Janssen Vaccines & Prevention B.V.*

Statistical Analysis Plan

Randomized, Double-blind, Placebo-controlled Phase 1/2a Study for Safety and Immunogenicity Evaluations for Regimen Selection of Ad26.RSV.preF and/or RSV preF Protein Combinations Followed by Expanded Safety Evaluation in Adults Aged 60 Years and Older

Protocol VAC18193RSV1004; Phase 1/2a

VAC18193 (JNJ-64400141)

* Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study. The sponsor is identified on the Contact Information page that accompanies the protocol

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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

SAP History VAC18193RSV1004		
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Initial Statistical Analysis Plan VAC18193RSV1004_SAP	22/11/2018	
Amended Statistical Analysis Plan VAC18193RSV1004_SAP_Amendment 1	29/01/2019	For details, please refer to Section Amendment.
Amended Statistical Analysis Plan VAC18193RSV1004_SAP_Amendment 2	16/03/2021	For details, please refer to Section Amendment.
Amended Statistical Analysis Plan VAC18193RSV1004_SAP_Amendment 3	09/02/2022	For details, please refer to Section Amendment.
Amended Statistical Analysis Plan VAC18193RSV1004_SAP_Amendment 4	28/03/2022	For details, please refer to Section Amendment.

TABLE OF CONTENTS

ABBREVIATIONS

AE	adverse event
CI	confidence interval
CRF	case report form
CTP	clinical trial protocol
CSR	Clinical Study Report
DRC	Data Review Committee
eCRF	electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
GMC	Geometric mean antibody concentration
FA	Full Analysis Set
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
ICS	Intracellular Cytokine Staining
IVRS	interactive voice response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PI	principal investigator
PP	Per Protocol
RTI	Respiratory Tract Infection
SAE	serious adverse event
SAP	Statistical Analysis Plan
SRP	Study Responsible Physician
SRS	Study Responsible Scientist
SD	standard deviation
TLF	Tables, Listings and Figures

SAP AMENDMENTS

Amendment 1(Creation date 29/01/2019)

The overall reason for the amendment: The SAP was amended to add clarifications on the 'Transforming the on-site assessments and diaries of solicited AEs into analysis format' text and to further clarify which visits will be used to create the summary table of the reported temperatures.

Other minor corrections in punctuation were made throughout the document.

Find below the sections that are affected:

5.3 Vital Signs and Physical Examination Findings
ATTACHMENT 2: Transforming the on-site assessments and diaries of solicited AEs into analysis format

Amendment 2(Creation date: 16/03/2021)

The overall reason for the amendment: To include the protocol-defined visit windows for the per-protocol immunogenicity analysis. Records outside the protocol-defined visit windows will not be included in the per-protocol immunogenicity analysis. The definition of the per-protocol immunogenicity set was also amended: instead of excluding the whole participant from the analysis for participants experiencing a major protocol deviation (MPD) expected to impact immunogenicity outcomes, only samples occurring after the MPD will be excluded.

Find below the sections that are affected:

2.1.2 Visit Windows
2.3 Analysis Sets

Amendment 3(Creation date: 09/02/2022)

The overall reason for the amendment: To align with the clinical trial protocol amendment 6. The concomitant medication section was also updated to align with other RSV vaccine (VAC18193) SAPs. The solicited adverse event SDTM datasets (FA/SR) were remapped to a new structure/model (FA/CE). Therefore, the adverse events section (and attachment 2) of the current SAP was updated to align with the remapping. Analysis of potential adverse events of special interest (AESI) and subgroup analysis were added to the safety analysis. There were minor updates in Section 6.1 to clarify the intracellular cytokine staining (ICS) analysis. The imputation rule of immunogenicity values above the upper limit of quantification (ULOQ) was updated to align with other RSV vaccine (VAC18193) SAPs.
Definition of time intervals for AESIs was added.

