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

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STATISTICAL ANALYSIS PLAN

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

Protocol:	FLU010
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SIGNATURE PAGE

Name and function	Date (ddMMMyyyy)	Signature
SGS LS author and reviewer:		
[redacted] biostatistical coordinator		
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Sponsor's approval: The approver agrees the statistical analysis will be performed according to this statistical analysis plan.		
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PROTOCOL HISTORY

Protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the changes on the statistical analysis**
Final 1.0	19DEC2018	NAP
Final 2.0	27FEB2019	none
Final 3.0	02APR2019	none
Final 4.0	14MAY2019	none
Final 5.0	10JUL2019	none

This statistical analysis plan (SAP) only considers the latest version of the protocol, and of the protocol amendments, as listed above.

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AR(H)(1)	(heterogeneous) first order autoregressive
AST	aspartate transaminase
AUC	area under the curve
CBER	Centre for Biologics Evaluation and Research
CI	confidence interval
CRF	case report form
CRP	C-reactive protein
CS(H)	(heterogeneous) compound symmetry
DCE	double-colour enzymatic
DY	relative day
ELISpot	enzyme-linked immunosorbent assay
GGT	gamma-glutamyl transferase
HI	Hemagglutination inhibition assay
ICF	informed consent form
ICH	International Council for Harmonisation
ILI	influenza-like illness
ITT	intent-to-treat
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
MNT	microneutralization test
NAP	not applicable
PBMC	peripheral blood mononuclear cell
qPCR	quantitative polymerase chain reaction (can be a reverse transcriptase PCR)
RBC	red blood cells

RND	all randomised subjects analysis set
SAE	serious adverse event
SAP	statistical analysis plan
SAF	safety analysis set
SCR	all screened subjects analysis set
SFC	spot-forming colony
SGS LS	SGS Life Sciences
SOP	standard operating procedure
SSC	symptom score card
STAT	statistics
TEAE	treatment-emergent adverse event
TOEP(H)	(heterogeneous) Toeplitz
UN	unstructured
vAUC	viral area under the curve (as determined by qPCR)
WBC	white blood cells
WI	work instruction

DEFINITION OF TERMS

case report form (CRF)	A printed, optical, or electronic document designed to record protocol required information to be reported to the sponsor for each trial subject.
display	Analysis table, figure or listing
phase	Interval of time in the planned conduct of a study associated with a specific purpose: for example, screening, treatment, follow-up.
study drug	Pharmaceutical form of an active ingredient or placebo, being tested or used as a reference in a clinical study.
treatment-emergent abnormality	Any post-baseline abnormality that was not present at baseline (e.g. haemoglobin normal at baseline and grade 1 post-baseline; glucose grade 1 at baseline and grade 3 post-baseline). Abnormalities in vaccination phase are evaluated versus vaccination baseline. Post-challenge abnormalities are evaluated versus challenge baseline.
Within 2 consecutive days	Whenever in the endpoint definition it is mentioned that two positive samples/symptoms have to occur 'within 2 consecutive days', this includes the following cases:

Day x am	**Day x pm**	**Day x+1 am**	**Day x+1 pm**	
pos	**pos**	neg	neg	Two consecutive + on the same day
neg	**pos**	**pos**	neg	Two consecutive + on consecutive days
pos	neg	neg	**pos**	Two + on two consecutive days with intermittent - sample(s)

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1. INTRODUCTION

This SAP describes the statistical analysis to be performed for the final analysis of protocol FLU010, Efficacy of MVA-NP+M1 in the Influenza H3N2 Human Challenge Model.

This SAP specifies the analysis displays to be presented and describes the methods and procedures in a more elaborated way than in the statistical methods section of the protocol.

The statistical analysis will process and present the results following the International Council for Harmonisation (ICH) standards, in particular the ICH-E3, ICH-E6, and ICH-E9 guidelines.

1.1 STUDY OBJECTIVES

According to the protocol, the primary objective of this 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 area under the curve (AUC) as determined by quantitative polymerase chain reaction (qPCR)).

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.

According to the protocol, the secondary objectives of this study are to determine:

- The incidence in each group (MVA-NP+M1 and saline Placebo) of laboratory-confirmed influenza (qPCR or culture)
- 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

According to the protocol, 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
- To determine the epigenetic response of different cell subsets to influenza infection.

1.2 STUDY DESIGN

This is a randomized, single-centre, double blind study. The study screens healthy volunteers and only enrolls those with microneutralisation test (MNT) < 20. The study consists of an outpatient vaccination phase, and at least 6 weeks later an inpatient challenge phase.

155 participants are randomized 3:2 to receive either MVA-NP+M1 (N=93) or Placebo (N=62) by intramuscular injection in the non-dominant arm deltoid. Vaccination-related local and systemic symptoms are followed by participant-directed diary cards for 7 days, and unsolicited adverse events are followed throughout the study from consent signature.

A total of 80 participants from the MVA-NP+M1 group and 54 from the saline Placebo group are challenged. Participants enter the quarantine facility on Day -2 or Day -1 and are discharged on Day 11. Participants receive a single intranasal administration of the H3N2 challenge agent via nasal spray. Challenge-related local and systemic symptoms are followed up to twice a day using investigator-directed symptom score cards for 11 days.

The schedule of assessments is in section 9.4.1 for the vaccination period and in section 9.4.2 for the challenge period.

1.3 EXPECTED 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 worst-case scenario a 25% reduction, or that the final numbers to undergo challenge 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).

1.4 RANDOMISATION AND BLINDING

As participants are confirmed to be eligible for the study, they are 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 are not included in the final database but recorded in a separate screening log. The failure details are documented in the 'participants' file.

Participants are assigned to 1 of 2 treatment groups. Allocation of each participant to a given treatment group is 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 is generated using randomly permuted blocks and is not stratified. Participants are randomised 3:2 to receive either MVA-NP+M1 or saline Placebo, with total enrolment of approximately 155 participants at an allocation of 93 to 62. 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, prepares the study vaccine that corresponds to the assigned participant randomization number. The recruiters calling vaccinated participants back to quarantine, are also blinded to the study status, therefore the Statistical Centre supplies the list of participants to be called to undergo challenge and quarantine.

The randomization list is retained by SGS Life Sciences Secure Data Office until the end of the study (database lock). One copy of the randomization list is sent in a sealed envelope to the site pharmacist before the start of the study.

One copy of code breaking envelopes is made available to the clinical site, to be used only in case of emergency. The reason for unblinding is documented in the appropriate section of the eSource. Participants who are unblinded for any reason during their participation in the study are not to be replaced and are withdrawn immediately from the study (except for safety monitoring).

1.5 INTERIM ANALYSIS

No formal interim analyses are planned. Topline results will be presented before database lock, with unblinding at group level only. TLFs to be included in this analysis are identified in section 8.

1.6 SOFTWARE

SAS version 9.4 or later will be used for programming.

1.7 VALIDATION MODEL

SGS Life Sciences (SGS LS) – Clinical Research statistics (STAT) standard operating procedures (SOPs) and work instructions (WIs) as effective at the project start will be followed throughout the project, provided the applicable regulatory requirements are still met.

The primary endpoint tables will be validated according to Model C: review by an independent person and independent programming. All other analysis tables/figures/listings will be validated according to Model B: review by an independent person (see SOP.STAT.020).

2. EFFICACY AND IMMUNOGENICITY ANALYSES

2.1 EFFICACY

2.1.1 Available data

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 using quantitative polymerase chain reaction (qPCR) and culture. Culture is only done for positive qPCR samples.

The following symptoms of influenza-related infection will be collected twice a day (except for lymphadenopathy, which will be collected once a day only) from Day 1 to Day 11 of challenge on a symptom score card (SSC):

- Local symptoms:
  - Nose (4): nasal congestion (blocked nose), runny nose, sneezing frequency, sinus pressure/pain or facial pain
  - Throat (2): sore throat, difficulty swallowing
  - Eyes (3): tearful/watery eyes, painful eyes, aversion to light
  - Chest/respiratory (3): dry cough, productive (wet) cough, difficulty breathing/tight chest
- General symptoms:
  - Gastrointestinal (4): nausea, stomach ache, vomiting, diarrhoea
  - Body/systemic (12): dizziness, head congestion, headache, muscle aches, feverish, chills or shivering, lack of appetite, felt cold, sweating, tiredness/weakness, sleeping more than usual, lymphadenopathy
  - The following symptoms will only be questions if at least 2 other symptoms with grade 2 or higher are present: nausea, stomach ache, vomiting, diarrhoea, tiredness/weakness, sleeping more than usual.

Each symptom's severity is graded from 0 (absent) to 3 (grade 3 - severe).

Additionally, the SSC also contains the question whether the subject feels well enough to go to work today (yes/no).

Oral body temperature is assessed daily during confinement as part of the vital signs evaluation. During this same period, tissue collection is planned daily to measure daily mucus production.

2.1.2 Endpoints and derivation rules

2.1.2.1 PRIMARY ENDPOINT

Primary endpoint is the viral area under the curve (vAUC) based on the qPCR values. AUC will be calculated using the linear trapezoidal rule, by summing all individual trapezoids, which will be calculated as follows:

$AUC_{ti\text{-}ti+1} = 1/2*(L_i + L_{i+1})*(t_{i+1} - t_i)$.

Where:

- L_i is the log-transformed viral load concentration at time point t_i.
- All time points (including unscheduled time points) from day 2 to day 10 will be considered.
- AUC will be calculated in hours, using actual datetimes of qPCR assessments.
- AUC will be rounded as detailed in section 5.3.4.
- Missing values will be imputed as detailed in section 5.3.1.

