/mL. It is stored as 1.0 mL aliquots between -65° and -80°C in 2.0 mL self-standing cryovials.

Before inoculation it is thawed on ice and diluted to $1.0x10^6$ $TCID_{50}$/mL with PBS, drawn up into a syringe and administered as a nasal spray using the Teleflex MAD301 and MAD130.

Participants will receive a single intranasal administration of the H3N2 challenge agent (A/Belgium/4217/2015) via nasal spray (Teleflex MAD301 and MAD130).

Participants will be in a semi-recumbent (45°) position, lying in bed and receive 0.25 mL of the challenge agent solution into each nostril.

After viral inoculation, participants are to remain in a supine position for 2 hours. Participants are not allowed to blow their noses during this period. All administrations will be performed by a member of the clinical site staff.

5.3 PACKAGING AND LABELLING

MVA-NP+M1 will be packaged in boxes of 25 vials. MVA-NP+M1 will be labelled according to local law and regulatory requirements. The labels will contain the protocol number, reference number, storage caution statements, dosing instructions, expiry date, and the notice "keep out of reach of children" and "For Clinical Trial Use Only".

5.4 STORAGE AND STUDY DRUG ACCOUNTABILITY

The Investigator (or his/her designee) is responsible for the safe storage of all study products assigned to the clinical site, in a locked, secure storage facility with access limited to those individuals authorized to dispense the study drugs and maintained within the appropriate ranges of temperature. All study drugs must be stored as specified at delivery and in the original packaging. Instructions for the study personnel, regarding the storage and handling of the study drugs, will also be provided to the clinical site.

MVA-NP+M1 must be stored at 2 to 8°C, should not be exposed to freezing temperatures and should be protected from light during storage at the clinical site. Saline Placebo can be stored at room temperature or with MVA-NP+M1 at 2 to 8°C.

A/Belgium/4217/2015 (H3N2) is a solution of $6.76 x10^6$ $TCID_{50}$/mL. It is stored as 1.0 mL aliquots between -65° and -80°C in 2.0 mL self-standing cryovials.

Before inoculation, it is thawed on ice and diluted to $1.0 x10^6$ $TCID_{50}$/mL with PBS, drawn up into a syringe and administered as a nasal spray using the Teleflex MAD301 and MAD130.

Regular temperature logging of the study product storage room at the clinical site should be performed. In case a deviation in storage conditions should occur, the clinical site must not further dispense the affected study drug and immediately notify the Sponsor.

The Investigator is responsible for ensuring that all study products received at the clinical site are inventoried and accounted for throughout the study. A vaccine accountability log will be used to record when the vaccine/Placebo is removed and used.

As misallocations of study products may have a detrimental effect on participants' safety and/or the study products' efficacy and are a potential source of bias, utmost care should be taken to correctly dispense the study drugs as assigned by the randomization system.

Study products should be dispensed under the supervision of the Investigator, a qualified member of the clinical staff, or by a hospital/clinic pharmacist. The Investigator must maintain accurate records demonstrating date and the number of products supplied to whom and by whom.

The study unblinded pharmacist will perform the check of study drugs held at the pharmacy to ensure accountability and appropriate storage conditions of all study drugs used. The study designated site monitor will perform the accountability at the end of the study after Database Lock once the treatments have been unblinded.

After the last visit of the last participant in the study (LPLV), any unused study drug will be returned to the Sponsor or destroyed at the clinical site with the Sponsor's written permission (in this case a certificate of destruction will be provided and filed in the Trial Master File (TMF)).

Hazardous materials such as used ampoules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

5.5 RANDOMIZATION AND BLINDING

As participants are confirmed to be eligible for the study, they will be assigned a single unique identifier across the study.

At screening, participants receive a unique screening number using the letter S and a number ranging from 001 to 999. Participants who fail screening and are not enrolled will not be included in the final database but will be recorded in a separate screening log. The failure details will be documented in the 'participants' file.

Participants will be assigned to 1 of 2 treatment groups. Allocation of each participant to a given treatment group will be determined from a randomization list (to be linked to the unique identifier) prepared prior to study start by SGS Life Sciences Secure Data Office using SAS® software (SAS Institute Inc., Cary, NC, USA).

The randomization list will be generated using randomly permuted blocks and will not be stratified. Participants will be randomised 3:2 to receive either MVA-NP+M1 or saline Placebo, with total enrolment of 155 participants at an allocation of 93 to 62. Each grouping of up to 20 participants will be given a specific date, approximately three weeks apart, to enter the quarantine facility in order to be challenged. If more than 20 participants from a vaccination group are eligible and available for challenge, participants who are willing to enter at another date will be enrolled with a later cohort to reach the correct allocation of up to 20 participants per challenge. The challenge period will include up to approximately 80 participants in the MVA-NP+M1 vs up to approximately 54 participants in the saline Placebo group.

The pharmacist or an appropriate qualified member of the study staff, who is unblinded to treatment and assigned by the principal Investigator, will prepare the study vaccine that corresponds to the assigned participant randomization number. The recruiters calling vaccinated participants back to quarantine, will also be blinded to the study status, therefore the Statistical Centre will supply the list of participants to be called to undergo challenge and quarantine.

The randomization list will be retained by SGS Life Sciences Secure Data Office until the end of the study (database lock). One copy of the randomization list will be sent in a sealed envelope to the site pharmacist before the start of the study. Throughout the study conduct, the monitor needs to check the completeness and status of

the envelopes and upon study completion the monitor can retrieve the envelopes and have them destroyed after Sponsor's written approval.

One copy of code breaking envelopes will be made available to the clinical site, to be used only in case of emergency. An additional copy of code breaking envelopes will be kept at SGS Life Sciences Secure Data Office. Upon request, SGS Life Sciences Secure Data Office will provide the code-break information to SGS Life Science Medical Affairs for SAE reporting purposes. Should a participant experience an adverse event (AE) for which it is necessary to break the blind during the study in order to determine the appropriate treatment for the event, the principal Investigator or designee will call the Sponsor medical monitor prior to unblinding. The reason for unblinding will be documented in the appropriate section of the eSource. Participants who are unblinded for any reason during their participation in the study will not be replaced and will be withdrawn immediately from the study upon resolution of all SAEs.

5.6 DOSE AND ADMINISTRATION

A rationale for the dose of study drug selected in this study is provided in Section 3.2.

Participants will be randomly and sequentially assigned, according to the randomization schedule and in a blinded fashion to 1 of 2 treatments.

An overview of the treatment in each of the treatment groups is provided in Table 2.

Table 2: Treatment Overview: Challenge number (+ additional vaccination)

Treatment Group	Number of Subjects	Treatment
Group A	80 (+13)	MVA-NP+M1
Group B	54 (+8)	Saline Placebo

Any deviation from the treatment regimen defined in the protocol must be documented in the eSource.

5.7 SAFETY MONITORING

5.7.1 *Safety Monitoring Committee*

A Safety Monitoring Committee will be made of the CRO Medical Monitor, Sponsor Medical Monitor, and the principal Investigator or designated Investigator to review ongoing, blinded, non-cleaned safety data. The committee will review any of the ongoing, closely evaluated adverse events that occur after vaccination and challenge. As the medical team sees the challenge participants every day, the risk for a meaningful adverse event to go unobserved is extraordinarily unlikely, and this will trigger an immediate meeting of the Safety Committee. If deemed necessary, the safety committee can stop the study and ask for review by the IDMC, who would have access to unblinded information.