Find below the sections that are affected:

1.2 Trial Design
2.1.1 Phase definitions
2.4 Definition of Subgroups

4.4 Concomitant medications
5.1.1 Definitions
5.1.2 Analysis of Adverse Events
5.1.3 Phase allocation of adverse events
6.1 Secondary and Exploratory Endpoints
6.1.2 Handling of Missing and/or Unquantifiable Immune Response Data
ATTACHMENT 2: Transforming Solicited AE data into Analysis Format

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Amendment 4 (Creation date: 28/03/2022)

The overall reason for the amendment: to clarify the protocol-defined visit windows for the per-protocol immunogenicity analysis in case of missing vaccination. Records outside the protocol-defined visit windows will not be included in the per-protocol immunogenicity analysis. In case of missing vaccination, the windows should be based on the day of this missing vaccination. The windows were also updated to align with study protocol.
Methods to define potential AESIs were updated.

Find below the sections that are affected:

2.1.2 Visit Windows
5.1.2 Analysis of Adverse Events

1. INTRODUCTION

This is the Statistical Analysis Plan (SAP) applicable for the VAC18193RSV1004 trial, for all analyses of the initial safety, the regimen selection and the expended safety cohorts mentioned in Section 11.6.1, 11.6.2 and 11.6.3 of the clinical trial protocol (CTP). This SAP will also be used as a guideline for any ad-hoc analyses of these cohorts too.

1.1. Trial Objectives

Please refer to Section 2.1 in the CTP.

1.2. Trial Design

Refer to Section 3.1.1 of the CTP.

1.3. Statistical Hypotheses for Trial Objectives

No formal statistical testing is planned in the initial safety cohort (Cohort 1), in the regimen selection cohort (Cohort 2) and in the expanded safety cohort (cohort 3).

1.4. Sample Size Justification

Please refer to Section 11.2 from the CTP.

1.5. Randomization and Blinding

Please refer to Section 5 from the CTP.

1.6. Changes to Planned Analysis

The Per-protocol Immunogenicity Analysis

Instead of excluding the whole participant data from the per-protocol analysis, the following will be done:

If a participant's immunogenicity sample is collected out of the protocol-defined visit window, the sample will be excluded from the per-protocol analysis. All the other samples (from the same participant) that are not impacted will be included in the per-protocol analysis (Section 2.1.2).

Samples taken after a participant experienced a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the per-protocol analysis (Section 2.3). All other samples (from the same participant) collected before the deviation (that are not impacted) will be included in the per-protocol analysis.

Imputation Rule for Immunogenicity values above the upper limit of quantification (ULOQ)

The imputation rule for immunogenicity values above the ULOQ was updated to align with other RSV vaccine (VAC18193) SAPs. Values above the ULOQ will be imputed with the ULOQ values instead of 2xULOQ.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Study phases

A baseline (or reference) value will be defined as the value of the last available assessment prior to the first vaccination on Day 1.

The safety analysis will present all results by period, except the serious adverse events (SAE) that will be presented by phase and period (See Section 0). Immunogenicity results will be presented per scheduled time point as appropriate. Listings will be shown per phase and time point.

Study day or relative day is defined as follows:

Study Day = visit date - date of Day 1 + 1; if visit date >= date of Day 1 (date of first vaccination).

Study Day = visit date - date of Day 1; if visit date < date of Day 1 (date of first vaccination).

2.1.1. Phase definitions

The phases in the study will be constructed as follows for all groups:

Table 1: Phase Definitions of Cohort 1, 2 and 3

Phase	Phase number	Period	Period number	Interval	
				From	To
Screening	1			00:00 of the date of signing the informed consent form[a]	One minute prior to Dose 1 on Day 1
Regimen	2	Post-Dose 1	1	Date and time of Dose 1 (Day 1)	Minimum of: a) 23:59 at the date of database cut-off b) Maximum (28 days after first vaccination at 23.59, scheduled visit 4 weeks after first vaccination at 23:59) c) 23:59 at the date of last contact (for early discontinuation of the study)
Follow-Up 1	3			1 minute after end of Post-Dose 1 period	Minimum of: a) 23:59 at the date of database cut-off b) One minute prior to date and time of the next vaccination c) 23:59 at the date of last contact (for completed and early discontinuation of the study)