2.1.2.2 SECONDARY ENDPOINTS

The following secondary endpoints will be derived:

- Attack rate: a successful attack is defined as having at least two positive swabs (derived for both qPCR and culture) within the timespan of two consecutive days
- Time to start of viral shedding (hours) = (datetime of first of two positive swabs within 2 consecutive days - challenge datetime)/(60*60)
  - Time will be rounded as detailed in section 5.3.4
  - All time points (including unscheduled time points) from day 2 to day 10 will be considered.
  - Subjects not having at least two positive swabs (within 2 consecutive days) will be censored on the last viral load assessment
  - This endpoint will be derived for both qPCR and culture
- Peak viral shedding = highest viral load concentration
  - All time points (including unscheduled time points) from day 2 to day 10 will be considered.
  - Subjects not having at least two positive swabs (within 2 consecutive days) will be excluded from this analysis (peak viral shedding not calculated).
  - This endpoint will be derived for both qPCR and culture

- Time to peak of viral shedding (hours) = (datetime of highest viral load concentration - challenge datetime)/(60*60)
  - Time will be rounded as detailed in section 5.3.4
  - All time points (including unscheduled time points) from day 2 to day 10 will be considered.
  - In case of identical peak values, the first in time will be considered.
  - Subjects not having at least two positive swabs (within 2 consecutive days) will be censored on the last viral load assessment
  - This endpoint will be derived for both qPCR and culture
- Time to cessation of viral shedding (hours) = (datetime of first negative swab following the last positive swab - challenge datetime)/(60*60)
  - Time will be rounded as detailed in section 5.3.4
  - All time points (including unscheduled time points) from day 2 to day 10 will be considered.
  - Subjects not having at least two positive swabs (within 2 consecutive days) will be excluded from this analysis (time to cessation not calculated).
  - An event is defined as having two consecutive negative swabs not followed by a positive swab. Subjects without an event will be censored on the last viral load assessment.
  - This endpoint will be derived for both qPCR and culture
- Duration of viral shedding (hours) = (datetime of first negative swab following the last positive swab - datetime of first positive of two positive swabs within 2 consecutive days)/(60*60)
  - Duration will be rounded as detailed in section 5.3.4
  - All time points (including unscheduled time points) from day 2 to day 10 will be considered.
  - Subjects not having at least two positive swabs (within 2 consecutive days) will be excluded from this analysis (duration of viral shedding not calculated).
  - The end of viral shedding is defined as two consecutive negative swabs not followed by a positive swab. If this does not occur, the end of viral shedding will be set to the last viral load assessment.
  - This endpoint will be derived for both qPCR and culture
- vAUC based on culture values will be derived following the same rules as for the primary endpoint

- Rate of virologically confirmed ILI: virologically confirmed ILI is defined as having a positive swab and a respiratory or flu-like symptom occurring on two consecutive days
  - A positive swab is defined as a positive qPCR.
  - All time points (including unscheduled time points) from day 2 to day 10 will be considered.
  - Positive swab and flu-like symptom have to occur on the same two consecutive days.
  - Respiratory or flu-like symptom can be any of the following signs or symptoms collected on the SSC: runny nose, sneezing frequency, sinus pressure/pain or facial pain, sore throat, difficulty swallowing, teary/watery eyes, painful eyes, aversion to light, dry cough, productive (wet) cough, difficulty breathing/tight chest, feverish, chills or shivering, sweating, lymphadenopathy
- Overall SSC AUC
  - AUC will be derived following the same rules as for the primary endpoint and rounded as detailed in section 5.3.4
  - SSC AUC will be calculated using the overall SSC score
  - Overall SSC score = arithmetic mean of all items
  - As lymphadenopathy is assessed only once a day, the value collected for that day will be used for both the AM and PM assessments in the calculation of SSC score.
  - Missing items will be handled as detailed in section 5.3.1

2.1.2.3 EXPLORATORY ENDPOINTS

The following secondary endpoints will be derived:

- Time to start of symptoms (hours) = (datetime of first of two non-zero overall SSC scores within 2 consecutive days - challenge datetime)/(60*60)
  - Time will be rounded as detailed in section 5.3.4
  - Subjects not having at least two non-zero overall SSC scores (within 2 consecutive days) will be censored on the last evaluable SSC assessment
- Peak symptoms = highest overall SSC score
  - Pre-challenge time points will not be considered.
  - Peak overall SSC score will be rounded as detailed in section 5.3.4
  - Subjects not having at least two non-zero overall SSC scores (within 2 consecutive days) will be excluded from this analysis (peak symptoms not calculated).

- Time to peak of symptoms (hours) = (datetime of highest overall SSC score - challenge datetime)/(60*60)
  - Time will be rounded as detailed in section 5.3.4
  - In case of identical peak values, the first in time will be considered.
  - Subjects not having at least two non-zero overall SSC scores (within 2 consecutive days) will be censored on the last evaluable SSC assessment
- Time to cessation of symptoms (hours) = (datetime of first zero overall SSC score following the last non-zero overall SSC score - challenge datetime)/(60*60)
  - Time will be rounded as detailed in section 5.3.4
  - Subjects not having at least two non-zero overall SSC scores (within 2 consecutive days) will be excluded from this analysis (time to cessation not calculated).
  - An event is defined as having two consecutive zero overall SSC scores not followed by a non-zero overall SSC score. Subjects without an event will be censored on the last evaluable SSC assessment.
- Time to feel well enough to go to work (hours) = (datetime of first positive answer (yes) following the last no answer - challenge datetime)/(60*60)
  - Time will be rounded as detailed in section 5.3.4
  - Subjects not having at least two negative answers (no) (within 2 consecutive days) will be excluded from this analysis (time to feel well enough to go to work not calculated).
  - Subjects having a negative answer as last assessment (including subjects not having any positive answer) will be censored on the last assessment.
- Duration of symptoms (hours) = (datetime of first zero overall SSC score following the last non-zero overall SSC score - datetime of first of two non-zero overall SSC scores within 2 consecutive days)/(60*60)
  - Pre-challenge time points will not be considered.
  - Duration will be rounded as detailed in section 5.3.4
  - Subjects not having at least two non-zero overall SSC scores (within 2 consecutive days) will be excluded from this analysis (duration not calculated).
  - The end of symptoms is defined as two timepoints with zero overall SSC score not followed by a timepoint with non-zero overall SSC score. If this does not occur, the end of symptoms will be set to the last evaluable SSC assessment.

- Total days of fever = total number of days on which body temperature > 38°C
    - All time points (including unscheduled time points) from day 1 to day 11 will be considered, except for pre-challenge time points.
- Total mucus production (g) = (summed weight of all used bags + all used tissues + all returned clean tissues) - (summed weight of clean bags containing clean tissues)
    - Total mucus production will not be calculated for challenge cohorts 1 to 4 (due to problems with data collection for these cohorts).
    - Total mucus production will only be calculated in case all tissues were returned (sum of clean and used tissues returned should be 20 tissues for each bag).
    - Negative results for total mucus production within 2 SE of the mean result (within treatment group), will be set to zero.
- Local SSC score = arithmetic mean of local symptom items

  Missing items will be handled as detailed in section 5.3.1
- General SSC score = arithmetic mean of general symptom items

  Missing items will be handled as detailed in section 5.3.1

2.1.3 Inferential statistics

All statistical comparisons will be made using two-sided tests at the 0.05 significance level unless specifically stated otherwise. As this is a proof-of-concept study, no correction method for multiple testing is foreseen. P-values should thus be interpreted accordingly.

Difference between MVA-NP+M1 and placebo in AUC (qPCR vAUC - primary analysis, culture vAUC, overall, local and general SSC AUC) and peak viral shedding/symptoms will be analysed using a Mann-Whitney U test. Additionally, adjusted difference between MVA-NP+M1 and placebo in AUC (qPCR vAUC, culture vAUC and overall SSC AUC) will be analysed using an ANCOVA model with treatment, sex, time since vaccination (see section 4.6.2) and challenge cohort as covariates.

Difference between MVA-NP+M1 and placebo in attack rate and virologically confirmed ILI will be analysed using a Fisher exact test.

Time to parameters will be analysed using Kaplan-Meier time to event analysis, with a log-rank test to compare MVA-NP+M1 and placebo.

Difference between MVA-NP+M1 and placebo in total days of fever will be tested using a zero inflated Poisson model.

Difference between MVA-NP+M1 and placebo in total mucus production will be tested with a t-test. Normality will be tested using a Shapiro-Wilk test. In case normality or homogenity of variances asumption are not valid, a Mann-Whitney U test will be used.

Difference between MVA-NP+M1 and placebo in overall SSC changes from baseline will be analysed using a mixed model for repeated measurements (MMRM). The

model will include treatment, sex, challenge cohort, timepoint and treatment by timepoint interaction terms as fixed effects, with baseline value and time since vaccination (see section 4.6.2) as covariates. Within-subject correlation will be modeled by assuming an unstructured (UN) covariance matrix for the error terms. If the model does not converge upon using UN, the following covariance structures will be tested for convergence (in order): heterogeneous Toeplitz (TOEPH), heterogeneous autoregressive first order (ARH(1)), heterogeneous compound symmetry (CSH), Toeplitz (TOEP), autoregressive first order (AR(1)) and compound symmetry (CS).

A similar MMRM model will be used for viral load (qPCR and culture) actual values, without the baseline covariate.

ANCOVA and MMRM models contain time since vaccination and challenge cohort, which are potentially highly correlated. This will be assessed by calculating the variance inflation factor in a regression model. In case of multicollinearity (max(VIF) > 10), challenge cohort will be dropped from the models.