5.7.2 *Independent Data Monitoring Committee*

An Independent Data Monitoring Committee (IDMC) will be set up to monitor and evaluate the safety of the study vaccine and challenge virus if required. The IDMC will consist of at least 2 clinical experts, and an independent statistician. The IDMC will be convened if any of the Stopping Rules are triggered and to assess any SUSARs. For the purpose of these meetings, the treatment code for any requested safety review may be provided to the IDMC, but not revealed to the Sponsor. If deemed necessary by the IDMC, treatment codes can be fully unblinded to the IDMC. Based on these safety reviews, the IDMC will make recommendations to the Sponsor regarding the continuation, modification, or termination of the study.

Further details will be described in a separate IDMC charter.

6. PRIOR AND CONCOMITANT THERAPY

6.1 PERMITTED CONCOMITANT THERAPIES

After vaccination, due to local soreness at the injection site and potential low-grade fever, paracetamol (maximum 4 g/day) and/or ibuprofen (maximum 1800 mg/day) will be allowed. After challenge, medications can be used to alleviate symptoms at the decision of the Investigator; however, medications that mask symptoms and which are required for comfort only will be discouraged, so that appropriate symptom scoring can take place. At the end of Day 8, if the influenza culture (not the qPCR) remains positive, the Investigator may elect to treat the participant with oseltamivir at a dose of 75 mg b.i.d. for five days. Participants will not be discharged from the quarantine unit until the qPCR is negative or the participant has no fever. All concomitant medications are to be collected in the eSource.

Stable hormone replacement therapy in postmenopausal participants is also permitted.

Further medication is permitted as per the inclusion criteria [Section 4.1].

6.2 PROHIBITED CONCOMITANT THERAPIES

Oral or nasal steroids will be prohibited and are listed in the challenge exclusion criteria [Section 4.2]. Also, refer to Stopping Rules or Non-Vaccination Criteria [Section 8.3].

7. ASSESSMENTS

The evaluation of post-vaccination solicited and unsolicited events will use a standard 7-day diary card that captures the following local and systemic symptoms. The following local and systemic solicited adverse events will be recorded by participants:

- **Local:** pain, redness, induration, warmth and pruritus at injection site.
- **Systemic**: feverishness, chills, myalgia, fatigue, headache, nausea, arthralgia, malaise and temperature.

Participants will also be asked to report any unsolicited adverse events throughout the study after signing the consent form.

The quarantine unit also uses a standardized scoring system which includes the following solicited symptoms:

- Upper respiratory: nasal congestion, runny nose, sneezing, sore throat, sinus pain, difficulty swallowing, tearful/watery/painful eyes/aversion to light.
- Lower respiratory: dry cough, productive cough, difficulty breathing.
- General: muscle aches, nausea/vomiting, fever/chills/shivering, sweating, headache, dizziness, tiredness, diarrhoea.
- Any suspected cardiac adverse event will be assessed with an ECG and cardiac troponin in consultation with a cardiologist.

7.1 TIMING OF ASSESSMENTS

An overview of the timing of treatment(s) and assessments is given in the Time and Events Schedule of the vaccination period as well as for the challenge phase.

A 10% deviation from theoretical post dose times will be allowed for all post-dose assessments. The windows for follow-up visits post-vaccination will be 7 ±1 day, 27 ±3 days, 55 ±3 days, day from vaccination to challenge

> 6 weeks, but less than 6 months. The windows for follow-up visits post-challenge confinement period will be 27 ±3 days and/ or 6 months post-vaccination (180 ±14 days) whichever is longer.

7.1.1 *Screening Period*

Screening

Screening for eligible and consenting participants will be performed within approximately 6 weeks prior to randomization/the first administration of study drugs. It will be possible to include participants who are screened with the appropriate MNT assay from another protocol or screening test, but the test needs to be performed or repeated within 6 weeks of vaccination.

Some eligibility criteria will be checked prior to assessing MNT in the study. These criteria involve:

- life style questions i.e. smoking, contraception, identify current BMI (upon Investigator discretion), recent or planned participation in other studies etc. [inclusion criteria 1 to 4 and exclusion criteria 1 & 7].
- current illnesses including current medication.

Any physical examination, vital signs and laboratory assessments will be completed at Screening 2 visit within the 3 weeks leading to the vaccination once MNT is confirmed. However, in order to ensure a sufficient number of participants are vaccinated in a given group, MNT may be performed at Screening 2 at the same time as Screening 2 assessments.

Participants will be given a full explanation of the nature of the study and written informed consent (approved by the local ethics committee) will be obtained according to local requirements before any study-related assessment is carried out.

At screening, participants will be asked to attend the clinical site to have assessments performed as indicated in the Time and Events Schedule. All results from the screening procedure needed to evaluate eligibility, including the clinical laboratory results, must be available prior to the first administration of the study drugs on Day 1. Any abnormal result at the screening visit will be assessed according to its clinical relevance, and if found relevant, the participant will not be included in the study.

Repeat tests may be performed and participants may be rescreened at the discretion of the Investigator.

All inclusion/exclusion criteria are to be checked on Screening 2 visit before participant's vaccination.

7.1.2 *Treatment Period*

7.1.2.1 *VACCINATION*

Vaccination - Day 1

Participants will attend the clinic for Vaccination on Day 1 at least 6 weeks before inoculation and challenge. This visit will also include a review of inclusion/exclusion criteria, blood draws for PBMCs, Serum and Transcriptomics, alcohol breath test, urine drug screen and urine pregnancy test.

Participants will then be vaccinated with either MVA-NP+M1 or saline Placebo depending on the randomization schedule. Following vaccination participants will remain in the clinic for at least 2 hours for monitoring. During this time diary cards will be dispensed and explained for completion over the following 7 days for solicited and unsolicited events and throughout the study for unsolicited adverse events.

Day 2

A blood draw for transcriptomics will be taken in the 24 (±3) hours post-vaccination. Participants will return to the clinic for safety assessments and transcriptomic blood draw.

Day 4

3 days after vaccination, participants will be contacted by phone as a reminder to complete their diary cards.

Day 8 and Day 28

7 and 27 days after vaccination participants will attend the clinic for follow-up assessments as per the Time and Events Schedule, primarily to assess safety and collect blood for immunogenicity assessments.

Day 56

Participants will be called to be assessed for potential intercurrent ILI and possible date of challenge. The decision whether to exclude the participant will be at the discretion of the Investigator.

7.1.2.2 *CHALLENGE*

Day -2 and Day -1

On Day -2, participants will be admitted to the Clinical Pharmacology Unit (CPU). Eligibility of the participants will be confirmed along with the Assessments listed as per Time and Events Schedule.

Should the participant present a positive Qualitative PCR pre-challenge, the participant will be excluded from this challenge group but may enter any of the subsequent challenge groups if the infection is cleared. The participant excluded at Day -2 from the challenge period may be replaced with a participant with the same treatment on Day -1.

Day 1

On Day 1, assessments will be performed as indicated in the Time and Events Schedule.

After the safety assessments, the participants will be inoculated with challenge virus H3N2 by a trained health care worker, followed by repeated blood sampling and NP swab samples as outlined in the Time and Events Schedule.

Day 2 to Day 11

After inoculation participants will remain in the CPU for a further 10 days. During this time, they will have vital signs monitored and targeted physical examinations as well as scoring symptoms twice a day (b.i.d.). Nasal swabs are taken twice a day (b.i.d.) at least 8 hours apart on Day 2 to Day 10, as per the Standard Operating Procedure (SOP) requirements. Immunogenicity assessments will be performed as indicated in the Time and Events Schedule.

Adverse events and the intake of concomitant medication(s) will be monitored continuously from informed consent until the last study-related activity.

