Janssen Vaccines & Prevention B.V.

Statistical Analysis Plan

An Exploratory, Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Prophylactic Efficacy of a Single Immunization of Ad26.RSV.preF Against Respiratory Syncytial Virus Infection in a Virus Challenge Model in Healthy 18 to 50 Year-Old Adults

Protocol VAC18193RSV2002; Phase 2a

VAC18193 (JNJ-64400141)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
AUC	Area under the curve
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
eCRF	electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
GMT	Geometric mean titers
FA	Full Analysis Set
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ITTc	Intent-to-Treat-Challenge
ICS	Intracellular Cytokine Staining
LLOD	Lower limit of detection
LLOQ	lower limit of quantification
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PI	principal investigator
PPI	Per-protocol Immunogenicity
RSV	Respiratory syncytial virus
RTI	Respiratory tract infection
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	standard error
TLF	Tables, Listings and Figures
ULOQ	Upper limit of quantification

DEFINITION OF TERMS

Active vaccine	Ad26.RSV.preF
Study vaccine	Ad26.RSV.preF or Placebo

1. INTRODUCTION

This is the Statistical Analysis Plan (SAP) applicable for the VAC18193RSV2002 trial. This SAP is applicable for the following analysis:

- **Primary analysis** will be performed when all subjects have completed the quarantine phase or discontinued earlier. The pre-challenge neutralization and pre-F ELISA, and post challenge RT-PCR, nasal mucous and tissue count, and clinical symptom data will be available although the analysis may be performed on snapshot data. All other data available at the time of primary analysis, including completed cellular data, will be included. Preliminary safety data, including Day 28 post-challenge, if available, will also be included.
- **Final analysis** will be performed when all subjects have completed the 6-month safety follow-up visit or discontinued earlier.

Depending on when the data are available, the primary and final analysis might be combined.

Additional interim analyses (blinded or unblinded) may be performed during the study for the purpose of informing future vaccine-related decisions in a timely manner, or upon health authority request.

This document contains all information needed for performing a full efficacy, safety and immunogenicity analysis. Which tables, listing and figures (TLF) need to be generated for each analysis will be described in separate data presentation specifications (DPS) documents.

1.1. Trial Objectives

Primary Objective

The primary objective is to assess a trend for the prophylactic efficacy of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF administered intramuscularly to adults aged 18-50 years in the RSV challenge model in terms of reduction of nasal wash viral load as measured by the area under the curve (AUC) over time by quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) compared to placebo.

Secondary Objectives

- To assess a trend for prophylactic efficacy of a single dose of Ad26.RSV.preF in the RSV challenge model in terms of reduction of nasal wash viral load as measured by the peak viral load of the RT-PCR compared to placebo.
- To assess the effect of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF on viral load, as measured by RT-PCR and quantitative culture of RSV, and clinical symptoms on Day 6 and Day 7 post-challenge compared to placebo.
- To assess a trend for prophylactic efficacy of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF in the RSV challenge model in terms of prevention of symptomatic RSV infection defined as two quantifiable RT-PCR measurements and one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category compared to placebo.

- To assess a trend for prophylactic efficacy of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF in the RSV challenge model in terms of prevention of symptomatic RSV infection defined as two quantifiable RT-PCR measurements and one or more positive clinical symptoms of any grade in any category from the symptom scoring system compared to placebo.
- To assess a trend for prophylactic efficacy of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF in the RSV challenge model in terms of the weight of mucous secretions and tissue count over time compared to placebo.
- To assess the safety and tolerability of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF administered intramuscularly.

Exploratory Objectives

- To assess a trend for prophylactic efficacy of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF in the RSV challenge model in terms of clinical symptoms as measured by the AUC over time of symptoms collected by a graded symptom scoring system compared to placebo.
- To assess a trend for prophylactic efficacy of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF in the RSV challenge model in terms of AUC for viral load (VL-AUC), as measured by quantitative culture of RSV from nasal wash samples, compared to placebo.
- To explore the relationship of humoral (including nasal wash samples if feasible) and cellular immunogenicity outcomes and the VL-AUC and the AUC for clinical symptoms.
- To assess a trend for prophylactic efficacy of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF in the RSV challenge model in terms of prevention of symptomatic RSV infection defined as two quantifiable RT-PCR measurements and/or positive serological measurement of RSV infection in the context of immunization and pre-existing antibody and one or more positive clinical symptoms of any grade in any category compared to placebo.
- To assess a trend for prophylactic efficacy of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF in the RSV challenge model in terms of respiratory parameters measured by spirometry during the study compared to placebo.
- To explore the relationships between clinical symptoms and viral load, as measured by RT-PCR and quantitative culture of RSV, in Ad26.RSV.preF subjects and placebo.
- To explore other immunologic parameters in relation to the VL-AUC by RT-PCR and AUC for clinical symptoms and occurrence of symptomatic RSV infection defined as two quantifiable RT-PCR measurements or more plus one clinical symptom of any grade.
- To explore the immune response of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF compared to placebo.
- To explore humoral and cellular responses to challenge with RSV-A Memphis 37b in immunized and non-immunized subjects.
- To explore the relationship between immunogenicity and pre-existing Ad26 neutralizing antibody.
- To explore other potential efficacy endpoints, as defined in the statistical analysis plan (SAP), to determine the best efficacy endpoint to use in subsequent clinical studies investigating the vaccine's efficacy.

1.2. Trial Design

This is a single center, randomized, placebo-controlled, double-blind Phase 2a human challenge study, to be conducted in approximately 44 healthy male and female subjects aged 18-50 years who have been pre-screened for susceptibility to RSV infection, ie, have levels of RSV neutralizing antibodies compatible with susceptibility to RSV infection.

Subjects will receive single intramuscular doses of $1x10^{11}$ vp of Ad26.RSV.preF or placebo. More than 44 subjects will be vaccinated to account for withdrawals between vaccination and challenge. The challenge study site, hVIVO, has the capacity to challenge and house under isolation 22 subjects at a time and thus the study will be conducted in several cohorts with up to 22 subjects per cohort. Within each cohort, subjects will be randomized 1:1 to $1x10^{11}$ vp of Ad26.RSV.preF or placebo. A schematic overview of the study design and groups is depicted in Table 1.