No adjustment will be made for multiplicity

SAS code can be found in section 9.1.

2.1.4 Presentation of results

2.1.4.1 qPCR viral shedding

qPCR vAUC table will show descriptive statistics and the p-value of the Mann-Whitney U test for comparison of MVA-NP+M1 and placebo (primary analysis). Additionally, a table will report the results of the ANCOVA model, including the least square means per treatment group with 95% CI, least square mean differences (MVA-NP+M1 - placebo) with 95% CI and 2-sided p-value for testing differences between treatment groups.

Log qPCR and culture values and SSC scores will be summarised by means of descriptive statistics at each timepoint. Actual values and changes will be tabulated separately. The adjusted means by treatment group at each timepoint from the MMRM will be tabulated and presented graphically.

A frequency tabulation will show the number and percentage of successful attacks, with exact 95% CI and will also report the Fisher exact p-value for comparison of MVA-NP+M1 and placebo (secondary analysis). A similar table will also be created for virologically confirmed ILI.

For time to start/peak/cessation of viral shedding/feel well enough to go to work, the following results will be reported: number and percentage of events, number and percentage of censored observations, Q1, median and Q3 time with 95% CI and p-value (MVA-NP+M1 vs. placebo) using log-rank test.

Duration of viral shedding and peak viral shedding tables will show descriptive statistics and for peak viral shedding also the p-value of the Mann-Whitney U test for comparison of MVA-NP+M1 and placebo.

A listing will be prepared showing all derived parameters and the log qPCR values.

Mean (SE) log qPCR and culture values and SSC overall score over time will be plotted. For all three time to parameters, Kaplan-Meier plots will be prepared.

A list of tables, figures and listings can be found in section 8

2.1.4.2 CULTURE VIRAL SHEDDING

The same viral shedding parameters as calculated based on qPCR values will be calculated based on culture values and will be presented in an identical way.

A list of tables, figures and listings can be found in section 8

2.1.4.3 INFLUENZA SYMPTOMS

Overall, local and general SSC AUC tables will show descriptive statistics and the p-value of the Mann-Whitney U test for comparison of MVA-NP+M1 and placebo. Additionally, a table will report the results of the ANCOVA model, including the least square means per treatment group with 95% CI, least square mean differences (MVA-NP+M1 - placebo) with 95% CI and 2-sided p-value for testing differences between treatment groups.

Overall, local and general SSC scores will be summarised by means of descriptive statistics at each timepoint. Actual values and changes will be tabulated separately. The adjusted means by treatment group at each timepoint from the MMRM will be tabulated and presented graphically.

For time to start/peak/cessation of symptoms/feel well enough to go to work, the following results will be reported: number and percentage of events, number and percentage of censored observations, Q1, median and Q3 time with 95% CI and p-value (MVA-NP+M1 vs. placebo) using log-rank test.

Duration of symptoms and peak symptoms tables will show descriptive statistics and for peak symptoms also the p-value of the Mann-Whitney U test for comparison of MVA-NP+M1 and placebo.

Total days of fever table will show descriptive statistics and the p-value of the zero-inflated Poisson model.

Total mucus production table will show descriptive statistics and the p-value of the Student t-test/Mann-Whitney U test.

A listing will be prepared showing all SSC derived values and scores at each analysis visit. A separate listing will be created for fever and total mucus production, showing total days of fever and body temperature at each analysis visit and total mucus production.

Distinct Mean (SE) plots over time will be created for overall, local and general SSC scores. For all three time to parameters, a Kaplan-Meier plot will be prepared.

A list of tables, figures and listings can be found in section 8

2.2 IMMUNOGENICITY

2.2.1 Available data

T cell response is assessed using a double-colour enzymatic (DCE) ELISpot assay for IFN gamma and granzyme B on the peripheral blood mononuclear cell (PBMC)

samples, taken on day 0, day 8 and day 28 of the vaccination period and day -1 and day 28 of the challenge period. For each of IFN gamma and granzyme B, three stimulation antigens will be assessed: NP (4 pools), M1 (2 pools) and a negative control (DMSO). For each pool, the number of spot-forming colonies (SFC) per well (i.e. 200,000 cells) will be reported for two replicate wells.

ELISpot assay results will possibly not be available for the final analysis. In that case, analyses of the T cell response described below will not be done.

Antibody responses are evaluated with micro neutralization (MNT) and hemagglutination inhibition (HI) tests, done at screening (MNT only) and day -1 and day 28 of the challenge period.

2.2.2 Derivation rules

T cell response results will be averaged over all replicates within each pool, then background subtracted (set to 0 if negative) and finally added across all pools within each antigen as follows (XX being either NP or M1):

- Background subtracted T cell response result for pool Y of antigen XX (SFC/well) =
  $BGsub_{xx}^{y}$ =
  average within pool Y of antigen XX – averaged negative control (DMSO) result
- Background subtracted T cell response result for antigen XX (SFC/10^6 cells) =

  $$BGsub_{xx} = 5 \times \sum_{n=1}^{k} \max(BGsub_{xx}^{n}, 0)$$

  (k is the number of pools within the antigen XX)
- Background subtracted T cell response result for NP+M1 (SFC/10^6 cells) = $BGsub_{NP} + BGsub_{M1}$

Negative control T cell response results will be averaged over all replicates and multiplied by 5 (to get SFC/10^6 cells).

T cell responder status will be derived using the Permutation-based Resampling (PR) method (Hudgens et al., 2004). See also SAS code in appendix. Briefly, for each of the NP and M1 peptide pools, an unadjusted p-value will be calculated by comparing the observed SFCs/well from the corresponding peptide pool replicate wells against the negative control replicate wells using a two-sample t-test. Next, within each antigen (NP or M1) the observed SFCs/well will be permuted across all the peptide pool and negative control wells 100,000 times, with unadjusted p-values calculated for each permuted replication. The lower of the two p-values will be retained as the permutation-adjusted p-value for each replication. Finally, for each of the peptide pools, the permutation-adjusted p-value will be calculated as the proportion of times when the permutation-adjusted p-value is less than the peptide pool-specific unadjusted p-value. This approach can only provide statistically significant results when there is an adequate number of permuted outcomes.

If a permutation-adjusted p-value of any of the pools within the antigen is less than 0.05, then the subject will be considered a responder for that antigen.

2.2.3 Inferential statistics

The difference in background subtracted T cell response results on Day 8 and on Day 28 between MVA-NP+M1 and placebo will be analysed using an analysis of covariance (ANCOVA) model with treatment as factor, baseline as covariate and the interaction of both. Difference in LS means and corresponding 95% CI will be reported. This will be done separately for the vaccination and challenge period and for Day 8 and on Day 28. The same model will be repeated for the change from baseline in background subtracted T cell response results.

The difference in T cell response status on Day 8 and on Day 28 between MVA-NP+M1 and placebo will be analysed using a Fisher exact test.

The difference in antibody response results on Day 28 between MVA-NP+M1 and placebo will be analysed using an analysis of covariance (ANCOVA) model on the log-transformed results with treatment as factor and baseline as covariate and the interaction of both. Difference in LS means and corresponding 95% CI will be back-transformed to obtain the geometric mean ratio and corresponding 95% CI.

2.2.4 Presentation of results

To assess the impact of missing DMSO replicates, all tables and figures on T-cell response will be prepared on two subsets of data (evaluated separately for NP and M1):

- Samples with at least 1 result
- Subset above, excluding samples with only 1 DMSO replicate result

Background subtracted and negative control T cell response results (IFN-gamma and granzyme B results; separately for NP, M1, NP+M1) will be summarised by means of descriptive statistics at each analysis visit. This will be done separately for the vaccination and challenge period. Actual values and changes from baseline will be tabulated separately.

T cell responder status will be presented in a frequency table at each analysis visit, separately for vaccination and challenge period.

Antibody response results will be summarised by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be tabulated separately. The ratio (MVA-NP+M1 / placebo) of the geometric means will also be shown with corresponding 95% CI.

Correlation of T cell responses, as assessed by the mean increase from baseline to post vaccination at day 8 and day 28 (for IFN-gamma and granzyme B results; separately for NP, M1, NP+M1), to the primary endpoint, symptom scores, and influenza incidence will be explored graphically, including Spearman correlation coefficients.

Graphs of the median actual values over time will be prepared for background subtracted and negative control IFN-gamma and granzyme B results (separately for NP, M1, NP+M1).

3. SAFETY ANALYSES

3.1 ADVERSE EVENTS AND SOLICITED SYMPTOMS

3.1.1 Available data

Unsolicited adverse events (AEs) are coded into system organ classes and preferred terms using the medical dictionary for regulatory activities (MedDRA). For each AE, start and stop dates and times are collected as well as severity (grade 1 to grade 5), a seriousness flag, an AE of special interest (AESI) flag (i.e. events which could have an autoimmune origin), treatment relatedness (both to treatment and challenge agent), action taken towards the study drug and outcome.

The following solicited symptoms will be collected:

- Day 1 to Day 7 following vaccination (patient diary):
  - Local symptoms: pain, redness, induration (swelling), warmth, pruritis (itching)
  - Systemic symptoms: feverishness, chills, fatigue, myalgia/arthralgia (muscle/joint pain), headache, nausea, malaise, temperature
- Day 1 to Day 11 following challenge (SSC):
  - Local symptoms: nasal congestion (blocked nose), runny nose, sneezing frequency, sinus pressure/pain or facial pain, sore throat, difficulty swallowing, teary/watery eyes, painful eyes, aversion to light, dry cough, productive (wet) cough, difficulty breathing/tight chest
  - Systemic symptoms: dizziness, head congestion, headache, muscle aches, feverish, chills or shivering, lack of appetite, felt cold, sweating, nausea, stomach ache, vomiting, diarrhoea, tiredness/weakness, sleeping more than usual, lymphadenopathy

    The following symptoms will only be questions if at least 2 other symptoms with grade 2 or higher are present: nausea, stomach ache, vomiting, diarrhoea, tiredness/weakness, sleeping more than usual.