7.1.3 *Follow-up Period*

All participants challenged or vaccinated only, whether they complete the treatment period or are withdrawn from the study, will be asked to complete a safety follow-up visit:

- 27 days post-vaccination (in-patient visit), if withdrawal occurred before the challenge.
- 27 days post-inoculation of challenge virus (in-patient visit), if participant was challenged.
- 6 months post-vaccination (180 days ±14), if this is greater than 27 days post-challenge, a phone call will be performed to assess any potential interim Serious Adverse Events in all vaccinated participants. This

phone call will be preceded by an e-mail. The participant will be called up to 3 times, if there is no response, to ensure this last follow-up call is completed,

except in the case of withdrawal of consent. In order to provide some flexibility for the participants regarding the site visits and to maintain the integrity of the study design, a time window of ±3 days is permitted for follow-up visits at Day 28 and ±14 days for follow-up visit at Month 6 (180 days), in case of time conflict or unforeseen circumstances.

Assessments will be performed as indicated in the Time and Events Schedule.

7.1.4 *Unscheduled Visits*

Unscheduled visits after randomization can be planned for instance:

- to obtain additional information to ensure safety of the participant. Additional blood and urine samples may be taken at the discretion of the Investigator
- to assess, confirm, and follow up on out-of-range clinical laboratory test, vital sign, or ECG values, or in case of a positive drug screen, alcohol breath test or pregnancy result.

Findings made during unscheduled visits should be reported in the eSource.

7.1.5 *Sample Collection and Handling*

Throughout the study, venous blood samples will be collected for analysis of immune response in blood RNA, and blood PBMCs, according to the time points defined in the Time and Events Schedule. The exact date and time of blood sampling and handling must be recorded in the source documentation.

Blood samples will be collected by venipuncture in the forearm into vacuum tubes as specified in the laboratory manual.

Further detailed procedures for PBMC, Transcriptomics and other blood samples collection, shipment, processing, and storage are described in the laboratory manual.

7.1.6 *Immunogenicity*

The whole blood is drawn and processed on the appropriate days will be packaged according to specifications and sent by Courier to Viroclinics in Rotterdam for PBMC processing as per Laboratory Manual.

The viral strains to be possibly used will be determined following the 2018/2019 influenza season but will include that of the challenge strain at a minimum.

ELISpot for interferon gamma/granzyme B will be conducted at Viroclinics and will be performed on cryopreserved PBMCs using peptides spanning the NP+M1 antigens of the vaccine, with the peptides of 15 amino acid length, overlapping by ten. The pools of peptides, and the layout of the plates, including controls, can be found in the laboratory manual.

The stimulation will be as per Laboratory Manual and the plates will be developed and read using a validated ELISpot reader. Samples also may be utilized to analyse for T cell responses using a multi-parameter intracellular staining (ICS) panel, as per the laboratory manual. The primary assay will be the ELISpot, which will take precedence over the ICS assay if the cell yield is limited.

PBMC samples collected prior to and on Days 8 and 28 after vaccination, and prior to and on Days 8 and 28 after challenge will be de-identified and may be tested for epigenetic changes such as DNA methylation and histone modifications in order to identify reliable epigenetic markers of recent exposure to influenza and vaccinia.

7.1.7 *Transcriptomics*

Blood collection by RNA stabilization may be used to evaluate gene expression for correlates of protection or correlates of disease. The transcriptomics samples will be collected using PAXgene® RNA tubes that will be stored in a monitored -20°C freezer.

7.1.8 *Efficacy Variables*

The efficacy variables include:

- The qPCR for the challenge H3N2 virus on Day 2 to Day 10 (b.i.d.)
- Influenza culture collected on Day 2 to Day 10 (b.i.d.) (performed only if the PCR is positive)
- Symptoms scores, total and individual collected on Day 1 to Day 11 (twice daily)
- Tissue weights for nasal discharge, collected as needed, from Day 1 to Day 11

7.1.9 *Efficacy Criteria*

The primary endpoint upon which the powering analysis is performed uses the vAUC for virologic shedding as measured by qPCR for all collected samples, compared between groups using a Mann-Whitney U Test (Wilcoxon rank sum). The powering is based on the Placebo data from two prior challenge studies with this H3N2 virus.

7.2 SAFETY EVALUATIONS

The safety assessment in this study will be based on AEs, clinical laboratory tests, ECG, vital signs, and physical examination, as described in the following sections.

7.2.1 *Study Products Potential Risks*

MVA-NP+M1

Potential risks associated with vaccination include local and systemic reactions.
Vaccination usually precipitates a local inflammatory reaction. This may include redness, swelling, scaling, tenderness, or itching. In previous studies using recombinant MVA vaccines, these local reactions have spontaneously resolved within weeks. Systemic reactions that could potentially occur following immunisation with a recombinant MVA vaccine include an influenza-like illness with low-grade fever, chills and malaise. In general, it appears that the frequency of systemic side effects in response to recombinant MVA vaccines is affected by a preceding poxvirus vaccination, with the proportion of volunteers experiencing any systemic side effects after the first vaccination being 69%, decreasing to 37% after the second and 22% after a third immunisation.

As with any other vaccine, Guillain-Barré syndrome (GBS) or immune mediated reactions that can lead to organ damage may occur. However, this has never been seen with a recombinant MVA vaccine to date. Serious allergic reactions including anaphylaxis may occur, as also with any vaccine. The incidence of this is unknown but is estimated at one per 10^5 to 10^6 vaccinations. Volunteers should be vaccinated in a clinical area where Advanced Life Support drugs and equipment are immediately available for the management of serious adverse reactions.

Placebo

No risk associated.

Challenge [H3N2]

All challenged participants will be at risk of becoming infected and developing typical influenza-like illness. Only one clinically significant adverse event (AE), “presumed myocarditis”, diagnosed 51 days post inoculation and following a subsequent respiratory infection, has been documented amongst all previously reported

challenge studies. Nevertheless, because the challenge agent is wild-type (although a seasonal strain which may be further passage-attenuated), it is possible that infrequent or rare clinically significant events may occur. A number of serious events have been associated with community-acquired Influenza infection [24]. Most were seen to occur primarily during pregnancy or in elderly individuals and those with chronic underlying medical conditions. Such events have been more frequently observed during pandemic years and have included pulmonary complications (including primary viral pneumonia, secondary bacterial pneumonia, and exacerbations of underlying chronic obstructive pulmonary disease, and asthma), along with worsening of underlying cardiac conditions such as congestive heart failure and ischemic heart disease. Much less frequent (and generally rare) complications have also been reported, including myositis, rhabdomyolysis, and neurologic complications such as encephalopathy (Reye's syndrome), encephalomyelitis, transverse myelitis, aseptic meningitis, focal neurologic disorders, and Guillain-Barré syndrome. The occurrence of Reye's syndrome has been reported predominately in children less than 14 years of age (90% of cases reported were in this age group) and the incidence has dramatically declined during the past 2 decades from a peak of 500 cases per year in the 1970s. This decline is thought to be related to the understanding of the role of salicylates in Reye's syndrome. Pericarditis and myocarditis have been noted in adults, along with electrocardiographic (ECG) abnormalities in up to 53% of infected adults, typically with no cardiac symptoms [25, 26]. However, most of these ECG abnormalities resolved within 28 days, and did not result in detectable myocardial damage (as measured by creatine kinase isoenzyme MB or troponin I levels) or reduced ejection fractions.

Because of the potential for severe illness, efforts to minimise this risk are to be implemented during all clinical studies with this challenge strain. First, all prospective participants will be carefully evaluated for the presence of any known risk factor for severe influenza illness, including underlying pulmonary and cardiac disease, pregnancy, and/or immunosuppressive conditions; individuals with such conditions will be excluded from participation. Secondly, all enrolled participants will be continuously monitored under quarantine by trained and suitably accredited clinical staff for the duration of the study, with qualified physicians available as needed 24h a day. Thirdly, the challenge strain has been confirmed to be susceptible to the standard of care antiviral agents oseltamivir and zanamivir, in the event that the severity of the illness warrants rescue therapy.