Table 1: Study Design

Group	***N***	***Day -28***	***Day 0****
Group 1	22	Ad26.RSV.preF ($1x10^{11}$ vp)	Challenge with RSV-A Memphis 37b**
Group 2	22	Placebo	

* ie, not less than 24 or more than 90 days after vaccination.
**Subjects will be challenged in two or more cohorts of up to 22 subjects per cohort. Within each cohort, subjects will be randomized 1:1 to $1x10^{11}$ vp of Ad26.RSV.preF or placebo.
***Note*:** The infection rate (based on mucus weight, symptoms and viral shedding) in the placebo group will be followed on an ongoing basis by an unblinded individual who does not have any other study function to ensure a sufficient infection rate has occurred. If the infection rate is lower than anticipated, additional subjects may be enrolled, initially four additional subjects in each arm and up to 70 in total. This is to ensure that a high enough number of evaluable subjects is reached in each arm.

For further information related to the design of the study refer to CTP, Section 3.1.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis is that a single dose of $1x10^{11}$ vp of Ad26.RSV.preF shows a trend of reduction in VL-AUC of the quantitative RT-PCR in healthy subjects challenged intranasally with the RSV-A Memphis 37b virus, compared with healthy subjects given placebo who are similarly challenged. For further information refer to CTP, Section 2.2.

1.4. Sample Size Justification

A sample size of 44 challenged subjects (22 vaccinated and 22 placebo subjects) was chosen as this would provide sufficient evidence to assess if the challenge model is a reasonable approach to examine vaccine efficacy.

As this is an exploratory study, the statistical assumptions taken for the calculation of the sample size will need to be demonstrated to be correct for the analysis to be conducted as planned. For example, if the infection rate, from the study is considerably below 65% then the study will be considered to be underpowered to be able to accurately determine the stated aims. The 65% infection rate used for the sample size calculations is referring to 65% of the placebo subjects having detectable viral loads. The infection rate in the placebo group will be followed on an ongoing basis by an unblinded individual who does not have any other study function to ensure a

sufficient infection rate has occurred. More details regarding the infection rate monitoring are outlined in the monitoring plan. For further information related to the sample size justification of the study refer to CTP, Section 11.2.

1.5. Randomization and Blinding

Please refer to CTP, Section 5.

2. CHANGES TO PLANNED ANALYSES

The CTP states that only abnormality in ECG parameters will be listed. Moreover, all ECG parameters collected during the quarantine period will also be summarized in tables as described in the Section 7.4

In addition, a sensitivity analysis of the primary endpoint is added. At the time of the final analysis the quantitative RT-PCR assay values under the lower limit of quantification (LLOQ) will be distinguished between 'Detected' (values between the lower limit of quantification and the limit of detection) and 'Not detected' (values bellow the limit of detection) values, and the primary end point will be recalculated as indicated in Section 6.1.1.

3. GENERAL ANALYSIS DEFINITIONS

3.1. Study phases

The baseline (or reference) value for safety and immunogenicity analysis will be defined as the value of the last available assessment prior to vaccination (Day -28). For ECG values the baseline (or reference) value will be defined as the value of the last available assessment prior to challenge on Day 0, since ECGs for safety assessment are performed only during the challenge period.

The baseline (or reference) value for the efficacy analysis will be defined as the value of the last available assessment prior to challenge on Day 0.

The safety analysis will present all results by period, based on the phase definition in Section 3.1.1.

The immunogenicity analysis will summarize all results in the following immunogenicity timepoints:

- Baseline (vaccination)
- 28 days post-vaccination*
- 28 days post-challenge

*Includes all assessments taken between 22 and 33 days after vaccination.

In case there are subjects for which samples were taken later than 33 days after vaccination, the results will appear in listings.

Moreover,

Study Day = visit date - date of Vaccination

Listings will be shown per phase and time point.

3.1.1. Phase definitions

The phases in the study will be constructed as follows:

Table 2: Phase Definitions

Phase	Phase #	Period	Period #	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form[a]	One minute prior to start of post-dose period
Vaccination	2	Post-Dose	1	Date and time of vaccination	Minimum of: a) 23:59 on 32 days after the vaccination (23:59 of day of vaccination + 32 days) b) 23:59 at the date of database cut-off date in case of interim c) One minute prior to date and time of the challenge d) 23:59 at the date of last contact (for early discontinuation)
Follow-up Vaccination	3			One minute after Post-Dose period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off date in case of interim c) One minute prior to Challenge
Challenge	4	Post-Challenge	2	Date and time of challenge (Study Day 0)	Minimum of: a) Maximum (28 days after challenge at 23.59, scheduled visit 4 weeks after challenge at 23:59) b) 23:59 at the date of database cut-off date in case of interim c) 23:59 at the date of last contact (for early discontinuation)
Follow-up Challenge	5			One minute after Post-Challenge period end	Minimum of: a) 23:59 at the date of database cut-off date in case of interim b) 23:59 at the date of last contact. (for completed or discontinued subjects)

[a] in case an earlier date is available (eg. for lab or vital signs), then use the very first date to include all data

The Follow-up Vaccination phase will only be created in case a subject was challenged to the later than 32 days after vaccination. Moreover, if for one subject no challenge was performed, the Follow-up Vaccination phase should be created and to capture any observations after the Vaccination phase.

3.2. Pooling Algorithm for Analysis Centers

No pooling algorithm will apply, only one site will be used.

3.3. Analysis Sets

Vaccination assignment will follow the as-treated principle.

3.3.1. Full Analysis Set (FA)

The **Full Analysis (FA) Set** includes all subjects who were randomized and received at least one dose of study vaccine, regardless of the occurrence of protocol deviations. All safety analyses will be based on the FA set. As a sensitivity analysis, key immunogenicity tables will also be based on the FA set.

3.3.2. Intent -to-Treat-Challenge Set (ITTc)

The **Intent-to-Treat-Challenge (ITTc)** population is a subset of the FA set that includes all randomized, vaccinated and challenged subjects. All efficacy analyses will be performed on the ITTc population. Important subject information tables might be repeated based on the ITTc population as well.

3.3.3. Immunogenicity Analysis Set

The **Per-protocol Immunogenicity (PPI) Set** will include all randomized and vaccinated subjects for whom immunogenicity data are available, excluding subjects with major protocol deviations expecting to impact the immunogenicity outcomes.

In addition, for subjects who experience a natural RSV infection (based on RT-PCR, or other sources), samples taken after the natural infection will not be included in the PPI set.

The analysis of immunogenicity will be based on the PPI set.