Solicited symptoms clearly not related to the treatment/challenge are captured as adverse events in the clinical database. Therefore, events captured as solicited symptoms in the clinical database are always considered (at least possibly) related to the treatment/challenge. Each symptom's severity is graded from 0 (absent) to 3 (grade 3 - severe), except for redness and temperature, which are reported in mm for longest diameter and °C respectively.

3.1.2 Derivation rules

Redness and temperature will be graded as follows:

Grade	Redness (mm)	Temperature (°C)
Normal (0)	< 25	< 38.0
Grade 1	25-50	38.0-38.4
Grade 2	51-100	38.5-38.9
Grade 3	> 100	39.0-40.0
Grade 4		> 40.0

Treatment-emergent adverse events (TEAE) are defined as AEs starting during or after first administration of any study drug. Treatment-emergent (TE) solicited symptoms are defined as solicited symptoms reported from Day 1 on.

Based on their start date and time, AEs will be allocated to the phase during which they started. Each AE will therefore be reported in only one phase. (See section 5.2.1 for further information about study phases). In case the AE start date or time is incomplete or missing and the AE could consequently be allocated to more than one phase, the AE will be allocated to the treatment phase unless the available parts of the AE start or stop date(time) provide evidence for allocating to the non-treatment phase (screening / challenge / follow-up).

Some of the final safety presentations will include the number of reported events during the trial's analysis phases, not only the number of subjects who reported at least one event. Any change in AE severity is reflected by a new AE record being entered in the safety database. As such, the number of events could be inadvertently overreported due to the way in which AE records are captured within the safety database.

Overlapping/consecutive (unsolicited) events are defined as events occurring in the same subject with the same MedDRA preferred term and primary system organ class that have at least one day overlap or for which the start date of an event is one day

after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

- In case overlapping/consecutive events start within a single phase (see section 5.2.1 for further information about study phases.), they are considered as one and the same AE. The individual events that contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, end, phase and total duration. They are counted/presented as one event in TLFs.
- In case overlapping/consecutive events start both in the challenge phase and in the follow-up phase, they are allocated to the active phase only (challenge phase) and are considered as one and the same AE. The individual events that contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, end, phase and total duration. They are counted/presented as one event in TLFs.
- In all other cases, overlapping/consecutive events are allocated to their respective phase and are considered as separate AEs. Examples of this are events starting both in the screening phase and in the vaccination phase or both in the vaccination phase and in the challenge phase.
- Remarks:
  - Events can only be combined into one and the same AE if both start dates and the stop date of the first event are known.
  - In case the completely missing end date is imputed (for phase allocation), this date is also considered as a complete date.
  - Time of day is not considered when determining overlap of events, only start and stop dates.

Below example illustrates above rules. Both events occur in the same subject, for whom the follow-up phase starts on 07SEP2019T00:00.

SDTM:

AEPT	**AEREL**	**AESEV**	**AESTDTC**	**AEENDTC**
HEADACHE	Y	1	06SEP2019T19:30	07SEP2019T08:40
HEADACHE	N	3	07SEP2019T10:00	07SEP2019T15:20

ADaM:

AEPT	**AEREL**	**AESEV**	**AESDTM**	**AEEDTM**	**AEDUR**	**APHASE**
HEADACHE	Y	1	06SEP2019T19:30	07SEP2019T15:20	2	CHALLENGE
HEADACHE	N	3	06SEP2019T19:30	07SEP2019T15:20	2	CHALLENGE

AE tables:

	Number of subjects	**Number of events**
Grade ≥3 AEs	1	1
Related AEs	1	1
Related Grade ≥3 AEs	0	0

Consecutive solicited events are defined as events occurring in the same subject with the same symptom name that occurs on consecutive days. These are combined into one AE, according to the following rules:

- Only the assessment day, as identified by QS.VISIT is used. For solicited events after challenge, am/pm information is not taken into account for the combination of events.

Day 3 am	Day 3 pm	Day 4 am	Day 4 pm	Day 5 am	Counted as
grade 1	grade 0	grade 0	grade 2	grade 1	1 event of grade 2
grade 1	grade 1	grade 0	grade 0	grade 2	2 events

- In case of missing intermittent assessments, it is assumed the event is still present on the missing days.

Treatment relatedness will be dichotomised as follows in tables:

- Treatment related: at least possibly related or missing
- Not treatment related: not related, unlikely

AE onset and duration will be calculated as follows when start and stop dates are fully known:

- AE onset day (vs. vaccination) = AE start date – date of vaccination + 1 day
- AE onset day (vs. challenge) = AE start date – date of challenge + 1 day
- AE duration (days) =
  - AE end date – AE start date + 1 day
  - study discontinuation/completion date – AE start date + 1 day (when the AE start date is fully known but the AE is not resolved at the end of the study)

    In this case the duration will be presented as “>x days” , x being the duration of the AE calculated by the end of the study.

3.1.3 Presentation of results

Tables will present TEAEs only. Pre-treatment AEs and follow-up AEs will only be listed. All tables will be presented by analysis phase (vaccination / challenge). Analysis phases are defined in section 5.2.1.

An overview table will show the number and percentage of participants with at least one event and the number of events for the following:

- TEAEs
- Solicited symptoms
- TEAEs or solicited symptoms
- Local solicited symptoms
- Local grade 3 solicited symptoms
- Systemic solicited symptoms
- Systemic grade 3 solicited symptoms
- Treatment-emergent AESI
- Serious TEAEs
- Non-serious TEAEs
- Grade ≥ 3 TEAEs
- Treatment-emergent grade ≥ 3 laboratory toxicity (see section 3.2.2)
- Fatal TEAEs
- TEAEs related to treatment (vaccination phase)
- TEAEs related to challenge (challenge phase)
- Serious TEAEs related to treatment (vaccination phase)
- Serious TEAEs related to challenge (challenge phase)
- Grade ≥ 3 TEAEs related to treatment (vaccination phase)
- Grade ≥ 3 TEAEs related to challenge (challenge phase)
- TEAEs for which the study was discontinued

Summary tables by MedDRA system organ class and preferred term will show the number and percentage of subjects with at least one event. The table of TEAEs will additionally show the number of events.

Separate tables will be prepared for the following:

- TEAEs
- Treatment-emergent AESI
- Serious TEAEs
- Non-serious TEAEs
- Grade ≥ 3 TEAEs
- TEAEs by worst severity
- Treatment related TEAEs
- Serious treatment related TEAEs
- TEAEs for which the study was discontinued

A summary table by symptom will show the number and percentage of participants with at least one symptom, overall, by type (local/systemic) and by symptom. The

table of solicited symptoms will additionally show the number of events. Distinct tables will be prepared for the following:

- solicited symptoms
- grade 3 solicited symptoms
- solicited symptoms by worst severity

All AEs, including pre-treatment events will be listed. Separate listings will be prepared for serious AEs, AEs for which the study was discontinued and fatal AEs. A listing showing all coding information will be prepared as well. Listings will also be prepared for solicited symptoms and grade 3 solicited symptoms.

More details can be found in the list of tables and listings (see section 8)

3.2 CLINICAL LABORATORY EVALUATION

3.2.1 Available data

Per protocol, the following laboratory parameters are expected:

- 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)

Normal ranges are available as provided by the laboratory.

3.2.2 Derivation rules

Toxicity grades will be computed according to the Centre for Biologics Evaluation and Research (CBER) toxicity grading list. The implementation of these toxicity grades for analysis is presented in appendix 9.2. Only the parameters described in appendix 9.2 will be computed, according to the declared limits for each grade.

For parameters for which no toxicity grades are defined, the following abnormality categories will be defined:

- Low: value < lower limit of normal range
- Normal: lower limit of normal range ≤ value ≤ upper limit of normal range
- High: value > upper limit of normal range

Note:

- Classification will be done in standardised units, using non imputed values and limits.
- For the worst-case analysis visit, as defined in section 5.2.5, an additional category low + high is defined in case there are both low and high values within the same phase.

3.2.3 Presentation of results

The statistical analysis will present results in standardised units.

Continuous laboratory parameters will be summarised by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be tabulated separately. Categorical parameters will be listed only.

Laboratory toxicity grades will be presented as cross-tabulations of the toxicity at each post-baseline analysis visit and at the worst-case analysis visit versus the baseline toxicity. Numbers and cumulative numbers of subjects with treatment-emergent toxicities will also be shown. Parameters having toxicity grades defined in both directions (hypo and hyper) will be shown by direction.

For laboratory parameters, laboratory abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit and at the worst-case analysis visit versus the baseline abnormality. Numbers of subjects with treatment-emergent abnormalities will also be shown.

All laboratory data will be listed, but only for subjects with any post-baseline abnormality or clinical significant value.

Box plots over time of the actual values and of the changes will be prepared for the following parameters: WBC counts and % lymphocytes counts.

3.3 VITAL SIGNS

3.3.1 Available data

The following vital signs parameters are collected: pulse rate, systolic (SBP) and diastolic blood pressure (DBP) in supine position, body temperature, oxygen saturation.

3.3.2 Derivation rules

Abnormalities are defined in below table.