Because the challenge virus preparation contains egg protein, individuals with known or suspected egg allergies should not participate, nor should individuals with a prior history of Guillain-Barré syndrome.

There is a theoretical risk that inducing influenza-specific T cells might exacerbate disease following challenge. No such worsening was observed in the 430 elderly participants who received QIV and MVA-NP+M1 in a recent study in the UK.

7.2.2 *Adverse Events*

Adverse events will be monitored continuously from informed consent until the last study-related activity (outpatient visit at 27 days ±3 days post-challenge or 6 months post-vaccination ±14 days, whichever is longer). At regular intervals during the study, participants will be asked non-leading questions to determine the occurrence of any AEs. All AEs reported spontaneously during the course of the study will be recorded as well.

For detailed definitions and reporting procedures of AEs, see Section 10.

AEs will be scored using the modified toxicity tables from the FDA (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 2)).

7.2.3 *Clinical Laboratory Tests*

Blood samples will be collected by venipuncture at the time points indicated in the Time and Events Schedule. Biochemistry and haematology testing will be performed on these samples, as well as immunology testing (HBsAg, anti-HCV, and HIV antibodies) on the sample from screening. In female participants of childbearing

potential, human chorionic gonadotropin (hCG) using serum pregnancy test will be performed at screening and urine pregnancy test at the other study visits as per the Time and Event Schedule.

Standard laboratory tests will be performed by ZNA Klinisch Laboratorium. The following biochemistry and haematology tests will be performed on the safety blood and laboratory samples:

- Biochemistry: creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamylaminotransferase (GGT), C-reactive protein (CRP), bilirubin, sodium and potassium. Sodium and potassium tests are only required in the challenge period.
- Haematology: haemoglobin, haematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV)

A urine drug screen for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates will be performed at screening visit 2 and upon admission at the clinical site (Period 1 & 2). A urine drug screen may be repeated to check false positive results.

An alcohol breath test will be performed at screening visit 2 and upon admission at the clinical site on Day 1 for Period 1 and on Day -2 (or Day -1) for Period 2. An alcohol breath test may be repeated to check false positive results.

The Investigator must review the laboratory results, document this review, and record any change occurring during the study he/she considers to be clinically relevant in the AE section of the eSource. Laboratory values outside the normal range will be flagged and their clinical relevance and significance will be assessed, documented and signed by the Investigator. A copy of all laboratory reports must be filed in the participant's records. These tests may be repeated at the Investigator's discretion.

7.2.4 *Vital Signs*

Vital sign parameters will be assessed after 5 minutes in supine position at the time points indicated in the Time and Events Schedule. The vital sign parameters that will be assessed are temperature, supine systolic and diastolic blood pressure (SBP and DBP, respectively), pulse rate, and pulse oximetry.

These parameters will be measured using a completely automated device consisting of an inflatable cuff and an oscillatory detection system. All values will be registered on a built-in recorder so that measurements are observer-independent.

Any change from baseline in vital sign values occurring during the study that is considered to be clinically relevant by the Investigator should be recorded in the AE section of the eSource system.

7.2.5 *Spirometry*

Spirometry is to be performed on Day -1 prior to challenge and on Day 10 post-challenge. This assessment may be performed during an Unscheduled Visit at the discretion of the Investigator.

7.2.6 *Electrocardiogram*

Digital twelve-lead ECGs will be recorded in supine position at the time points indicated in the Time and Events Schedule.

The interpretations of the ECGs will be performed and recorded by the Investigator or his/her designee at the clinical site. Any change from baseline/pre-vaccination ECG occurring during the study that is considered to be clinically relevant by the Investigator should be recorded in the AE section of the eSource system. Specifically, the qualified reader will look for signs of myocarditis, which include non-specific ST-segment and

T-wave abnormalities, sinus tachycardia and conduction abnormalities, such as bundle-branch blocks or atrioventricular conduction delays.

7.2.7 *Physical Examination*

Physical examination or symptom-directed examination will be performed at the time points indicated in the Time and Events Schedule.

Physical examination at screening will include height and weight. To obtain the actual body weight, participants must be weighed at screening 2 while lightly clothed. The height should be measured barefoot.

Any change in physical examination occurring during the study that is considered to be clinically relevant by the Investigator should be recorded in the AE section of the eSource system.

7.2.8 *Other Assessments*

Participants will be instructed in the collection of standard issued tissues (according to the laboratory manual) used to capture nasal congestion and discharge, and the samples will be collected by the quarantine staff daily, weighed, and the result recorded (early AM and in the evening).

7.3 TOTAL VOLUME OF BLOOD SAMPLING

The total volume of blood from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study as per the Laboratory Manual.

If necessary, in order to obtain additional information to ensure participant's safety, additional blood samples (up to 10 mL) and/or urine samples may be taken at the discretion of the Investigator.

8. STUDY TERMINATION/COMPLETION

8.1 STUDY COMPLETION

Participants will be considered to have completed the study if they have completed the entire stay of the challenge and completed the follow-up visit 27 days post-challenge or 6 months post-vaccination whichever is longer.

8.2 REMOVAL OF PARTICIPANTS FROM STUDY

Participants have the right to withdraw from the study at any time for any reason, including their future care. The Investigator should however try to find out why a participant withdraws from the study and document the reason for withdrawal in the eSource.

Participants **may** be withdrawn from the study in the event of:

- A severe AE or serious AE (SAE)
- Difficulties in obtaining blood or other samples;
- Failure of the participant to comply with the protocol requirements or to cooperate with the Investigator.

Participants **must** be withdrawn from the study in the event of:

- Withdrawal of consent;
- For safety reasons, it being in the best interest of the participant that he/she be withdrawn, in the Investigator's opinion;
- A positive pregnancy test or if the participant is non-compliant with the contraception requirements (see Section 4.1);

- Development of a medical condition that requires concomitant treatment with a prohibited therapy (see Section 6.2);
- Breaking of the randomization code during administration of the study drugs, by the Investigator or by a member of his/her clinical staff. If the code is broken by the Sponsor, for safety reporting purposes, the participant may remain in the study.

In the event of a participant being withdrawn from the study, the site monitor and Sponsor should be informed. In case of withdrawal due to an SAE (for details on AE reporting see Section 10), the Sponsor should be notified within 24 hours. In case of withdrawal for other reasons; the Sponsor should be notified within 2 days from the event.

If there is a medical reason for withdrawal, the participant will remain under the supervision of the Investigator until satisfactory health has returned.

Participants who are withdrawn from the study prior to completion of the scheduled study procedures for any reason (AE, withdrawal of consent, etc.) should be invited to complete the assessments as much as possible. As long as the participant consents, all relevant assessments of the day on which the participant withdrew from the study should be completed, at least those related to safety, and the participant should come for a safety follow-up visit at Day 28 post-vaccination or Day 28 post-challenge (if challenged) and/ or will receive a call 6 months post-vaccination whichever is longer. In case of an AE, the appropriate follow-up will be done.

Participants who withdraw or are withdrawn from the study for reasons other than safety, may be replaced by those who underwent vaccination, and added to the final challenge cohort, if vaccinated volunteers are available. This decision will be made based upon discussion and mutual agreement between the Sponsor and the Investigator.

Participants who are vaccinated and not entered into the challenge phase will be phoned at 6 months after vaccination to assess any potential intercurrent SAEs.

8.3 STOPPING RULES OR NON-VACCINATION CRITERIA

The following events constitute contraindications to administration of vaccine at that point in time; if any one of these events occurs at the time scheduled for vaccination, the participant may be vaccinated at a later date, or withdrawn from the study at the discretion of the Investigator.