4. DATA MONITORING COMMITTEE REVIEW

An internal data monitoring committee (DRC) will be commissioned for this study, comprised of sponsor personnel not directly involved in the conduct of the study, who have expertise in clinical study conduct and vaccines. There are no planned DRC reviews. The DRC will only convene to discuss any significant or unexpected safety issues. The investigator and SRP will inform the DRC of any AE of concern. In such a case, the study team or DRC members will indicate which analyses are needed, with this SAP serving as a guidance. If deemed necessary for safety review, the DRC may request the randomization codes and review unblinded data, if applicable.

5. SUBJECT INFORMATION

Subject information will be shown for the Full Analysis set.

5.1. Demographics and Baseline Characteristics

Demographic characteristics and screening/baseline characteristics will be tabulated and summarized with descriptive statistics per vaccine regimen and over all subjects.

The following demographic and baseline characteristics will be summarized.

- Sex (Female/Male)
- Age (years)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m2)

5.2. Disposition Information

The number and percentage of subjects

- screened
- in the FA set
- in the PPI
- in the ITTc set
- randomized, vaccinated and challenged
- randomized, vaccinated and not challenged
- not randomized, not vaccinated
- not randomized, vaccinated
- randomized, not vaccinated

Discontinued subjects (study, vaccination discontinuation and discontinuation from challenge) with the reason of discontinuation will be tabulated per vaccine group and overall.

Also, the number of subjects and percentage per phase will be tabulated.

5.3. Protocol Deviations

Major protocol deviations will be summarized.

5.4. Concomitant Medications

The analysis of concomitant therapies will be done using the WHO drug coded terms.

There will be special attention to analgesics/antipyretics such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin, administered during 8 days following each vaccination (00:00 of day of vaccination + 7 days).

Based on their start and stop date, concomitant therapies will be reported in each applicable phase.

If a concomitant therapy record misses components of its start and/or stop dates (day and/or month and/or year):

- In case of partial start or stop dates, the concomitant therapy records will be allocated to periods using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the periods, and the concomitant therapy record will be allocated to the period(s) where these date parts match. This rule may lead to assignment to multiple periods.
- In case of a completely missing start date, the concomitant therapy will be considered as having started before the trial.

In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial.

6. EFFICACY

6.1. Primary Efficacy Endpoint

The primary endpoint is the area under the viral load-time curve (VL-AUC in $\log_{10}$ copies/ml) of RSV-A Memphis 37b as determined by quantitative RT-PCR assay of nasal wash samples. Nasal wash samples are taken every 12 (±1) hours beginning two days (ie, in the morning) after inoculation of the challenge virus. VL-AUC is calculated based on the viral load values measured twice daily, starting with the baseline value, and ending with the last available value before discharge.

In the calculation of the AUC, not only the date, but also the timing (the real hours, minutes and seconds as captured in the database should be used, but the AUC result should be reported in hours), of the assessment, is taken into account:

$$\boldsymbol{AUC\ VL} = \sum_{\boldsymbol{i=2}}^{\boldsymbol{T}} \frac{[\boldsymbol{VL_{t_i}} + \boldsymbol{VL_{t_{(i-1)}}}]}{\mathbf{2}} [\boldsymbol{t_i} - \boldsymbol{t_{(i-1)}}] \quad \textbf{(1)}$$

where

$t_i = (actual)\ timepoint\ i$

$t_{i-1} = (actual)\ timepoint\ (i-1)$

$T = last\ timepoint$

$t_1 = first\ timepoint\ after\ challenge$

$VL_{t_i} = log_{10}\ viral\ load\ at\ \ (actual)\ timepoint\ i$

$VL_{t_{(i-1)}} = log_{10}\ viral\ load\ at\ \ (actual)\ timepoint\ (i-1)$

6.1.1. Primary Efficacy Analysis

For this primary efficacy endpoint, the exact Wilcoxon Rank Sum test will be performed and the one-sided p-value will be interpreted at the 5% and 20% significance level, specifically only analysing the statistical significance of a reduction in VL-AUC in the active versus placebo groups.

At the time of database lock of the primary analysis, the results of the quantitative RT-PCR assay will be reported as:

- Either an actual viral load value in log10 copies/mL
- Or 'Not Quantifiable' for values below lower limit of quantification (LLOQ).

At the time of database lock of the final analysis, additional detail will be added for the values below the lower limit of quantification and results will be reported at that time as:

- Either an actual viral load value in log10 copies/mL
- 'Detected' for value between the lower limit of quantification (LLOQ) and the limit of detection (LOD) of the assay
- 'Not Detected' for values below the LOD of the assay

For the primary analysis, values below the LLOQ (indicated as 'Not Quantifiable' in the database) will be imputed with 0.

At the time of the final analysis, the same analysis will be repeated, so values below the LLOQ (indicated as 'Detected' or 'Not Detected') will be imputed with0.

As a sensitivity analysis at the time of final analysis, the analysis will be repeated but now imputing the 'Detected' with LLOQ/2 and the 'Not Detected' with 0.

These imputations will be used when calculating the AUC based on equation (1). In addition, in case there are missing results in the first timepoint after challenge and/ or the last timepoint after challenge of the AUC, the missing value should be imputed with 0. No other missing values will be imputed.

6.2. Secondary and Exploratory Efficacy Endpoints

The **secondary efficacy** endpoints are the following:

- Total clinical symptom score over time, with special interest to day 6 and 7. The total clinical symptom score is determined as the sum of the scores (grades) of the 13 self-reportable symptoms on the Subject Symptoms Card (SSC).

  Note: 'The symptom scores will be translated into numerical values as follows:
  0 = 'I have No symptom'
  1 = 'just noticeable'
  2 =' It's clearly bothersome from time to time, but it doesn't stop me from participating in activities'
  3 ='It's quite bothersome most or all the time and it stops me from participating in activities'
  4 =' Symptoms at rest'

- The viral load of RSV-A Memphis 37b as determined by quantitative RT-PCR assay of nasal wash samples over time, with special interest on Day 6 and Day 7 post challenge.
- The peak viral load is defined as the maximum viral load as determined by quantitative RT-PCR assay of nasal wash samples, observed over the whole quarantine period.
- The viral load of RSV-A Memphis 37b as determined by quantitative culture of RSV of nasal wash samples and the corresponding AUC, with special interest on Day 6 and Day 7 post challenge. The AUC will be calculated based on equation (1). In case the first timepoint after challenge and/ or last timepoint after challenge is missing, it will be set to zero. No other missing time point will be imputed.