Vital sign	**Pulse rate (bpm)**		**SBP (mmHg)**		**DBP (mmHg)**	**Temp (°C)**
Abnormality	**Tachy cardia**	**Brady cardia**	**Hyper tension**	**Hypo tension**	**Hyper tension**	**Fever**
Normal	55-100	55-100	90-140	90-140	≤ 90	
Grade 1	101-115	50-54	141-150	85-89	91-95	38.0-38.4
Grade 2	116-130	45-49	151-155	80-84	96-100	38.5-38.9
Grade 3	> 130	< 45	> 155	< 80	> 100	39.0-40.0
Grade 4						> 40.0

3.3.3 Presentation of results

All tables will be presented by analysis phase (vaccination / challenge). Analysis phases are defined in section 5.2.1.

Vital signs parameters will be summarised by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be tabulated separately.

Abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit versus the baseline abnormality and as cross-tabulations of the worst-case abnormality versus the baseline abnormality. Numbers of subjects with treatment-emergent abnormalities will also be shown.

All vital signs data will be listed, but only for subjects with any post-baseline abnormality or clinical significant value.

3.4 ELECTROCARDIOGRAMS

3.4.1 Available data

The following electrocardiogram (ECG) parameters will be collected: heart rate (HR), QRS interval, PR interval, QT interval and corrected QT interval (Fridericia).

3.4.2 Derivation rules

Abnormalities for HR, QRS and PR interval are defined in below table.

	HR (bpm)	**PR (ms)**	**QRS (ms)**
Low	< 40	< 110	-
Normal	40-100	110-220	≤ 120
High	> 100	> 220	> 120

Note: For the worst-case analysis visit, as defined in section 5.2.5, an additional category low + high is defined in case there are both low and high values within the same phase.

For QTc interval (ms), the following categories are defined:

- Actual values:
  - ≤ 450 (normal)
  -]450; 480]
  -]480; 500]
  - > 500
- Changes:
  - ≤ 30 (normal)
  -]30; 60]
  - > 60

Note: The worst-case, as defined in section 5.2.5, is the highest value and associated change.

3.4.3 Presentation of results

Uncorrected QT interval will only be listed.

Continuous ECG parameters will be summarised by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be tabulated separately.

Abnormalities of the actual values will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit, and at the worst-case analysis visit versus the baseline abnormality. Numbers and cumulative numbers (QTcF only) of subjects with treatment-emergent abnormalities will also be shown.

Abnormalities of the QTcF changes will be presented as tabulations of the change abnormality at each post-baseline analysis visit and at the worst-case analysis visit. Cumulative numbers of subjects with change abnormalities will also be shown.

All ECG data will be listed, but only for subjects with any post-baseline abnormality or clinical significant value or change.

3.5 LUNG FUNCTION

3.5.1 Available data

The following lung function parameters will be collected during the challenge period: FEV1 (L), FEV1 as % of predicted, FEV1/FVC ratio, FEV1/FVC ratio (%), FVC (L) and FVC as % of predicted.

3.5.2 Derivation rules

Not applicable

3.5.3 Presentation of results

FEV1 as % of predicted and FVC as % of predicted will be summarised by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be tabulated separately.

All lung function data will be listed.

3.6 PHYSICAL EXAMINATIONS

Abnormal physical examination findings will be listed.

4. GENERAL CHARACTERISTICS ANALYSES

4.1 SUBJECT DISPOSITION

The following subject data will be tabulated:

- The number of subjects in each analysis set
- Dates of first signed informed consent, last visit and last contact (overall only)
- The number and percentage of subjects who completed or discontinued the study and the number and percentage of subjects for each study discontinuation reason by phase (vaccination / challenge)

All information collected in the CRF concerning allocation, code breaking and study discontinuation and information on phases will be listed.

4.2 PROTOCOL DEVIATIONS AND ELIGIBILITY

The number and percentage of subjects with major protocol deviations will be tabulated, overall and per class of deviation.

All available information concerning major protocol deviations, violations on eligibility criteria and subjects not treated will be listed.

4.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

4.3.1 Available data

The following parameters will be available:

- Demographics: sex, race, height, weight at screening, date of birth, date of signing informed consent form (ICF),
- Tobacco history and smoking status
- Screening tests: serology, alcohol breath test and urine drug screen, pregnancy tests

4.3.2 Derivation rules

The following parameters will be derived:

- Age = (date of ICF - date of birth)/365.25

  Note: Age will be rounded as detailed in section 5.3.4.
- Body mass index (BMI) at screening (kg/m^2) = (weight at screening (kg)) / (height at screening (m))^2

  Note: Screening is defined in section 5.2.4. The BMI will be recalculated and rounded as detailed in section 5.3.4, even when already available in the database.

4.3.3 Presentation of results

Demographics will be presented using descriptive statistics for age, height, weight and BMI and frequency tabulations for sex, race and smoking status.

All demographic data will be listed. Listings will also be created for tobacco history, serology, alcohol breath test and urine drug screen and pregnancy tests.

4.4 MEDICAL HISTORY AND CONCOMITANT DISEASES

4.4.1 Available data

For each medical history and concomitant disease finding, a start and stop date or ongoing flag is collected.

4.4.2 Derivation rules

The following parameters will be derived:

- Medical history finding: not ongoing at the screening visit
- Concomitant disease finding: still ongoing at the screening visit

4.4.3 Presentation of results

All medical history and concomitant diseases data will be listed separately.

4.5 PRIOR AND CONCOMITANT THERAPIES

4.5.1 Available data

All therapies are coded using WHODrug. No ATC selection is performed. For each therapy, a start date or prior flag and stop date or ongoing flag are collected.

4.5.2 Derivation rules

Based on their start and stop date(time), prior and concomitant therapies will be allocated to each phase and period during which they were administered. A therapy can therefore be reported in more than one phase or period.

Phases and periods are defined in section 5.2.1. Therapies with (partially) missing dates will be allocated to each phase / period unless the available parts of the therapy start or stop date(time) provide evidence the therapy was not taken during that phase / period.

4.5.3 Presentation of results

All prior and concomitant therapies data will be listed.

4.6 EXPOSURE TO STUDY DRUG AND TREATMENT COMPLIANCE

4.6.1 Available data

Vaccination occurs in 7 cohorts, with an approximate 3-week interval. Subjects are vaccinated only once, but for each cohort, vaccination can occur on multiple scheduled dates. Challenge occurs at least 6 weeks later, in 8 cohorts, with a 3-week interval. In case the challenge cohort is different from the vaccination cohort, this is documented in a structured comment in the clinical database.

4.6.2 Derivation rules

Time between vaccination and challenge will be calculated in days as date of challenge - date of vaccination + 1

4.6.3 Presentation of results

The number and percentage of subjects who were vaccinated will be shown, both total and by vaccination cohort. A similar table will be prepared for the challenge. Time between vaccination and challenge will be be presented using descriptive statistics.

More details can be found in the list of tables and listings (see section 8)

5. GENERAL METHODOLOGY

5.1 ANALYSIS SETS

5.1.1 Analysis sets

The following analysis sets will be considered in the statistical analysis:

All randomised subjects set (RND):	subjects who were *randomised* into this study
Safety analysis set (SAF):	subjects who were *exposed* to the vaccine, according to the vaccine actually received
Intent-to-treat set (ITT)	randomised subjects who received the challenge inoculation, according to randomised treatment group
Per-protocol set (PP)	ITT subjects without any major protocol deviations impacting the primary endpoint and *remain in the quarantine facility for the full extent of the challenge phase*
Challenge safety set (CSAF)	randomised subjects who received the challenge inoculation, according to actual treatment received

Programming notes:

- Randomised is defined as having a complete randomisation date in the database or any information to confirm randomisation.
- Being exposed to the vaccine is defined as having a complete exposure date in the database or any information to confirm vaccination.
- If a subject does not remain in the quarantine facility for the full extent of the challenge phase, this will be reported as a major protocol deviation.
- Major protocol deviations impacting the primary endpoint will be flagged as such in the database.

Unless stated otherwise, the ITT will be used for the efficacy and immunogenicity tables, listings and figures. The SAF will be used for the safety and general characteristics tables, listings and figures. The primary efficacy analysis will be repeated on the PP and CSAF (only in case PP and/or CSAF differ from ITT).

5.1.2 As planned versus as actual analysis

For analyses done on the safety analysis set and challenge safety set, the actual treatment of the subject will be considered.

For all other analyses, the planned treatment will be used.

5.2 PHASES AND TIME POINTS

5.2.1 Phases

All events and assessments will be allocated to phases.

Phase	Start	End
Screening	Date of signing the ICF, with 00:00 added as time part	Vaccination date(time) – 1 minute
Vaccination	Vaccination date(time)	Challenge date(time) – 1 minute
Challenge	Challenge date(time)	End date of Day 28 post-challenge visit, with 23:59 added as time part
Follow-up	End of challenge phase + 1 minute	Date of last contact, with 23:59 added as time part

Per definition, and for each subject, the last available phase ends on the date of last contact (or the cut-off date for the topline analysis), with 23:59 added as time part.

AEs will be allocated to phases as described in section 3.1.2. All other assessments will be allocated to phases based on the assessment date(time).

In case of (partially) missing date(time) fields which cannot be allocated to a phase based on the available date(time) information, the visit label will be used to allocate to the correct phase. If this is not possible (unscheduled visits or visits on a turning point between phases), assessments will be allocated to the vaccination phase unless the available parts of the assessments start or stop date(time) provide evidence for allocating to the challenge/screening/follow-up phase.

5.2.2 Baseline and change from baseline

Baseline will be defined by phase.

The vaccination baseline value is the last available and non-missing value before the first administration of any study drug and will be used for data collected during the vaccination period.