- Acute disease at the time of vaccination. Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to participants with a minor illness such as diarrhoea, mild upper respiratory infection with or without low-grade febrile illness, i.e. temperature of ≤37.7°C/99.5°F.
- Temperature of >38°C (100.4°F) at the time of vaccination.
- Receipt of a licensed inactivated vaccine (e.g. pneumococcal vaccine) within 2 weeks prior to enrolment. There must be a minimum of 2-week interval between the trial vaccination procedures and the use of any other licensed inactivated vaccines. Participants with routine/travel vaccinations booked within this interval will be either advised to postpone their appointments or will have the trial vaccination postponed until the minimum interval required is met.
- Receipt of a licensed live vaccine (e.g. herpes zoster vaccine) within 4 weeks prior to enrolment. There must be a minimum of 4-week interval between the trial vaccination procedures and the use of any other licensed live vaccines. Volunteers with routine/travel vaccinations booked within this interval will be either advised to postpone their appointments or will have the trial vaccination postponed until the minimum interval required is met.

If any one of the following halting rules are met, vaccination of participants will be suspended until after a review of safety data by the IDMC. Other study activities for safety and immune responses will continue during IDMC review. The IDMC will recommend that the study continues as planned, stops, or resumes with modification.

- Solicited local AEs: If >10% of doses of a vaccine are followed by the same Grade 3 solicited local AE
- Solicited systemic AEs: If >10% of doses of a vaccine are followed by the same Grade 3 solicited systemic AE
- Unsolicited AEs: If 10% (n=15) of subjects develop a Grade 3 unsolicited adverse event of the same type that is considered possibly, probably or definitely related to vaccination
- Death occurs that is considered possibly, or definitely related to vaccination
- A life-threatening reaction occurs that is considered possibly, probably, or definitely related to vaccination
- Occurrence of a SUSAR
- Occurrence of an acute allergic reaction or anaphylactic shock following the administration of vaccine investigational product

If any one of the following halting rules are met, challenge of participants will be suspended until after a review of safety data by the IDMC. Other study activities for safety and immune responses will continue during IDMC review. The IDMC will recommend that the study continues as planned, stops, or resumes with modification.
Occurrence in any participant of:

- A reduction of peak expiratory flow (PEF) below 50% of the baseline value, or moderate or severe lower respiratory symptoms occurring within 14 days of challenge
- Pulse oximetry that on repeat monitoring over one hour falls below a value of 90%
- Grade 3 or 4 AE or clinical laboratory abnormality considered related to the challenge agent AND of concern to the Investigator or Medical Monitor. Grade 3 headache or fatigue which resolves within 24 hours will not be a reason for halting unless of concern to the Investigator or Medical Monitor.
- More than three cases of influenza that are sufficiently severe to warrant antiviral therapy
- Laryngospasm, bronchospasm, or anaphylaxis associated with the study drug or challenge within 72 hours of study drug or challenge administration
- Any SAE for which causality is either unknown or related to challenge
- Any case of suspected myocarditis
- Any death

9. STATISTICAL METHODS

9.1 STATISTICAL ANALYSIS

No formal interim analyses are planned for this trial.

Statistical analyses will be performed by a qualified vendor under the supervision and responsibility of the Sponsor, using SAS® (SAS Institute Inc., Cary, NC, USA; version 9.2 or higher) and/or Phoenix™ WinNonlin® (Pharsight Corporation, Palo Alto, CA, USA; version 6.1 or higher). Unscheduled interim analyses may be performed at the request of the IDMC to monitor the safety of the investigative vaccine throughout the study (also Section 5.7). Details will be described in a separate IDMC charter.

The following populations will be considered for analysis:

- intent-to-treat (ITT) population, defined as all randomized participants who received the challenge inoculation, according to the assigned (randomized) treatment group

- per-protocol (PP) population, consisting of a subset of the ITT population without any major protocol deviations and including those participants who remain in the quarantine facility for the full extent of the challenge phase
- safety population, consisting of all participants vaccinated in the vaccine phase, according to the vaccination actually received
- challenge safety population, which includes all of those in the above defined ITT, according to the vaccination actually received.

Unless specified otherwise, the ITT population will be used for efficacy and immunogenicity analysis. The safety populations will be used for safety/tolerability analysis and analysis of demographics.

All statistical methods shall be detailed in a Statistical Analysis Plan (SAP) to be issued by SGS statistical team and finalized before database lock. The SAP will be approved by the Vaccitech Ltd statistical consultant.

The final efficacy analysis will be performed once all participants have completed 27 days from the time of inoculation (Day 28 post-challenge) or 6 months post-vaccination, whichever is last.

For continuous variables, descriptive statistics will include mean, standard deviation (SD), median, minimum, maximum, and range. For categorical variables, descriptive statistics will include frequencies and percentages.

9.1.1 *Baseline Characteristics*

For all participants who undergo vaccination, descriptive statistics will be provided per vaccination group for demographic (e.g. age, height, weight, BMI, race, sex) and other initial participant characteristics (physical examination, medical and surgical history, concomitant diseases).

Prior and concomitant medications will be coded using the World Health Organization (WHO)_DRUG Dictionary.

9.1.2 *Efficacy Data*

A more detailed description of all efficacy analyses will be included in the trial's SAP, including planned supportive and sensitivity analyses, as well as methods for imputing missing data.

9.1.2.1 *PRIMARY ENDPOINT*

The trial's primary endpoint is a comparison of the viral shedding of influenza virus in MVA-NP+M1 versus placebo recipients following human challenge, as measured by the cumulative area under the curve (vAUC). Difference in vAUC, as measured and quantitated by log-transformed qPCR, will be evaluated using a Mann-Whitney U Test. AUC will be calculated using the trapezoidal rule. In case no viral load was detected, the $\log_{10}$ viral load will be imputed.

Mean (± Standard Error (SE)) viral load over time will be summarized and presented graphically in $\log_{10}$ scale by treatment group.

9.1.2.2 *SECONDARY ENDPOINTS*

The attack rate, defined as percentage of inoculated participants with at least two positive swabs as determined by qPCR, will be summarized in percentages and 95% confidence intervals (CIs) by treatment group. The difference between the two treatment groups will be compared by a Fisher's exact test.

Time to start, time to peak and time to cessation of viral shedding from virus inoculation and duration of viral shedding will be summarized by the Kaplan-Meier method. Differences between the treatment groups will also be tested using the log-rank test. Differences in peak between treatment groups will be tested using a Mann-Whitney U test.

The same analyses as performed for qPCR will be performed on quantitative culture.

Secondary endpoints include the rate of virologically confirmed ILI (defined as a respiratory or flu-like symptom occurring on two consecutive days, along with a positive PCR or culture) measured between groups. Incidence of laboratory-confirmed influenza will be compared between vaccine groups using Fisher's Exact Test.

Another key secondary endpoint of relevance to the biologic effect of this vaccine will be the comparison of the symptom severity as an AUC. This endpoint takes into account both the severity and the duration of symptoms. Total and individual symptom scores from Day 1 to Day 11 post-challenge, will be compared by AUC using a Mann-Whitney U test.

T cell responses (as defined by ELISpot assay) will be evaluated in relation to the primary endpoint, symptom scores and influenza incidence.

9.1.2.3 *EXPLORATORY ENDPOINTS*

Time to start, time to peak and time to cessation of total symptoms from virus inoculation and duration of total symptoms will be summarized by the Kaplan-Meier method. Differences between the treatment groups will also be tested using the log-rank test.

Total days of fever for MVA-NP+M1 vs. Placebo will be compared by means of a zero-inflated Poisson model. Fever is defined as >38.0 degrees Celsius.

Total mucus production between Days 1 and 11 post-challenge, as measured by total tissue weight, will be compared between vaccine groups using a t-test or Mann-Whitney U Test.