  The viral load values from the quantitative culture of RSV (plaque assay) range from 1.70 to 5.90 in log10 PFU/ml. The following imputation rules will be used:

  - <1.70 log10 PFU/ml **not detected** -> 0
  - <1.70 log10 PFU/ml **detected** -> 1.70
  - <2.70 log10 PFU/ml **not detected** -> 0
  - <2.70 log10 PFU/ml **detected** -> 2.70
  - >5.90 log10 PFU/ml -> 6.00
  - INVALID -> missing

- Weight of mucus produced over time and the corresponding AUC. The AUC will be calculated based on equation (1). In case the first timepoint after challenge and/ or last time point after challenge is missing, it will be set to zero, no other missing time point will be imputed.
- Number of tissues used per time point.

- Proportion of subjects with symptomatic RSV infection. Symptomatic RSV infection is defined in two ways:
    - Conservative: the subject has two or more quantifiable RT-PCR measurements on different samples and the subject has one of the following:
        - symptoms from two different categories (Upper Respiratory, Lower Respiratory, Systemic) from the SSC, regardless of grade and assessment timepoint *OR*
        - any Grade 2 symptom from any category.
    - Liberal (RT-PCR): two or more quantifiable RT-PCR measurements plus any clinical symptom of any severity from the SSC.

The SSC categories are defined as follows:

- *Upper Respiratory symptoms:* runny nose, stuffy nose, sneezing, sore throat, earache
- *Lower* Respiratory *symptoms:* cough, shortness of breath, chest tightness, wheeze
- *Systemic symptoms:* malaise, headache, muscle and/or joint ache, chilliness/ feverishness

Note: the quantifiable RT-PCR assessment and the symptoms should not necessarily occur at the same day.

The **exploratory efficacy** endpoints are the following:

- Proportion of subjects with symptomatic RSV infection based on RT-PCR or serology. Symptomatic RSV infection is defined as:
    - Liberal (RT-PCR or Serology): the subject has two or more quantifiable RT-PCR measurements or serology confirmation of RSV (4-fold increase in G a or G b Elisa, 28 days after challenge), and any clinical symptom of any severity.
- AUC of the total clinical symptom score. The AUC for the total clinical symptom score will be calculated based on equation (1). In case the first and/or last time point is missing, it will be set to zero, no other missing time point will be imputed.
- Clinical symptom scores per item over time
- Respiratory parameters measured by spirometry:
    - Forced expiratory volume in 1 second (%) – FEV1
    - Forced vital capacity (%) – FVC
    - FEV1/FVC Ratio (%) – FEV1/FVC

6.2.1. Secondary and Exploratory Efficacy Endpoint Analysis

For viral loads of RSV-A Memphis 37b as determined by quantitative RT-PCR assay and by quantitative culture of RSV, number of observations, mean, standard error, median, first and third interquartile will be tabulated and means with standard errors will also be graphically presented per time point.

For clinical symptoms scores, total clinical symptom scores, mucus weight and number of tissues, number of observations, mean, standard error, median, first and third interquartile will be tabulated and means with standard errors will also be graphically presented per time point.

For peak viral load based on the quantitative RT-PCR assay, number of observations, mean, standard error, median, first and third interquartile will be tabulated for both groups and graphically presented with boxplots. Exact Wilcoxon Rank Sum tests will also be performed to compare the mean in the active versus placebo groups and the corresponding p-values will be presented. Note the study is only powered for the primary efficacy endpoint and not for any of the secondary one, interpreting these p-values should be done with caution.

For AUCs of viral loads, clinical symptoms and mucus weight, number of observations, mean, median, first and third interquartile (q1, q3) will be calculated for both groups and graphically presented with boxplots. Exact Wilcoxon Rank Sum tests will also be performed to compare AUCs in the active versus placebo groups and the corresponding p-values will be presented. Note the study is only powered for the primary efficacy endpoint and not for any of the secondary one, interpreting these p-values should be done with caution.

Descriptive statistics (number of observations, mean, standard errors, median, q1, q3) of values and changes from baseline for FEV_1, FVC, and FEV_1/FVC will be summarized at each scheduled timepoint. Mean with standard errors of actual values and changes from baseline will also be graphically presented. Finally, spirometry values that are below the clinically important limits, provided in the table below, will be classified as 'abnormally low' and the percentage of subjects with 'abnormally low' values will be summarized.

Table 3: Spirometry Clinical Important Limits

Parameter	Clinically Important Limits
FEV_1	80%
FVC	80%
FEV_1/FVC	70%

The proportion of subjects with symptomatic RSV infection per group for each one of the three with symptomatic RSV infection definitions, Conservative, Liberal (RT-PCR), Liberal (RT-PCR or Serology), will be tabulated and presented graphically with bar charts. Moreover, the difference in proportions and corresponding confidence intervals (CIs) will be calculated, if available. These will also be presented graphically with a forest plot.

The relation between viral load and clinical symptoms will be graphically explored. Moreover, summary statistics of efficacy endpoints might be repeated, for the infected and for the not infected subjects based on the three symptomatic RSV infection definitions.

Finally, subject specific profiles of viral loads total clinical symptom scores, mucus weight and tissue count will be created.

7. SAFETY

Safety analyses will be performed on the FA. Continuous variables will be summarized using the following statistics, as appropriate: number of observations, median, quartiles (Q1 and Q3), minimum and maximum. Frequencies and percentages (one decimal place) will be generated for categorical variables. No formal comparisons between groups will be provided.

One type of safety tables will be shown. The by regimen layout, safety data will be analyzed by vaccine regimens as designed per protocol; data will be presented by period. Denominator for the percentages is the number of subjects in the considered population and period for a certain regimen (incidence per 100 subjects/phase).

7.1. Adverse Events (AE)

7.1.1. Definitions

Solicited AEs, collected for 7 days after vaccination, shown in the tables are extracted from the diary pages of the CRF. For unsolicited AEs, only AEs with start date (grade and/or relation) within the 28-day period following vaccination or challenge will be presented in the safety tables except for SAE, which will be captured and tabulated in the outputs covering the whole study period. All other collected unsolicited adverse events will be presented through listings.

Solicited local AEs will be by definition considered as related to the study vaccine.

The severity of the AEs will be classified as grade 1 to 4. Solicited events that are graded less than grade 1, are not considered as AE. In case no grades are available, the grading of the solicited events will occur according to the grading list in Attachment 1.