The challenge baseline value is the last available and non-missing value before the administration of challenge inoculation and will be used for data collected during the challenge period.

Change from baseline is defined as follows:

Change from baseline at time point t = value at time point t – baseline value.

5.2.3 Relative day

Relative days (DY) will be calculated both with respect to the vaccination and to the challenge, according to the following rule:

- Concerned date < reference date: DY = concerned date – reference date
- Concerned date ≥ reference date: DY = concerned date – reference date + 1

The reference dates are the vaccination date and the date of challenge.

5.2.4 Analysis visits

For vaccination and challenge assessments on or after their respective reference datetime, the analysis will use the visits and time points indicated on the subject's case report form (CRF). Unscheduled assessments on or after the reference datetime will only be listed.

The screening value is the last available and non-missing value before vaccination. Reason for this approach is the use of retest results for subject eligibility assessment.

5.2.5 Worst-case

A worst-case analysis visit will be created for parameters for which abnormalities and/or toxicity grades are defined to summarise values considered as the worst-case. For abnormalities it is derived per parameter and in case both the lowest and the highest values are considered abnormal, a subject can have two worst-case analysis visits for a same parameter within each phase. For toxicity grades the worst-case is the value associated to the highest toxicity grade and is derived per parameter and toxicity direction (low / high).

Worst-case will be derived within each post-screening phase, including unscheduled assessments.

5.3 IMPUTATION AND ROUNDING RULES

5.3.1 Missing values

As culture is only done for positive qPCR values, missing culture results with a qPCR value 'not detected', will be considered as zero (log10).

For the calculation of AUCs, the following rules will be used to impute missing values:

- Intermittent missing values will be interpolated. This is implicitly done when using the linear trapezoidal rule.
- In case of trailing missing values, a triangle will be calculated to estimate the area between the timepoint of the last non missing value and the last scheduled assessment, which will be assumed to have a zero value.
- In case of leading missing values, a triangle will be calculated to estimate the area between the first non missing assessment and the first scheduled assessment, which will be assumed to have a zero value.
- In case of trailing missing values with no assessment datetime, the last scheduled assessment datetime will be imputed with challenge datetime + 10 days + 12 hours (for viral load) or + 11 days (SSC)
- In case of leading missing values with no assessment datetime, the first scheduled assessment datetime will be imputed with challenge datetime – 1 min + 1 day (viral load) or with challenge datetime – 1 min (SSC)

Overall/Local/General SSC score will only be calculated if sufficient signs and symptoms are available for each body system: 3/4 nose; 1/2 throat; 2/3 eyes; 2/3 chest/respiratory; 3/4 gastrointestinal and 8/12 body/systemic. Symptoms that are questioned if at least 2 other symptoms with grade 2 or higher are present should only be considered as missing if the condition is met and no value is available.

In case percentage of missing data exceeds 5% for qPCR viral load or for overall SSC, a sensitivity analysis will be done for the AUC based endpoints by using a placebo-based multiple imputation which assumes that all missing viral load concentrations/signs and symptom scores are missing not at random (MNAR). This approach can be considered conservative as subjects from the active treatment arm would adopt the outcome model estimated from the placebo arm.

For the safety analysis, no imputation will be done of missing values (i.e. observed cases analysis).

5.3.2 Handling partially or completely missing datetimes in calculations

Partially missing datetime of event will be imputed as follows for the calculation of AUC:

- Missing time will be imputed with challenge time - 5 min for morning samples and challenge time + 12 h for evening samples.
- Missing date will be imputed based on the scheduled timepoint: missing date on Day 3 = challenge date + 2 days

Partially missing date of event will be imputed as follows for the calculation of time to start and time to peak of viral shedding:

- Missing time will be imputed with challenge time - 5 min for morning samples and challenge time + 12 h for evening samples.
- Missing day will be imputed with 1
- Missing day and month will be imputed with 01JAN

Partially missing date of event will be imputed as follows for the calculation of time to cessation of viral shedding:

- Missing time will be imputed with challenge time - 5 min for morning samples and challenge time + 12 h for evening samples.
- Missing day will be imputed with last day of the month
- Missing day and month will be imputed with 31DEC

Partially missing start and stop dates of events will be imputed as follows for the calculation of duration of viral shedding:

- Missing time will be imputed with challenge time - 5 min for morning samples and challenge time + 12 h for evening samples.
- Missing start day will be imputed with 1
- Missing start day and month will be imputed with 01JAN
- Missing stop day will be imputed with last day of the month
- Missing stop day and month will be imputed with 31DEC

Note: If imputation of the start date results in a start date posterior to the stop date / anterior to challenge, the start date will be imputed with the stop date / challenge date respectively. If imputation of the stop date results in a stop date anterior to the start date / posterior to date of last contact, the stop date will be imputed with the start date / date of last contact respectively.

5.3.3 Values below or above a threshold

Safety values expressed as below (or above) the detection limit will be imputed by the value of the detection limit itself. Listings will always show the non-imputed values.

Viral load values reported as > XX will be imputed with XX. Viral load values reported as < XX will be imputed with XX/$\sqrt{2}$. For values reported as 'not detected', the log10 viral load will be imputed with 0.

Immunogenicity values reported as > XX will be imputed with XX. Immunogenicity values reported as < XX will be imputed with XX/2.

5.3.4 Rounding of derived variables

Derived variables will be rounded to the appropriate number of significant digits (see Definition of terms) at ADaM level:

- Age and BMI will be rounded to 1 decimal
- Log-transformed values will not be rounded.
- vAUC will be rounded to integer
- SSC score (and peak) and SSC AUC will be rounded to 2 decimals
- Time to and duration variables will be rounded to 1 decimal

All derivations will be done before rounding. Rounding will be done using the round half to even tie-breaking rule (see Definition of terms).

5.3.5 Outliers

There will be no outlier detection. All measured values will be included in the analyses.

5.4 PRESENTATION OF RESULTS

5.4.1 Calculation of descriptive statistics and percentages

For continuous parameters, full descriptive statistics will only be presented if there are at least 2 non-missing observations. Alternatively, only the number of non-missing data points and mean are shown.

Descriptive statistics will include the number of non-missing data points, the arithmetic mean, the standard deviation (SD), the median, minimum and maximum.

Descriptive statistics of efficacy parameters will additionally include standard error (SE) and 95% confidence interval (CI) on the mean (based on t-distribution, without continuity correction). Descriptive statistics of antibody response will show geometric mean and corresponding 95% confidence interval (CI) rather than arithmetic mean. Geometric mean and CI are calculated as the exponentials of the arithmetic mean and corresponding CI (based on t-distribution, without continuity correction) of the log-transformed data. Descriptive statistics of T cell response will show 95% CI on the median (based on ranks) and not on the mean.

Survival estimates will include the arithmetic mean with its SE, the median, first and third quartiles with their 95% CI, and the number of subjects who are assessed, censored and who have an event.

Mean, median, SE, SD and CI will be presented with one more decimal place than the individual values, with a maximum of 5 decimal places. Minimum and maximum will be presented with the same number of decimal places than the individual values, with a maximum of 4 decimal places.

P-values will be presented with four decimal places, ratios with three decimal places and test statistics with two decimal places.

For event-type data, the denominator will be all subjects in the analysis set and phase, unless specified otherwise, in which cases a footnote to the table will specify the denominator. All treatments will be shown, even if no events are present.

For frequency tabulations and cross-tabulations, missing values will not be included in the denominator count when computing percentages. For cross-tabulations of post-baseline results versus baseline results, a ‘missing’ category will be shown for baseline results if applicable.

Percentages will be shown with one decimal place.

5.4.2 Presentation of treatments

The following treatment labels will be used in the tables, listings and figures:

- PLACEBO
- MVA-NP+M1
- OVERALL

Overall is a grand total summarising all subjects over treatments, only shown for the general characteristics and adverse events analysis.

5.4.3 Ordering in tables, figures and listings

All tables will be presented per treatment, unless specified otherwise.

All listings will be ordered by treatment, subject, analysis visit and time point, unless specified otherwise.

6. CHANGES TO THE PLANNED ANALYSIS

6.1 CHANGES NOT COVERED BY PROTOCOL AMENDMENTS BEFORE DATABASE LOCK

NAP

6.2 CHANGES NOT COVERED BY PROTOCOL AMENDMENTS AFTER DATABASE LOCK

NAP

6.3 CHANGES TO THE FINAL STATISTICAL ANALYSIS PLAN

SAP version number	SAP version Date (ddMMMyyyy)	Changes
Final 2.0	08MAY2020	Definition of terms: "treatment-emergent abnormality": Clarification has been added that abnormalities in vaccination phase are evaluated versus vaccination baseline and post-challenge abnormalities are evaluated versus challenge baseline.
		Section 2.1.2: Derivation rule for "Time to feel well enough to go to work (hours)": Censoring on the last assessment will not only occur for subjects not having any positive answer, but for any subject having a negative answer as last assessment.
		Section 2.2.1: Instead of four, only three stimulation antigens will be assessed with the ELISpot assay: NP, M1 and DMSO (not NP+M1). It has also been clarified that the results will be reported in SFC per well (i.e. 200,000 cells) for two replicate wells. Clarification has been added that only MNT is done at screening.