Table 1: Phase Definitions of Cohort 1, 2 and 3

Phase	Phase number	Period	Period number	Interval	
				From	To
Regimen	2	Post-Dose 2	2	Date and time of Dose 2 (Day 57)	Minimum of: a) 23:59 at the date of database cut-off b) Maximum (28 days after second vaccination at 23.59, scheduled visit 4 weeks after second vaccination at 23:59) c) 23:59 at the date of last contact (for early discontinuation of the study)
Follow-Up 2	4			1 minute after end of Post-Dose 2 period	Minimum of: a) 23:59 at the date of database cut-off b) One minute prior to date and time of the next vaccination c) 23:59 at the date of last contact (for completed and early discontinuation of the study)
Regimen	2	Post-Boost (Month 12)	3	Date and time of Month 12 Boost	Minimum of: a) 23:59 at the date of database cut-off b) Maximum (28 days after the Month 12 boost vaccination at 23.59, scheduled visit 4 weeks after the Month 12 boost vaccination at 23:59) c) 23:59 at the date of last contact (for early discontinuation of the study)
Follow-Up Boost (Month 12)	5			1 minute after end of Post-Boost (Month 12) period	Minimum of: a) 23:59 at the date of database cut-off b) One minute prior to date and time of the next vaccination c) 23:59 at the date of last contact (for completed and early discontinuation of the study)
Regimen	2	Post-Boost (Month 24)	4	Date and time of Month 24 Boost	Minimum of: a) 23:59 at the date of database cut-off b) Maximum (28 days after the Month 24 boost vaccination at 23.59, scheduled visit 4 weeks after the Month 24 boost vaccination at 23:59) c) 23:59 at the date of last contact (for completed and early discontinuation of the study)

Table 1: Phase Definitions of Cohort 1, 2 and 3

Phase	Phase number	Period	Period number	Interval	
				From	To
Follow-Up Boost (Month 24)	6			1 minute after end of Post-Boost (Month 24) period	Minimum of: a) 23:59 at the date of database cut-off b) 23:59 at the date of last contact (for completed and early discontinuation of the study)

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

In case the one-dose regimen is selected (Groups 11 through 16 from Cohort 2) after the evaluation of Cohort 2, then the post dose 2 and follow up 2 will not be applicable.

2.1.2. Immunogenicity Visit Windows

For immunogenicity summaries and tabulations per time point, assessments will be allocated to an analysis visit based on the planned visit as captured in the CRF. Visits that are out of the protocol-defined visit windows (see table below) will not be included in the immunogenicity summaries and tabulations per timepoint. However, they may be included in sensitivity analyses.

Table 2: Visit Windows for Immunogenicity Analysis – Cohort 1

Analysis time point label (Relative to Day 1)	Reference day	Target day (from reference day)	Window of target day (days)
Day 1	Day of vaccination 1	1	(-∞, 1]
Day 15	Day of vaccination 1	15	[13, 17]
Day 29	Day of vaccination 1	29	[26, 32]
Day 57	Day of vaccination 1	57	[54, 60]
Day 85	Day of vaccination 2[a]	29	[26, 39]
Day 183	Day of vaccination 1	183	[169, 197]
Day 365	Day of vaccination 1	365	[305, 425]
Day 393	Day of vaccination 3[b]	29	[26, 32]
Day 547	Day of vaccination 3[b]	183	[169, 197]
Day 730	Day of vaccination 3[b]	365	[335, 395]

Notes: [a] in case of missed vaccination 2, the actual date of missed vaccination 2 (i.e. the date of the day 57 visit) is used as a reference day.

[b] in case of missed vaccination 3, the actual date of missed vaccination 3 (i.e. the date of the day 365 visit) is used as a reference day.