7.1.2. Analysis of Adverse Events

Number and percentage of subjects with at least one particular AE (unsolicited/solicited) will be tabulated. Unsolicited AEs will be summarized by System Organ Class and Preferred Term. Solicited AEs will be summarized by class (local, systemic) and preferred term.

For solicited AEs following tables will be provided: summary, by worst severity grade, grade 3, related (systemic only), time to onset (in days) and duration (in days) for most frequent events and body temperature. Note: For solicited events, duration is defined as number of days from the start of the event until resolution of the event. The time to first onset is defined as (date of first onset – reference date + 1). The reference date is the start date of the regimen period.

For unsolicited AEs following tables will be provided: summary table (including SAE, fatal outcome, AESI and discontinuation), all events, most frequent, grade 3, permanent stop of vaccine, related, SAE.

Listings and/or subject narratives will be provided as appropriate, for those subjects who die, discontinue study vaccinations due to an AE, or experience a severe or serious AE.

7.1.3. Phase allocation of Adverse Events

Solicited events are always allocated to the Post Dose period.

Solicited AEs from the diary will be added to the ADAM for unsolicited AEs according to the same principles. This means the same event occurring on different days will be allocated to one row with the start date of the AE being the first date of the event and the end date for the event is the last subsequent day of the event. A change in grade will trigger a new row to be added. The same occurs in case of non-subsequent events (for example grade 1 nausea on day 1, 2 and 3 and also on day 6 and 7, which will be allocated to two rows; the duration of the event is 7 days). For further details related to transforming the on-site assessments and diaries of solicited AEs into analysis format please refer to Attachment 2.

Step 1: Allocation of events to the periods:

Adverse events in the SDTM database are allocated to periods based on their start date/time. If the start date/time of an event falls between (or on) the start and stop date/time of a period, the AE is attributed to that period (treatment-emergent principle).

- In case of partial start or stop dates (i.e. time and/or day and/or month and/or year missing), the events are allocated to the periods using the available partial information on start and end date; no imputation will be done. If, for instance, the AE start date only month and year are available, these data are compared to the month and year information of the periods. This rule may lead to multiplication of the event as a consequence of its assignment to multiple periods.

- In case of a completely missing start date, the event is allocated to the first active treatment phase (post dose period), except if the end date of the AE falls before the start of the first active treatment phase (post dose period).

- In case of a completely missing end date, the date is imputed by the cut-off date of the analysis for subjects still ongoing in the study, and by the end date of the last period for subjects who discontinued or completed the trial.

Step 2: Combination of events:

Overlapping/consecutive events are defined as events of the same subject with the same preferred term which have at least 1 day overlap or for which the start date of an event is 1 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:

1) If overlapping/consecutive events start in one of the following periods - Screening or follow up (i.e. non-active periods) - followed by an AE in - post-dose or challenge period (active period) - they are allocated to their respective periods and are considered as separate events.

2) In case overlapping/consecutive events start within a single period, they are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

3) In case overlapping/consecutive events start in both an active period followed by a non active period, they are allocated to the active period only and are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, treatment period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

4) In case an active period is followed by another active period, and the overlapping/consecutive events start in both periods, they are allocated to their respective period and are considered as separate AEs. The same rule applies for 2 non-active periods.

Remarks:

1. Events can only be combined into one and the same AE if their start and stop dates are known.

2. In case the completely missing end date is imputed (for period allocation), this date is also considered as a complete date.

3. Time is not considered when determining overlap of events.

7.1.4. Missing Data

Missing data will not be imputed. Subjects who do not report an event will be considered as subjects without an event. The analysis of the solicited AEs will include only documented safety data.

7.1.5. Solicited Local (Injection Site) Reactions

The analysis of local solicited adverse events, for all subjects after vaccination will include:

- Erythema
- Induration/swelling
- Pain/tenderness

7.1.6. Solicited Systemic Adverse Events

The analysis of systemic solicited adverse events for adult subjects after vaccination will include:

- Fatigue
- Headache

- Myalgia
- Arthralgia
- Chills
- Nausea
- Fever (ie, body temperature ≥ 38 °C)

7.2. Clinical Laboratory Tests

For laboratory safety parameters, only abnormalities emerging will be tabulated by worst abnormality grade using the FDA table in Attachment 1. Blood and urine for laboratory safety assessments will be collected within 56 days of vaccination, pre-vaccination, at 7 days post vaccination, prior to challenge on Day –1 or Day –2, post challenge at day 12 and Day 28. Moreover, blood for assessment of cardiac enzymes will also collected on Days 3, 7, and 11.

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered as emerging in a particular period if it is worse than the baseline value. If the baseline is missing, the abnormality is always considered emerging. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also emerging. In case a laboratory test result is censored (no numeric value is available, but only a verbatim term) then a numeric value will be imputed by a value exceeding the cut-off value with one unit. (<x: subtract 1 unit from x, >x: add 1 unit to x; <3.45 is imputed with 3.44).

In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used. In determining toxicity grades, the following rules are applied:

- worst grades/abnormalities are determined over the whole observational period for each trial period separately, including all post-baseline measurements of that period.

- The abnormalities 'abnormally low' and 'abnormally high' are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can by more than 100%)

- Note: as the grading scale for some parameters in the grading table has some gaps (zones where no toxicity grade definition exists), laboratory results falling in these zones will be allocated to the adjacent worst-case grade.

- If a laboratory value falls within the grading as specified in the grading table but also within the local lab normal limits, the value is considered as normal.

- HGB: for hemoglobin grades are based on both actual values and changes. Those grading will be listed separately. In addition, for the grading on the changes of HGB, the corresponding actual value should be at least grade 1.

- Only the lab values are used in determining the toxicity grades. For some lab parameters, extra clinical assessments are available to attribute grade 4 toxicity (eg. requiring hospitalization or dialysis), but these are not taken into account in the lab analysis

For the grades, no distinction will be made between test results of samples obtained under fasting and under non-fasting conditions: in case limits under fasting and non-fasting conditions differ, the limits of the conditions (fasting/non-fasting) of scheduled visits as planned in the CTP will always be used, also for samples obtained under a different condition (e.g. samples of withdrawal visits).

7.3. Vital Signs and Physical Examination Findings

Similar to laboratory tests, only vital signs abnormalities emerging after vaccination and after challenge will be tabulated by worst abnormality grade.