Immunogenicity data, using interferon gamma/granzyme B ELISpot as the primary outcome measure, will be compared between vaccine groups using a t-test or Mann-Whitney U Test. Descriptive statistics will be calculated including number of observations, mean, median, geometric mean titre (GMT), minimum and maximum with 95% confidence interval (CI).

Transcriptional response to vaccination and viral challenge may be assessed by deep sequencing of RNA using PAXgene® RNA tubes.

Epigenetic responses of T-Cells may be assessed during the study, and the methods will be detailed in the SAP.

Descriptive comparison of the ratios of the GMTs of the MNT and HI results between the two treatment groups will be calculated along with the corresponding 95% CI based on the $\log_{10}$ difference of the two groups.

Importantly, with a 83% attack rate and 30% efficacy, approximately 20 of the 80 vaccination participants will have a zero area under the curve, and these participants can be compared to those with the highest vAUC in correlate of protection analyses. An exploratory correlate of protection analysis will be detailed in the SAP prior to breaking the blind on the immunogenicity data.

9.1.3 *Safety Data*

Safety parameters will be tabulated and analysed descriptively.

Adverse Events

The original terms used in the eSource documents by Investigators to identify AEs will be fully described and coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

The reported AEs will be allocated to phases based on their start date. All AEs will be listed. All AEs with onset after Day 1 of vaccination will be summarized by treatment group. Summaries, listings, and narratives may be provided, as appropriate. Summaries will include at a minimum SAEs, and for both solicited and unsolicited AEs, the severe (grade 3+ events), related AEs, and AEs following challenge.

Clinical Laboratory Tests

Each continuous biochemistry and haematology laboratory test will be evaluated by means of descriptive statistics (i.e., number of participants, mean, SD, median, minimum, and maximum) on the actual values, at each assessment time point and by vaccination group.

Relative changes in clinical laboratory test values compared to values at baseline will be evaluated according to the appended toxicity scale or in accordance with the normal ranges of the clinical laboratory (below, within, or above normal range) for parameters for which no toxicity grades are defined.

A listing of participants with any clinical laboratory test result outside the reference ranges will be provided.

Vital Signs

Pulse rate, temperature, SBP, and DBP will be evaluated by means of descriptive statistics (actual values and changes from Day 1 to Day 2 of the vaccine phase and from Day 1 of the challenge phase and frequency tabulations at each assessment time point and by vaccination group).

Pulse oximetry will be measured during the entire challenge phase.

The percentage of participants with values beyond clinically important limits (as defined in the Toxicity Tables) will be summarized.

Electrocardiogram

ECG variables will be evaluated by means of descriptive analysis by the Investigator at each assessment time point.

The percentage of participants with ECG abnormalities will be summarized.

The ECG variables that will be analysed by electronic capture from the ECG include heart rate, PR interval, QRS interval, QT interval.

Physical Examination

Abnormal findings in physical examination will be listed.

9.2 DETERMINATION OF SAMPLE SIZE

The sample size was chosen to have sufficient power to detect a 30% difference in the vAUC, assuming a drop out of approximately 15-20% from the vaccination group. Since there is 15% over-enrolment during the vaccination phase compared to challenge, it is assumed that in a worse-case scenario a 25% reduction, or that the final numbers to undergo challenge per group could be as low as 72 MVA-NP+M1 and 48 Placebo recipients. The placebo vAUC data were estimated using qPCR data accumulated during two previous challenge studies, where vAUC was calculated using the trapezoidal rule. The allocation ratio is chosen not at 2:1 (which would be 80:40), but rather at 80:54 to ensure sufficient placebo recipients within each challenge period to adequately assess the take rate of the challenge for that given cohort. Sample sizes of 80 and 54 participants in the MVA-NP+M1 and placebo groups, respectively, will yield approximately 90% power to detect at least a 22% difference in vAUC at a two-sided, alpha=0.05 level. If enrolment is lower than anticipated, approximately two-thirds of the planned sample size will still yield at least 80% power to detect a 30% difference in vAUC (two-sided alpha = 0.05).

10. ADVERSE EVENT REPORTING

10.1 DEFINITIONS

Definition of Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal result of diagnostic procedures, including clinical laboratory test abnormalities.

Definition of Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death
- is life-threatening, i.e., the participant was at risk of death at the time of the event (e.g., ventricular fibrillation and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing inpatient hospitalization: Hospitalization refers to an overnight admission into hospital for the purpose of investigating and/or treating the AE. Hospitalization for an elective procedure, or routinely scheduled treatment for a pre-existing condition that has not worsened, is not an SAE.
- results in persistent or significant disability/incapacity, i.e., causing substantial disruption of the participant's ability to conduct normal life
- is a congenital anomaly/birth defect
- is medically significant, i.e., may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant's health or may require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

Definition of Unlisted (Unexpected) Adverse Event

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information in the Investigator Brochure.

Definition of Events of Special Interest

Adverse events of special interest (AESI) for this study are listed in Appendix 1. AESI should be recorded and reported using the same procedures as for SAEs. They should therefore be recorded over the duration of the study to which the participant is recruited and reported to the Sponsor according to the process in Section 10.7.

10.2 INTENSITY OF ADVERSE EVENTS

Each AE must be rated on a 5-point scale of increasing intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0:

Note: the semi-colon within the description of the grade indicates 'or'.

Grade 1:

Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2:

Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3:

Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated, disabling; limiting self-care activities of daily life (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4:

Life-threatening consequences; urgent intervention indicated.

Grade 5:

Death related to AE.

10.3 CAUSALITY ASSESSMENT

Causality of each AE will be assessed according to the WHO-Uppsala Monitoring Centre (UMC) system for standardized case causality assessment.

Note: all of the assessment criteria per causality should be reasonably complied to.

Certain:

- Event or laboratory test abnormality with plausible time relationship to study drug.
- Cannot be explained by disease or other drugs.
- Response to withdrawal plausible (pharmacologically, pathologically).
- Event definitive immunologic or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon).

Probable/Likely

- Event or laboratory test abnormality with reasonable time relationship to study drug administration
- Unlikely to be attributable to disease or other drugs.

Possible

- Event or laboratory test abnormality with reasonable time relationship to study drug administration
- Could also be explained by disease or other drugs.

Unlikely

- Event or laboratory test abnormality with a time to study drug administration that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations.

Not related

- Implausibly related to study intervention

10.4 ACTION TAKEN REGARDING THE STUDY DRUGS

The action taken towards the study drug must be described as follows:

- Participant permanently discontinued from study
- Unknown
- Not applicable.

10.5 OUTCOME

The outcome of each AE must be rated as follows:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal
- Unknown.

10.6 RECORDING OF ADVERSE EVENTS

All (S)AEs occurring during the clinical investigation must be documented in the (e)source documents.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common aetiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record their opinion concerning the relationship of the (S)AE to the study drug in the eSource. All measures required for (S)AE management must be recorded in the source documents and reported according to Sponsor's instructions.

All AEs occurring at any time during the study (including the follow-up period) will be followed by the Investigator until satisfactory resolution (e.g., value back to baseline value) or stabilization or until final database lock. If necessary, in order to obtain additional information to ensure safety to the participant, additional blood and urine samples may be taken at the discretion of the Investigator. Certain long-term AEs related to therapy cannot be followed until resolution within the setting of this study. If additional follow up or treatment is deemed as needed, it is up to the Investigator to inform the participant and to ensure adequate medical care by the participants treating physician (GP or specialist).

10.7 REPORTING OF SERIOUS ADVERSE EVENTS

All SAEs independent of the circumstances or suspected cause must be reported on a Serious Adverse Event Form by the Investigator to Vaccitech and SGS Life Sciences Medical Affairs within 24 h of their knowledge of the event.