SAP version number	SAP version Date (ddMMMyyyy)	Changes
		Section 2.2.2: Derivation rules for background subtracted T cell response result has been changed to account for the fact that each peptide pool contains a different set of peptides and may therefore have a different response profile. Results can therefore not be averaged over pools. Therefore, background subtracted results must first be calculated per pool. If negative, these background subtracted results must be set to 0. The background subtracted T cell response result for a specific antigen (either NP or M1) is the sum of the background subtracted results of the pools within that antigen (4 pools for NP and 2 pools for M1). A derivation rule has been added for the negative control T cell response results (missing from previous SAP version): The negative control T cell response result is the result aver all replicates. Derivation rule for T cell responder status has been changed to specify that the derivation should be applied for each of the antigens NP and M1 separately and to clarify that and unadjusted p-value and a permutation-adjusted p-value will be calculated for each peptide pool, instead of for each antigen. Furthermore, the unadjusted p-value will not be calculated using a Mann-Whitney U Test, but using a two-sample t-test. Responder status cannot be determined if results from only one negative control well are available, but the same also applies to the peptide pools results. Finally, to come to the T cell responder status, since the permutation-adjusted p-values are calculated per pool, an additional step has been added to specify that a subject will be considered a responder if a permutation-adjusted p-value of any of the pools within the antigen is less than 0.05.

SAP version number	SAP version Date (ddMMMyyyy)	Changes
		Section 2.2.4: Specification has been added that next to background subtracted T cell response, the negative control T cell response results will also be summarised by means of descriptive statistics at each analysis visit. Similarly, graphs of the median actual values over time will also be prepared for negative control results.
		Section 5.1.1: "Per-protocol set (PP)": Major protocol deviations may also contain deviations not having impact on the primary endpoint. Therefore, rather than excluding subjects with any major protocol deviation, this specification has been updated to only exclude subjects with major protocol deviations impacting the primary endpoint. A programmer note has been added that major protocol deviations impacting the primary endpoint will be flagged as such in the database.
		Section 5.3.3 Imputation rules have been added for immunogenicity values below or above a threshold: Immunogenicity values reported as > XX will be imputed with XX. Immunogenicity values reported as < XX will be imputed with XX/2.
		Section 8.1: Title of table “Influenza Symptoms - General SSC Score Changes Mixed Model for Repeated Measures” has been corrected to “Influenza Symptoms - Overall SSC Score Changes Mixed Model for Repeated Measures”. To keep a logic order of TLFs, the number has been changed from 14.2.3.15 into 14.2.3.11. Therefore, numbers of tables 14.2.3.11 to 14.2.3.14 in previous SAP version have been incremented.

SAP version number	SAP version Date (ddMMMyyyy)	Changes
		Section 8.3: Title of figure “Log qPCR Mean Adjusted Changes vs. Time Profiles” has been corrected to “Log qPCR Mean Adjusted Actual Values vs. Time Profiles”.
		Section 9.1: Proc multtest in sample code for “Permutation-based Resampling Method” has been adjusted to perform 20,000 instead of 20,000 permutations, and to be processed by subject and timepoint instead of only by subject.
Final 3.0	15JUN2020	Section Definition of terms: Details have been added to clarify the meaning of 'within two consecutive days'.
		Sections 2.1.2.2 and 2.1.2.3: For endpoint 'Time to start of viral shedding' it was specified that the first positive sample to be considered for the time calculation is the first of two consecutive samples, as this is also the event. Similar clarification was added for duration of viral shedding, time to start of symptoms and duration of symptoms
		Section 2.2: After expert input and on request of the sponsor, it has been decided that T-cell response analysis needs to be done on two subsets of samples. The restricive rule of needing at least two replicates for the derivation of response status has been removed in section 2.2.2. The definition of both subsets has been added in section 2.2.4.
		Section 5.4.1: It has been specified that geometric mean will replace arithmetic mean in tables where it has to be shown.
		Section 9.1: A seed has been specified in the code of the proc multtest to allow reproduction of the results.

7. REFERENCES

Guidance for Industry - Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007 (https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/default.htm)

ICH Topic E6(R2) Guideline for Good Clinical Practice – Step 4, 9 November 2016.

Statistical considerations for the design and analysis of the ELISpot assay in HIV-1 vaccine trials. Hudgens MG et al. JIM 2004 288:19-34

8. LIST OF TABLES AND LISTINGS

Topline TLFs are flagged as 'TL'.

8.1 TABLES

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14.1.2.1	Demographic Data	SAF	TL
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LABORATORY DATA

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9. APPENDICES

9.1 SAS CODE

Mann-Whitney U test

```
proc npar1way data=dataset wilcoxon;
  var AVAL;
  class TRTP;
run;
```

Fisher exact test

```
proc freq data= dataset;
  table AVAL *TRTP/fisher;
run;
```

Survival analysis with log rank test

```
proc lifetest data= dataset method=KM;
  time AVAL * CENSOR(1);
  strata TRTP / test=logrank;
run;
```

Zero-inflated Poisson

```
proc hpfmm data=dataset;
  class TRTP;
  model AVAL = TRTP / dist=Poisson ;
  model      +          / dist=Constant;
run;
```

T-test with checking model assumptions of homogeneity of variances and normality

```
proc glm data= dataset order=internal;
  class TRTP;
  model AVAL = TRTP;
  output out = norm r = resid;
  means TRTP / hovtest;
quit;
```

```
ods select testsfornormality;
proc univariate data=norm normal; var resid; run;
```

ANCOVA model

```
proc mixed data=dataset;
  class TRTP CHCOHORT SEX;
  model AVAL = TRTP CHCOHORT VACTIME  SEX/solution;
  lsmeans TRTP / diff=control('Placebo') cl;
run;
```

Multicollinearity testing

```
proc reg data=dataset;
  model AVAL = TRTP CHCOHORT VACTIME  SEX/selection=none vif;
run;
```

MMRM model

```
proc mixed data=dataset;
  class USUBJID ATPTN TRTP CHCOHORT SEX;
  model LGAVAL= TRTP ATPTN ATPTN*TRTP CHCOHORT VACTIME SEX /
ddfm=KR S;
  repeated ATPTN /subject= USUBJID type=UN;
  lsmeans ATPTN*TRTP / cl pdiff alpha=0.05;
run;
```

Note: if covariance structure other than UN (unstructured), then ddfm = BW should be used as option to handle degrees of freedom.

Multiple imputation

```
proc mi data= inputdata NIMPUTE=100 SEED=22087 OUT=mnardata;
  class TRTP;
  var LGAVALTP1- LGAVALTP22;
  fcs reg;
  mnar model (LGAVALTP1- LGAVALTP22)/modelobs=( TRTP ='Placebo'));
run;
```

Permutation-based Resampling Method

```
%macro vect(len=, place=);
  %do nn=1 %to &len;
    %if(&nn ^= &place) %then 0;
    %if(&nn = &place) %then 1;
  %end;
%mend vect;
%macro mymult(data_in=, k=);
  proc multtest data=&data_in perm n=100000 order=data stepperm out=permresults
seed = 1;
    by usubjid atpt;
    class well;
    test mean(count/upper);
      %do peps = 1 %to &k;
        contrast "peptide&peps" -1 %vect(len=&k, place=&peps);
      %end;
  run;
%mend mymult;

%mymult(data_in=inputdataset,k=2)
data respstat;
  set permresults;
  if 0 lt perm_p lt 0.05 then RESPSTAT = 1;
  else if perm_p ge 0.05 then RESPSTAT = 0;
run;
```

9.2 INFLUENZA SYMPTOM SCORE CARD OF FLU010 - BE-80-1800488

Group	Subject	Screening number:

[a] Fill in the SSC twice daily, at approximately 12h intervals (AM and PM) starting on Day1.
[b] Score the severity of the symptoms with 0: absent, 1: mild, 2: moderate or 3: severe – each field should be filled out.
[c] For the current score of a symptom, fill in the worse severity during the period between 2 SSC's.

	Day1		Day2		Day3		Day4		Day5		Day6		Day7		Day8		Day9		Day10		Day11
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM
Time point of collection (HH:MM)																					
Medication taken during the last 12h?	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Feel well enough to go to work today?	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Respiratory tract (upper + lower)																					
Blocked nose																					
Runny nose																					
Sneezing frequency																					
Sinus pressure/pain or facial pain																					
Sore throat																					
Difficulty swallowing																					
Teary/ watery eyes																					

Painful eyes																				
Aversion to light																				
Dry cough																				
Productive (wet) cough																				
Difficulty breathing / tight chest																				
Generalized																				
Dizziness																				
Head congestion																				
Headache (migraine excluded)																				
Muscle aches																				
Feverish																				
Chills or shivering																				
Lack of appetite																				
Felt cold																				
Sweating																				
Only to be questioned if ≥ 2x2 scored above																				
Nausea																				
Stomach ache																				
Vomiting																				
Diarrhoea																				
Tiredness/ weakness																				
Sleeping more than usual																				

Interviewer initials																				
Investigator initials																				
Lymphadenopathy?																				
Moderate/ severe sign/symptom of lower respiratory tract involvement?	Y/N		Y/N		Y/N		Y/N		Y/N		Y/N		Y/N		Y/N		Y/N		Y/N	