Heart rate (beats per minutes, bpm), respiratory rate (breaths per minute), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) will be collected. The respective vital signs abnormalities are defined in Table 4. Moreover, only the vital signs values will be used, no clinical interpretations, therefore, grade 3 and 4 is shown combined as grade 4 always requires clinical interpretation.

Table 4: Vital Signs Toxicity

Vital Signs	Grade 1	Grade 2	Grade 3/4
Tachycardia – beats (HR) per minute	101 – 115	116 – 130	>130
Bradycardia – beats (HR) per minute	50 – 54	45 – 49	< 45
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	>155
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	>100
Hypotension (systolic) - mm Hg	85 – 89	80 – 84	< 80
Respiratory Rate - breaths per minute	17-20	21-25	>25

Temperature from diary and on-site assessments from day of vaccination will be allocated to predefined temperature intervals (from 37.5° C until 40°C, in steps of half degree increments; eg <37.5, 37.5-<38, 38-<38.5, … >40). A table will be created, showing the maximum temperature for both diary and onsite assessments combined.

A listing of temperatures from Day -2 or -1 will also be provided.

Temperature collected during the post challenge period will be summarized descriptively over each timepoint.

Finally, a listing of subjects with fever according to the FDA grading table, across the entire study period, will be provided.

Any abnormal physical examination result will be documented as AEs, by the investigator.

7.4. Electrocardiograms

ECGs will be carried on Days -2 or -1, 3, 7 and 11 for safety assessment.

The following measurements will be analysed:

- HR (bpm)
- PR (ms)
- QRS (ms)
- Uncorrected QT (ms)

QT values will be corrected for RR, even if provided in the DB. The following QT correction methods will be used (rounded to the integer value):

$$QTcB(ms) = QT(ms)\ x\ \sqrt{\frac{1000}{RR(ms)}}: \text{Bazett's square} - \text{root corrected QT}$$

$$QTcF(ms) = QT(ms)\ x\ \sqrt[3]{\frac{1000}{RR(ms)}}: \text{Fridericia's cube} - \text{root corrected QT}$$

If RR is missing, but HR is available from the same ECG reading, the following replacement will be made in the above formulas.

$$\frac{1000}{RR(ms)} = \frac{HR(bpm)}{60}$$

If HR is missing, it will be calculated using RR (if available) and rounded to the integer value (see formula above). HR from the vital signs section (i.e. pulse) will not be used in this ECG analysis section.

Any rounding will be performed after computation of the applicable parameters, and before any further handling.

Abnormalities for the Actual Values

The actual values for HR, PR, QRS and QTc will be categorized into abnormalities using the boundaries defined in the following table (Limits in this table overrule those presented in the protocol.):

Abnormality Codes	HR	PR	QRS	QTcorrected
"abnormally low"		NAP	NAP	
"abnormally high"		≥ 210 bpm	≥ 120 ms	
"abnormally low Grade 1"	[50-54]			
"abnormally low Grade 2"	[45-49]			
"abnormally low Grade 3"	<45 bpm			
"abnormally high Grade 1"	[101,115]			
"abnormally high Grade 2"	[116,130]			
"abnormally high Grade 3"	>130			
"]450 ms, 480 ms]"				450 ms < QTc ≤ 480 ms
"]480 ms, 500 ms]"				480 ms < QTc ≤ 500 ms
"More than 500 ms"				QTc > 500 ms

- No abnormalities will be defined for actual uncorrected QT values.
- Uncorrected QT ≥ 500 ms will be flagged and only shown in listings.

Abnormalities on the Changes from Reference (QTc Parameters)

Abnormalities on the change from reference will only be defined for corrected QT, as follows:

1. < 30 ms
2. [30; 60] ms
3. > 60 ms

Only increases by ≥30 ms will be considered as abnormalities.

Note: The QTc definitions for abnormalities follow the ICH E14 guidance.

Parameters to Analyze

- actual values: HR, PR, QRS, QT and QTc
- abnormality classifications for the actual values: HR, PR, QRS, QTc
- abnormality classification for the increases from reference: QTc
- worst emergent abnormalities: HR, PR, QRS, QTc, QTc change

Percentages will be calculated relative to the total number of subjects with data.

Note: RR values will only be listed, as well as any original QTc parameter, if provided in the DB. Recalculated HR values will be flagged.

In Case of Missing Date or Time Parts

ECG records with missing assessment date- or time-parts (any: day, month or year) will not be used for descriptive statistics, unless the scheduled target day or time is known and a unique study day allocation is possible taking this additional information into account. These assessments will be allocated to the right study day using the available date (time) information, and the information on their assessment schedule. In case it is not possible to assign a study day to those measurements they will only appear in a listing, including a flag.

Emergent Definition for Abnormalities

Abnormalities defined on actual values: the abnormality worsened as compared to the abnormality at reference; this also includes the shift from 'abnormally high' to 'abnormally low' and vice-versa. Post-reference abnormalities are always treatment-emergent with regard to missing abnormalities at reference. The abnormalities 'abnormally high' and 'abnormally low' are considered equally important.

Abnormalities on changes from reference are always defined as emergent (QTc).

8. IMMUNOGENICITY

The analysis of immunogenicity will use the PPI set.

8.1. Exploratory Parameters

The following humoral and cellular immune responses may be measured as part of the evaluation of exploratory objectives, if available:

Immunogenicity against the insert:

Humoral immune response

- RSV neutralization RSV-A Memphis 37b
- Intranasal pre-F antibody, from nasal wash samples.
- RSV F protein enzyme-linked immunosorbent assay (ELISA; pre- and/or post-fusion F antibodies).
- RSV G/N ELISA
- RSV neutralization A strain (titers of neutralizing antibodies).
- RSV neutralization B and/ or a different A strain (titers of neutralizing antibodies),
- Functional and molecular antibody characterization.

Cell-mediated immune response

- ELISpot IFNγ assay (units: SFU/10^6 PBMC). An ELISpot assay is used to quantify the amount of peripheral blood mononuclear cells (PBMCs) able to produce IFNγ upon RSV F-protein peptide stimulation.

- Intracellular cytokine staining (ICS, unit: % of subset) or cytokine analysis. Analysis of CD4 and CD8 T-cell subsets and their cytokine expression patterns will be determined by flow cytometry after RSV F-protein peptide stimulation (including, but not limited to CD4/CD8, interleukin-2 [IL-2], IFNγ, TNFα and Th1/Th2 subtyping).