The SAE form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

Follow-up and outcomes should be reported for all participants who experience an SAE.

It is critical that the information provided on the Serious Adverse Event Form matches the information recorded in the (e)source documents for the same event.

Copies of additional laboratory tests, consultation reports, post-mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. Follow-up reports relative to the participant's subsequent course must be submitted to SGS Life Sciences Medical Affairs until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

10.8 PREGNANCY

All initial reports of pregnancy in participants must be reported to Vaccitech and SGS Life Sciences by the Investigator within 24 h of his/her knowledge of the event using a Pregnancy Form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study (Section 8).

The Investigator will contact the participant at the expected time of delivery for follow-up. Abnormal pregnancy outcomes (e.g. spontaneous or induced abortion, stillbirth, neonatal death, congenital abnormality, birth defect) are considered SAEs and must be reported using the Serious Adverse Event Form.

10.9 REPORTING OF SERIOUS ADVERSE EVENTS TO COMPETENT AUTHORITIES/ETHICS COMMITTEES

SGS Life Sciences Medical Affairs assumes responsibility for appropriate reporting of AEs to the regulatory authorities. SGS Life Sciences Medical Affairs will also report to the Investigator all SAEs that are unlisted (unexpected) and associated with the use of the drug. The Investigator (or SGS Life Sciences Medical Affairs where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol, unless otherwise required and documented by the IEC/IRB.

Adverse events reporting, including suspected unexpected serious adverse reactions (SUSARs), will be carried out in accordance with applicable local regulations.

After termination of the clinical study (determined as LPLV), any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the participants who have participated in the study, together with proposed actions, will be reported by the Sponsor/SGS Life Sciences Medical Affairs to the competent authority(ies) concerned as soon as possible.

11. ETHICAL ASPECTS

11.1 STUDY-SPECIFIC DESIGN CONSIDERATIONS

Potential participants will be fully informed of the nature of the study and of the risks and requirements of the study before any study-related assessment will be carried out. During the study, participants will be given any new information that may affect their decision to continue participation. They will be informed that their participation in the study is voluntary and that they may withdraw from the study at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and who provide their consent voluntarily will be enrolled in the study.

11.2 REGULATORY ETHICS COMPLIANCE

11.2.1 *Investigator Responsibilities*

The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor, the IRB/IEC, or the regulatory authority(ies).

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current International Council for Harmonization (ICH) guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected,

consistent with the principles originating from the Declaration of Helsinki (1964 and revisions), and that the clinical study data are credible.

11.2.2 *Independent Ethics Committee or Institutional Review Board (IEC/IRB)*

An IRB/IEC should safeguard the rights, safety, and well-being of all study participants. Special attention should be paid to studies that may include vulnerable participants.

Before the start of the study, the Investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any updates or any other written materials to be provided to the participants)
- Sponsor-approved participant recruiting materials
- Investigator Brochure (or equivalent information) and addenda
- available safety information
- information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's current curriculum vitae or other documentation evidencing qualifications (unless not required, as documented by the IEC/IRB)
- information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- any other documents that the IEC/IRB may require to fulfil its obligation.

This study will be undertaken only after the IEC/IRB has given full written approval of the final protocol and amendments (if any), the ICF(s) and updates (if any), applicable recruiting materials, and any other written information to be provided to the participants, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the Investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for its review and approval, where appropriate:

- protocol amendments
- revision(s) to the ICF and any other written materials to be provided to the participants
- new or revised participant recruiting materials approved by the Sponsor
- revisions to compensation for study-related injuries or payment to participants for participation in the study
- Investigator's Brochure addenda or new edition(s)
- summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- reports of AEs that are serious, unlisted, and associated with the Investigational Medicinal Product (IMP)
- new information that may adversely affect the safety of the participants or the conduct of the study
- deviations from or changes to the protocol to eliminate immediate hazards to the participants
- report of death of any participants under the Investigator's care
- notification if a new Investigator is responsible for the study at the clinical site

- Development Safety Update Report, Short-Term Study Specific Safety Summary and Line Listings, where applicable
- any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s), except when necessary to eliminate immediate hazard to the study participants. If a deviation from or a change to the protocol was implemented to eliminate an immediate hazard to study participants, then the implemented deviation or change, the reasons for it, and, if appropriate, the protocol amendment should be submitted to the IEC/IRB as soon as possible.

The Investigator (or Sponsor where required) will notify the IEC/IRB about the study completion within 90 days after the end of the study (defined as LPLV).

11.2.3 *Informed Consent*

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and the reviewing IEC/IRB. The informed consent should be in accordance with the principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrolment in the study, the Investigator or an authorized member of the clinical staff must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may refuse to participate or withdraw consent to participate at any time, without penalty or loss of benefits to which the participant was entitled. Finally, they will be told that the Investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized Sponsor staff without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access and agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

The language about the study used in the oral and written information, including the ICF, should be non-technical and practical and should be understandable to the participant (or the participant's legally acceptable representative). The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained consent, a copy of the ICF must be given to the participant.

If a participant (or legally acceptable representative) is unable to read or write, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to the participants, is read and explained to the participant (or legally acceptable representative), and after the participant (or legally acceptable representative) has orally consented to the participant's participation in the study and, if capable of doing so, has personally dated and signed the ICF, the witness should personally date and sign the consent form. By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the participant (or legally acceptable representative), and that informed consent was freely given by the participant (or legally acceptable representative).

The Investigator or designee is to document the process followed for consent collection in the source file and confirm that a copy of the ICF was provided to the study participant.

11.2.4 *Privacy of Personal Data*

The collection and processing of personal data from participants enrolled in the study will be limited to those data that are necessary to investigate the safety, quality, and utility of the IMP used in the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data need to agree to keep the identity of the study participants confidential.

The informed consent obtained from the participants includes explicit consent for the processing of personal data and for the Investigator to allow direct access to participants' original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

12. ADMINISTRATIVE REQUIREMENTS

12.1 PROTOCOL AMENDMENTS

Neither the Investigator nor the Sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the Sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IEC/IRB approval nor when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazard to the participants, in which case an amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the Investigator and IEC/IRB must be provided to the Sponsor or his designee. When the change(s) involves only logistic or administrative aspects of the study, the IEC only needs to be notified.

12.2 PARTICIPANT IDENTIFICATION, ENROLMENT, AND SCREENING LOGS

The Investigator agrees to complete a participant identification and enrolment log to permit easy identification of each participant during and after the study. This document will be reviewed by the site Monitor for completeness.

The participant identification and enrolment log will be treated as confidential and will be filed by the Investigator in the study file. To ensure participant confidentiality, no copies will be made. All reports and communications related to the study will identify participants by assigned number only.

The Investigator must also complete a participant screening/enrolment log which documents all participants who were seen to determine eligibility for inclusion in the study and those who have been successfully randomized in the study. This log is to be shared with the Sponsor on a regular basis to allow Sponsor oversight.

12.3 SOURCE DOCUMENTATION

The LabPas system is an electronic data capturing and information management system that will also serve as an eSource system for this study. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those that are paper-based, will be collected directly in LabPas. The Source Document Identification Overview will specify which information will be eSource and which will be paper-based. The monitor will check data at the monitoring visits to the CPU. The Investigator will ensure that the data collected are accurate, complete, and legible. Data will be monitored within

LabPas by the study monitor who has only reading rights. Any changes required following monitoring will be made by site personnel or the Investigator and will be documented with a full audit trail within LabPas.

At a minimum, source documentation must be available for the following data : participant identification, eligibility, and study identification; study discussion and date of informed consent, dates of visits, results of safety and efficacy parameters as required by the protocol, record of all AEs, follow-up of AEs, concomitant medication, study drug receipt/dispensing/return records, study drug administration information, laboratory, date of study completion, and reason for early discontinuation of study drugs or withdrawal from the study, if applicable.