9.3 TOXICITY GRADES

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, CBER, September 2007

PARAMETER	Unit	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Amylase [pancreatic]		1.1-1.5 *ULN	>1.5-2.0 *ULN	>2.0-5.0 *ULN	>5.0 *ULN
Alanine amino transferase		1.1-2.5 *ULN	>2.5-5.0 *ULN	>5.0-10.0 *ULN	>10.0 *ULN
Albumin	g/L	31-28	<28-25	<25	-
	g/dL	3.1-2.8	<2.8-2.5	<2.5	-
Alkaline phosphatase		1.1-2.0 *ULN	>2.0-3.0 *ULN	>3.0-10.0 *ULN	>10.0 *ULN
Aspartate amino transferase		1.1-2.5 *ULN	>2.5-5.0 *ULN	>5.0-10.0 *ULN	>10.0 *ULN
Bilirubin [total]		1.1-1.5 *ULN	>1.5-2.0 *ULN	>2.0-3.0 *ULN	>3.0 *ULN
Blood urea nitrogen	mmol/L	8.2-9.3	>9.3-11.1	>11.1	-
	mg/dL	23-26	>26-31	>31	-
Calcium low	mmol/L	2.10-2.00	<2.00-1.87	<1.87-1.75	<1.75
	mg/dL	8.4-8.0	<8.0-7.5	<7.5-7.0	<7.0
Calcium high	mmol/L	2.62-2.74	>2.74-2.87	>2.87-2.99	>2.99
	mg/dL	10.5-11.0	>11.0-11.5	>11.5-12.0	>12.0
Cholesterol	mmol/L	5.20-5.43	>5.43-5.82	>5.82	-
	mg/dL	201-210	>210-225	>225	-
Creatinine	mmol/L	0.133-0.150	>0.150-0.177	>0.177-0.221	>0.221
	mg/dL	1.5-1.7	>1.7-2.0	>2.0-2.5	>2.5
Creatine [phospho] kinase		1.25-1.50 *ULN	>1.50-3.00 *ULN	>3.00-10.00 *ULN	>10.00 *ULN

Glucose fasting low	mmol/L	3.83-3.61	<3.61-3.05	<3.05-2.50	<2.50
	mg/dL	69-65	<65-55	<55-45	<45
Glucose fasting high	mmol/L	5.55-6.11	>6.11-6.94	>6.94	-
	mg/dL	100-110	>110-125	>125	-
Glucose non-fasting low	mmol/L	3.83-3.61	<3.61-3.05	<3.05-2.50	<2.50
	mg/dL	69-65	<65-55	<55-45	<45
Glucose non-fasting high	mmol/L	6.11-6.94	>6.94-11.10	>11.10	-
	mg/dL	110-125	>125-200	>200	-
Lipase		1.1-1.5 *ULN	>1.5-2.0 *ULN	>2.0-5.0 *ULN	>5.0 *ULN
Magnesium	mmol/L	0.62-0.53	<0.53-0.45	<0.45-0.37	<0.37
	mg/dL	1.5-1.3	<1.3-1.1	<1.1-0.9	<0.9
Phosphate	mmol/L	0.81-0.74	<0.74-0.65	<0.65-0.52	<0.52
	mg/dL	2.5-2.3	<2.3-2.0	<2.0-1.6	<1.6
Potassium low	mmol/L	3.6-3.5	<3.5-3.3	<3.3-3.1	<3.1
	mEq/L	3.6-3.5	<3.5-3.3	<3.3-3.1	<3.1
Potassium high	mmol/L	5.1-5.2	>5.2-5.4	>5.4-5.6	>5.6
	mEq/L	5.1-5.2	>5.2-5.4	>5.4-5.6	>5.6
Protein	g/L	60-55	<55-50	<50	-
	g/dL	6.0-5.5	<5.5-5.0	<5.0	-
Sodium low	mmol/L	134-132	<132-130	<130-125	<125
	mEq/L	134-132	<132-130	<130-125	<125

Sodium high	mmol/L	144-145	>145-147	>147-150	>150
	mEq/L	144-145	>145-147	>147-150	>150
Prothrombin time		1.00-1.10	>1.10-1.20	>1.20-1.25	>1.25
Partial thromboplastin time		1.0-1.2	>1.2-1.4	>1.4-1.5	>1.5
Fibrinogen low	µmol/L	5.88-4.41	<4.41-3.68	<3.68-2.94	<2.94
	mg/dL	200-150	<150-125	<125-100	<100
Fibrinogen high	µmol/L	11.76-14.70	>14.70-17.65	>17.65	-
	mg/dL	400-500	>500-600	>600	-
Eosinophils	giga/L	0.65-1.50	>1.50-5.00	>5.00	-
	counts/mm^3	650-1500	>1500-5000	>5000	-
Hemoglobin [female] [1]	mmol/L	7.27-6.67	<6.67-5.76	<5.76-4.85	<4.85
	g/dL	12.0-11.0	<11.0-9.5	<9.5-8.0	<8.0
Hemoglobin [male] [1]	mmol/L	8.18-7.58	<7.58-6.36	<6.36-5.15	<5.15
	g/dL	13.5-12.5	<12.5-10.5	<10.5-8.5	<8.5
Hemoglobin, as decrease from baseline [2]	mmol/L	<0.00 to -0.91	<-0.91 to -1.21	<-1.21 to -3.03	<-3.03
	g/dL	<0.0 to -1.5	<-1.5 to -2.0	<-2.0 to -5.0	<-5.0
Lymphocytes [absolute count]	giga/L	1.00-0.75	<0.75-0.50	<0.50-0.25	<0.25
	counts/mm^3	1000-750	<750-500	<500-250	<250
Neutrophils [absolute count]	giga/L	2.0-1.5	<1.5-1.0	<1.0-0.5	<0.5
	counts/mm^3	2000-1500	<1500-1000	<1000-500	<500
Platelets	giga/L	140-125	<125-100	<100-25	<25

	counts/mm^3	140000-125000	<125000-100000	<100000-25000	<25000
White blood cells low	giga/L	3.5-2.5	<2.5-1.5	<1.5-1.0	<1.0
	counts/mm^3	3500-2500	<2500-1500	<1500-1000	<1000
White blood cells high	giga/L	10.8-15.0	>15.0-20.0	>20.0-25.0	>25.0
	counts/mm^3	10800-15000	>15000-20000	>20000-25000	>25000

[1] Preferred, defined on actual values. [2] Alternative; decrease implies negative changes. Only one should be computed, either [1] or [2].

9.4 SCHEDULE OF ASSESSMENTS

9.4.1 Period 1- Screening and Vaccination Schedule

Period 1	**Screening 1**	**Screening 2**	**Baseline Vaccination**	**Out-patient Clinic Visit**	**Phone[m]**	**Out-patient Clinic Visit**	**Out-patient Clinic Visit**	**Phone[m]**	**Unscheduled visit[l]**	**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)[n]**
Informed Consent	x[a]	x[a]									
Inclusion/Exclusion	x[b]	x[b]									
Randomization			x								
Medical History/Demography		x									
Physical Examination		x[c]				x	x		x		
Vital Signs		x				x	x		x		
Supine 12-lead ECG		x									
Haematology		x							x		
Biochemistry[d]		x							x		
Microneutralization (MNT) [a]	x	x[a]									
Urinalysis		x							x		
HIV,, Hep C, HBsAg		x									
Urine Drug Screen		x	x						x		
Alcohol breath test		x	x						x		
Serum/Urine Pregnancy[e]		x[e]	x						x		

Blood sample for cellular immunogenicity assays PBMCs[f], and Serum			x[g]			x	x				
Transcriptomics - whole blood collection (PAXgene® RNA)			x[g]	x[h]		x	x				
Vaccination			x								
Dispense/Remind/Collect Diary Cards			x[j]		x[i]	x[k]					
AEs/Con-meds	x	x	x	x	x	x	x	x	x		x[n]

[a] 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
[b] Some inclusion/exclusion criteria will be checked at Screening 1 visit to ensure participants are potentially eligible prior to MNT test
[c] Physical examination at screening will include height and weight measurements
[d] Biochemistry test includes creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamylaminotransferase (GGT), C-reactive protein (CRP), and bilirubin
[e] Serum sample will be used for pregnancy test at screening and urine pregnancy test will be used in subsequent visits
[f] PBMCs to be sent to Viroclinics for processing
[g] PBMC, Serum and Transcriptomics samples at Day 1 are to be collected pre-vaccination
[h] Transcriptomics sample on Day 2 is to be collected 24 hours (± 3 hours) post-vaccination
[i] Phone call to participants to remind them to complete Diary Card
[j] Distribute Diary Cards to participants
[k] Collect completed Diary Cards from participants (up to Day 8)
[l] Assessments during Unscheduled Visits are performed at the discretion of the Investigator
[m] During phone visits, AEs and ILIs will be collected and participants will be reminded about their potential next visits including the challenge period start
[n] 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

9.4.2 Period 2 – Challenge Schedule

Period 2	**In-Clinic Confinement**													**Unsched Visit[c]**	**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[f] ±3**
Screening/Administrative/Other Assessments															
Eligibility Criteria	x														
Medical and Medication History Review	x														
Ambulatory Visit															x
Admission to study unit / discharge	*Admission[a]*	*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[g]		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[e]	x[a]		x						x				x	
Haematology	x[a]		x						x				x	
Symptom Score (Questionnaire) – b.i.d.			x	x	x	x	x	x	x	x	x	x[d]		
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) [b]	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[h]			x	x	x	x	x	x	x	x	x	x		
Blood sample for humoral immunogenicity (MNT) and Hemagglutination Inhibition (HI) assays[i]	x[a]													x
Blood sample for cellular immunogenicity assays PBMCs[j]	x[a]													x
Transcriptomics - whole blood collection (PAXgene® RNA)	x[k]	x[k]		x			x			x				x

[a] 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.

[b] 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.

[c] Assessments during Unscheduled Visits will be performed at the discretion of the Investigator

[d] Symptom Score Questionnaire to be administered b.i.d. from Day 1 to Day 10 but only once prior discharge on Day 11

[e] 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
[f] 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
[g] 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
[h] Tissue collection to start 12 hours post-Challenge
[i] Additional sera collected for future correlate work
[j] PBMCs to be sent to Viroclinics for processing
[k] 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.

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Reason for signing: Approved	Name: Tom Evans Role: Sponsor Date of signature: 15-Jun-2020 11:23:43 GMT+0000
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