  **Cytokine analysis for Th1/Th2 profiling will be done in cases where no ICS data can be generated due to insufficient number of PBMCs for ICS assay (see exploratory endpoints below for description)*

- Cytokine analysis, Cytokine profiles of (in vitro) stimulated PBMC supernatant will be analysed to assess the quantity and quality of the elicited immune responses, including Th1/Th2 balance. Analysis will include, but is not limited to, IFNγ, IL-2, IL-4, IL-5, IL-13, and TNFα, if available.

Immunogenicity against the vector:

- Adenovirus neutralization assay

This assay assesses neutralizing antibody responses against the Ad26 vectors.

8.2. Handling of Missing and/or Unquantifiable Immune Response Data

Missing immune response data will not be imputed.

Depending on the assay, a lower limit of quantification (LLOQ) will be available or a provisional cutoff will be set at the analysis level. Values below the LLOQ or cut-off will be treated as follows:

- Values will be imputed based on the type of analysis. For the calculation of the geometric mean titer, values below LLOQ will be imputed to LLOQ/2. While for the calculation of the geometric mean of the increase from baseline, values below LLOQ will be imputed to LLOQ. The LLOQ values per assay are available in the database.

- For ICS assays: no valid LLOQ is available. A provisional cut-off is put at 0.02%. (only for total cytokine response). For the individual cytokine combinations of IFNg, TNFa and IL2, negative values will be imputed with 0. For descriptive statistics or graphs on actual values, values below the cut-off will be imputed to a value of cut-off/2. For Th1 and Th2, a provisional cut-off of 0.001% is used. These values might change in the future, depending on progressing insight. For descriptive statistics or graphs on actual values, values below the cut-off will be imputed to a value of cut-off/2.

- For all assays: values above the upper limit of quantification (ULOQ) will be imputed with 2xULOQ.

8.3. Immune Response Analysis

No formal hypothesis on immunogenicity will be tested.

8.3.1. Immunogenicity against the insert:

8.3.1.1. Humoral assays

For **VNA** and **ELISA** assays, if available, following results will be calculated: N, geometric mean[§] and corresponding 95% CI of the actual values and fold increases from baseline will be tabulated and graphically presented. *[§]calculate the mean and corresponding 95%CI of the log_2 transformed values, back-transform this mean [i.e. 2^mean] and CI [i.e. 2^CI].*

Tables showing fold increases will also present the percentage of subjects with an x-fold increase (for several values of x).

Actual values and fold changes from baseline are tabulated and shown as dot plots with dots for subject values, and the corresponding geometric mean and 95% CI per time point for each assay. In addition, GMT plots over time, combining the regimens in one graph (without individual subject dots) will also be created.

Ratios of actual values and of fold changes from baseline between humoral assays may also be presented.

Subject profiles of the actual values over time will be graphically presented.

Reverse distribution curves of the actual values are provided for selected time points.

In the graphs, original values will be displayed on the log_2 scale.

Scatterplot with humoral assays may be provided for the most important time points. In these scatter-plots the actual values will be shown, even if they are below the LLOQ, but the LLOQ cut-off will be visualized in the graph per assay if some values are below LLOQ.

8.3.1.2. Cellular assays

For **ICS** and **PBMC secreted** cytokines, if available, analyses may include:

Total Cytokine response: the % of subsets expressing at least IFNg, TNFa or IL2 will be calculated for CD4 and CD8, separately.

For total cytokine responses, tables with number of observations, median, first and third interquartile per timepoint will be provided.

Subject profiles of the actual values over time will be graphically presented.

Actual values are shown as box plots with dots for subject values, and the corresponding median and the first and third quartile (Q1, Q3) per time point.

In addition, box plots over time, combining the regimens in one graph (without individual subject dots) will also be created.

For all cytokine combinations (IFNg and/or TNFa and/or IL2) pie charts reflecting the distribution of each of the cytokine combinations (the proportion of a specific cytokine combination of the CD4 or CD8 T-cells secreting at least one cytokine) and bar charts reflecting the median magnitude of each combination will be graphically presented. Tables with the corresponding descriptive statistics will be provided.

Th1 and Th2: Th1 is defined as all CD4+ IFNγ+ and Th2 as all CD4+ IL4+ cells. Subject profiles and graphs of the actual values over time (box-plot type) will be created. In addition, at time points of interest, scatterplots of Th1 vs Th2 might be created.

For the graphs, original values will be displayed on the $\log_{10}$ scale.

The technical details for the calculation of the ICS values to be used in the graphs will be outlined in the DPS.

For **ELISpot,** if available following results will be calculated: N, median, quartiles and range of the actual values will be tabulated and graphically presented per timepoint.

Subject profiles of the actual values over time will be graphically presented.

Actual values are shown as box plots with dots for subject values, and the corresponding median and interquartile range per time point for each assay. In addition, box plots over time, combining the regimens in one graph (without individual subject dots) will also be created. For the graphs, original values will be displayed on the $\log_{10}$ scale. Scatterplot with humoral and cellular assays may be provided for the most important time points.

8.3.2. Immunogenicity against the vector

For **VNA** against the vector**,** if available following statistics will be calculated: N, geometric mean[§(see above for the calculation)] and corresponding 95% CI of the actual values.

Subject profiles of the assays against the insert will be repeated, highlighting subjects with pre-existing immunity at baseline against the vectors.

Scatterplots of the Adeno assay versus the assays against the inserts may be provided for the most important time points. In these scatter-plots the actual values will be shown, even if they are below the LLOQ.

9. EFFICACY VERSUS IMMUNOGENICITY

The relationship between immunogenicity parameters and VL-AUC, AUC of clinical symptoms and of mucus weight will be graphically explored, with scatterplots for the most important time points. Moreover, descriptive statistics of humoral and cellular assays might be presented by symptomatic RSV infection definition.

ATTACHMENTS

Attachment 1: Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

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.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered as normal.