Direct access to (e)Source documentation (medical records) must be allowed for the purpose of verifying that the data.

It is required that the author of an entry in the (e)Source documents be identifiable.

Source data may be directly captured from devices, transferred from third parties (e.g., laboratory data), or entered manually into the eSource system in use at the CPU. In such case, the majority of the source data will only be available electronically. The remainder of the data, captured initially on paper, may be entered retrospectively into the eSource system.
Following the ICH-GCP guidelines, direct access to (e)Source documentation (medical records) must be allowed.

12.4 CASE REPORT FORM COMPLETION

All source data, except those that are paper-based, will be collected directly into the eSource system. Paper-based source data will be manually transcribed to the eSource system. Only the data required for the clinical database will be transferred electronically from the eSource system to the clinical database.

The study data will be directly entered into the eSource by study personnel and transmitted in a secure manner to the Sponsor.

All eSource entries, corrections, and alterations must be made by the Investigator or other authorized study-site personnel.

Worksheets may be used for the capture of some data to facilitate completion of the eSource. Any such worksheet will become part of the participant's source documentation. All data related to the study must be recorded into the eSource. Data must be entered into the eSource in English. Designated site personnel must complete the eSource as soon as possible after a participant visit, and the forms should be available for review at the next scheduled monitoring visit.

The Investigator must verify that all data entries on the eSource are accurate and correct.

12.5 MONITORING

The monitoring of the study will be done under the responsibility of the Sponsor by SGS Life Sciences.

The monitor will perform on-site monitoring visits as frequently as necessary but in accordance with the Monitoring Plan. The monitor will record the dates of the visits in a study site visit log that will be kept at the clinical site. The first post initiation visit will be made as soon as possible after enrolment has begun. At these visits, the monitor will compare the data captured in the eSource system for completeness and accuracy and perform data source verification to any data that has been captured as paper source or entered in the system later on. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eSource system are known to the Sponsor and clinical staff and are accessible for verification by the site Monitor. If electronic records are maintained at the investigational site, the method of verification must be discussed with the clinical staff.

Direct access to (e)Source documentation (medical records) must be allowed at all times for the purpose of verifying that the data recorded in the eSource system are consistent with the paper Source data (if applicable). Findings from this review of captured data will be discussed with the clinical staff. During on-site monitoring visits (notified and agreed upfront with the clinical staff), the relevant clinical staff will be available, the (e)Source documentation will be accessible, and a suitable environment for review of study-related documents will be provided. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct.

12.6 DATA MANAGEMENT

Data management of the study will be performed under the responsibility of the Sponsor by SGS Life Sciences. After the data entered in the eSource system are released by the Investigator, the data will be uploaded into the clinical database to perform cleaning activities. Computerized data cleaning checks will be used in addition to manual review, including listings review, to check for discrepancies and to ensure consistency and completeness of the data. Queries emerging during data cleaning will be generated by the clinical data manager in the eSource system. The Investigator or his designee will answer the queries and update the source data, if needed.
The clinical database will be locked as soon as it is considered clean. Before the clinical database will be locked, the study eSource system will be locked by the clinical staff. Only authorized and well-documented updates to the study data are possible after database lock. The locked database is used in the final statistical analysis for study reporting. Measures will be undertaken to protect participant data handed over by the Investigator to the data management department and during inspections against disclosure to unauthorized third parties. Participant confidentiality will be maintained at all times.

12.7 DATA QUALITY ASSURANCE

The accuracy and reliability of the study data will be assured by the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and by periodic monitoring visits by the Sponsor or designate.

Written instructions will be provided for the collection, preparation, and shipment of blood samples.

The Sponsor or his designee will review the eSource system for accuracy and completeness during (on-site) monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate. After upload of the data into the clinical study database, their accuracy verified using appropriate validation programs.

In accordance with Good Clinical Research Practice Guidelines and Recommendations, the Sponsor will be entitled to audit the facilities used in the clinical and laboratory parts of the study, as well as to access all the data files pertaining to the study. Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

12.8 ON-SITE AUDITS

Representatives of the Sponsor’s clinical quality assurance department may visit the clinical site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The Investigator and clinical staff are to be present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or his designee.

Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator

should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

12.9 STUDY TERMINATION

The Sponsor has the right to terminate the study at any time. In case of an early termination of the study for safety reasons, or temporary halt by the Sponsor, the IEC/IRB should be notified within 15 calendar days and should be provided with a detailed written explanation for the termination/halt.

An end-of-study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete study has ended. This notification will be submitted within 90 days after the end of the study.

12.10 RECORD RETENTION

In compliance with the ICH/GCP guidelines, the Investigator/Institution will maintain all eSource and all paper source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents will be retained for a longer period if required according to the applicable regulatory requirements or per agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for any other reasons withdraws from his responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents without having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation related to the study, the Investigator must permit access to such reports.

12.11 USE OF INFORMATION AND PUBLICATION

All information, including but not limited to, information regarding MVA-NP+M1 or the Sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the Investigator and not previously published, and any data generated as a result of this study are considered confidential and remain the sole property of the Sponsor. The Investigator agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the Sponsor's prior written consent.

The Investigator understands that the information generated in this clinical study will be used by the Sponsor in connection with the continued development of the study product, and thus may be disclosed as required to other clinical Investigators or regulatory agencies. To permit information derived from the clinical studies to be used, the Investigator is obliged to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated under the responsibility of the Sponsor. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating Investigator.

Clinical narratives may be written for the following events (for example):

- All deaths (irrespective of drug relationship)
- All other SAEs during treatment with the study drugs
- All discontinuations of the study drugs due to AEs (irrespective of drug relationship)
- At the discretion of the team and after statistical analysis of the data, certain discontinuations not related to AEs or treatment failure, i.e., related to lost to follow-up or withdrawal of consent (irrespective of treatment group)
- Any events of special interest explicitly requested by the regulatory agencies.

The principal Investigator will sign off the final version of the Clinical Study Report. A summary of this final version will be provided to the Investigators, the applicable regulatory authorities, and the IECs/IRBs, if required by the applicable regulatory requirements, within 1 year after the end of the study (LPLV).

The Sponsor shall have the right to publish study data and information without approval from the Investigator. If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews of 30 days will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the Investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the Investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

12.12 REGISTRATION OF CLINICAL STUDIES AND DISCLOSURE OF RESULTS

The Sponsor will register the existence of a clinical study and disclose its results as required by law.

12.13 CONFIDENTIALITY

All study documents are provided by the Sponsor to the Investigator and appointed clinical staff in confidence. None of this material may be disclosed to any party not directly involved in the study without the Sponsor's written permission.

The Investigator must assure that participants' anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the participants' study numbers, names, addresses, and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from the Sponsor.

13. REFERENCES

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2. Literature references
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APPENDIX 1: ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest represent a subset of adverse events that include autoimmune diseases and other systemic disorders of interest which could potentially have an autoimmune aetiology. Adverse events of special interest are listed below. The Investigator should use clinical and scientific judgment in deciding whether other adverse events (i.e., events not listed here) could have an autoimmune origin and should therefore be reported as adverse events of special interest.

Bell's Palsy

Guillain Barre Syndrome

Myocarditis

Stevens-Johnson Syndrome

APPENDIX 2: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

https://www.fda.gov/downloads/BiologicsBloodVaccines/ucm091977

A. TABLES FOR CLINICAL ABNORMALITIES

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	**Mild (Grade 1)**	**(Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B. TABLES FOR LABORATORY ABNORMALITIES

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

*** ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.