Blood, Serum, or Plasma	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium – Hyponatremia mmol/L	132 – 134	130 – 131	125-129	< 125
Sodium – Hypernatremia mmol/L	144-145	146 – 147	148-150	>150
Potassium – Hyperkalemia mmol/L	5.1 – 5.2	5.3 – 5.4	5.5-5.6	>5.6
Potassium – Hypokalemia mmol/L	3.5-3.6	3.3-3.40	3.1-3.2	<3.1
Glucose – Hypoglycemia mmol/L	3.83-3.61	<3.61-3.05	<3.05-2.5	<2.5
Glucose – Hyperglycemia Fasting – mmol/L	5.55-6.11	>6.11-6.94	>6.94	Insulin requirements or hyperosmolar coma
Glucose – Hyperglycemia Random – mmol/L	6.11-6.94	>6.94-11.10	>11.10	
Blood Urea Nitrogen mmol/L	8.2-9.3	>9.3 – 11.1	> 11.1	Requires dialysis
Creatinine – umol/L	133 – 150	>150 – 177	>177-221	>221 or requires dialysis
Calcium – hypocalcemia mmol/L	2.10-2.00	<2.00-1.87	<1.87-1.75	<1.75
Calcium – hypercalcemia mmol/L	2.62-2.74	>2.74-2.87	>2.87-3	3
Magnesium – hypomagnesemia mmol/L	0.62-0.53	<0.53-0.45	<0.45-0.37	<0.37
Phosphorous – hypophosphatemia mmol/L	0.81-0.74	<0.74-0.65	<0.65-0.52	0.52
CPK – mg/dL	1.25-1.5xULN	1.6-3.0xUNL	3.1-10xULN	>10 x ULN
Albumin – Hypoalbuminemia g/L	31-28	<28-25	<25	--
Total Protein – Hypoproteinemia g/L	60-55	<55-50	<50	--
Alkaline phosphate – U/L	1.1 – 2xULN	2.1-3xULN	3.1-10xULN	> 10 x ULN
AST U/L	1.1-2.5xULN	2.6-5xULN	5.1-10xULN	>10 x ULN

Blood, Serum, or Plasma	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
ALT U/L	1.1-2.5xULN	2.6-5xULN	5.1-10xULN	>10 x ULN
Bilirubin – when LFT is normal	1.1-1.5xULN.	1.6-2.0xULN	2.0-3.0 x ULN	>3.0 x ULN
Bilirubin – accompanied by graded LFT (ALT or AST)	1.1-1.25xULN	1.26-1.5xULN	1.51-1.75 x ULN	> 1.75 x ULN
Amylase- U/L	1.1-1.5xULN.	1.6-2.0xULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Lipase- U/L	1.1-1.5xULN.	1.6-2.0xULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Cholesterol – mmol/L	64.89-67.80	>67.80-72.64	>72.64	--
Hemoglobin (Female) - g/L	110 – 120	95 – 109	80 – 94	< 80
Hemoglobin (Female) change from baseline value- g/L	Any decrease – 15	16-20	21 – 50	> 50
Hemoglobin (Male) - g/L	125 -135	105 – 124	85 – 104	< 85
Hemoglobin (Male) change from baseline value - g/L	Any decrease – 15	16-20	21 – 50	> 50
WBC Increase – 10E9/L	10.8-15.0	>15.0-20.0	>20.0-25	>25
WBC Decrease - 10E9/L	3.5-2.5	<2.5-1.5	1-<1.5	<1
Lymphocytes Decrease - 10E9/L	1.00-0.75	<0.75-0.50	<0.50-0.25	<0.25
Neutrophils Decrease - 10E9/L	2.0-1.5	<1.5-1.0	<1.0-0.5	<0.5
Eosinophils - 10E9/L	0.65-1.50	>1.50-5.00	>5.00	Hypereosinophilic
Platelets Decreased - 10E9/L	140-125	<125-100	<100-25	<25
PT – seconds (prothrombin time)	1.0-1.10xULN	1.11-1.20xULN	1.21-1.25xULN	>1.25xULN
PTT – seconds (partial thromboplastin time)	1.0-1.2xULN	1.21-1.4xULN	>1.41-1.5xULN	> 1.5 x ULN
Fibrinogen increase – umol/L	11.76-14.70	>14.70-17.65	>17.65	--
Fibrinogen decrease - umol/L	5.88-4.41	<4.41-3.68	<3.68-2.94	<2.94 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

”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

Attachment 2: Transforming the on-site assessments and diaries of solicited AEs into analysis format

When creating the analysis dataset for solicited AEs, solicited AEs (recorded by day on the SR and FA domains) need to be converted into the same format as unsolicited AEs (recorded by event). For this purpose, the start date of the AE will be considered as the date of first occurrence of the solicited AE. If on subsequent day(s), the same grade is reported, the last reported date is used as the end date of the AE. A new record is created in case the grade of the event changes. If there is a time gap of at least one day between two (or more) occurrences of the same solicited AE, then the second (and/or next) occurrence will be considered as a new AE. In case no data is reported for a day, this is analyzed as no event reported. If the on-site assessment differs in grade or relatedness with the Day 1 diary data, the on-site assessment should be recorded as a separate record in the database.

The example below shows how the solicited AE should be converted into a format of unsolicited AEs:

Data from the Subject Diary
Subject: 0001
Solicited systemic AE: Headache

	On site assessment	DIARY DATA							
Solicited AE	Day 1 01Jan16	Day 1 01Jan16	Day 2 02Jan16	Day 3 03Jan16	Day 4 04Jan16	Day 5 05Jan16	Day 6 06Jan16	Day 7 07Jan16	Day 8 08Jan16
Grade	2	1	1	0	3	3	1	0	0
Relatedness	Doubtful	Probable							

The data should be converted and stored in the AE dataset as follows:

Subject No.	AE	Start Date (Char)	Stop Date (Char)	Severity	Relatedness	AEID
0001	Headache	01Jan16	01Jan16	2	Doubtful	1
0001	Headache	01Jan16	02Jan16	1	Probable	1
0001	Headache	04Jan16	05Jan16	3	Probable	1
0001	Headache	06Jan16	06Jan16	1	Probable	1

If a solicited AE ends after day 8:

- The last day that AE was reported and the maximum severity (or/and diameter for local AEs) after Day 8 are captured in the CRF. For this a separate record needs to be created, in case this severity deviates from the previous record.

For the **calculation of duration**, the first and last day is used, irrespective of whether interruptions occurred in between by missing reporting days or Grade 0 events. In the above example, the 4 records contribute to the same AE, therefore AEID (AE identification) is set to the same value and the duration of the AE is set to 6 for all records.

Notes:

- For solicited AEs time should not be taken into account to allocate an event to a phase, the event is per definition of solicited AEs collected post-dose and should therefore not be allocated to inactive phases.
- To complete the start and end-date based on diary data, the date will be calculated based on the day the AE is reported relative to vaccination and not on the reported date. For example, if the vaccination is on 1st JAN2016, and the AE starts on DAY 3, the start date will be set to the 3rd of January 2016 independent of the reported actual date.