Table 3: Visit Windows for Immunogenicity Analysis – Cohort 2

Analysis time point label (Relative to Day 1)	Reference day	Target day (from reference day)	Window of target day (days)
Day 1	Day of vaccination 1	1	(-∞, 1]
Day 15	Day of vaccination 1	15	[13, 17]
Day 29	Day of vaccination 1	29	[26, 32]
Day 57	Day of vaccination 1	57	[54, 60]
Day 85	Day of vaccination 2[a]	29	[26, 39]
Day 183	Day of vaccination 1	183	[169, 197]
Day 365	Day of vaccination 1	365	[335, 395]

Day 547	Day of vaccination 1	547	[517, 577]
Day 730	Day of vaccination 1	730	[700, 760]
Day 912	Day of vaccination 1	912	[882, 942]
Day 1095	Day of vaccination 1	1095	[1065, 1125]

Notes: [a] in case of missed vaccination 2, the actual date of missed vaccination 2 (i.e. the date of the day 57 visit) is used as a refe rence day.

Table 4: Visit Windows for Immunogenicity Analysis – Cohort 3

Analysis time point label (Relative to Day 1)	Reference day	Target day (from reference day)	Window of target day (days)
Day 1	Day of vaccination 1	1	(-∞, 1]
Day 15	Day of vaccination 1	15	[13, 17]
Day 29	Day of vaccination 1	29	[26, 32]
Day 57	Day of vaccination 1	57	[54, 60]
Day 85	Day of vaccination 1	85	[82, 95]
Day 183	Day of vaccination 1	183	[169, 197]
Day 365	Day of vaccination 1	365	[305, 425]
Day 393	Day of vaccination 2[a]	29	[26, 32]
Day 547	Day of vaccination 2[a]	183	[169, 197]
Day 730	Day of vaccination 1	730	[700, 760]
Day 744	Day of vaccination 3[b]	15	[13, 17]
Day 758	Day of vaccination 3[b]	29	[26, 32]
Day 912	Day of vaccination 3[b]	183	[169, 197]
Day 1095	Day of vaccination 1	1095	[1065, 1125]

Notes: [a] in case of missed vaccination 2, the actual date of missed vaccination 2 (i.e. the date of the day 365 visit) is used as a reference day.

[b] in case of missed vaccination 3, the actual date of missed vaccination 3 (i.e. the date of the day 730 visit) is used as a reference day.

2.2. Pooling Algorithm for Analysis Centers

Data from all study center will be pooled together.

2.3. Analysis Sets

Vaccine assignment will follow the as-treated principle.

The **Full Analysis (FA) Set** will include all participants who were randomized and received at least one dose of vaccine (active or placebo), regardless of the occurrence of protocol deviations or the type of vaccine (ie, Ad26.RSV.preF, RSV preF protein, Ad26.RSV.preF/RSV preF protein combination or mixture). All safety and participant information analyses will be based on the FA set.

The **Per-protocol RSV Immunogenicity (PPI) Set** will include all participants who were randomized and received the complete first dose and for whom immunogenicity data are available. Samples taken after a participant experienced a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPI analysis (based on the date/time of the deviation: DV.DVSTDTC). The list of major protocol deviations expected to impact immunogenicity will be documented in the major protocol deviations criteria document that is finalized prior to database lock. These will also be indicated in the locked database.

In addition, the following samples will not be included in the PPI set:

- For participants who experience a natural RSV infection (based on RT-PCR, or other sources), samples collected after the natural infection will not be taken into account in the assessment of the immunogenicity of the selected regimen.
- If a subject misses one or more active dose(s) of the selected regimen but continues the planned visit schedule, samples after the missed active dose(s) will not be taken into account.

The analysis of all secondary and exploratory immunogenicity endpoints related to RSV will be based on the PPI set. Depending on the number of samples excluded, a post-hoc exploratory analysis might be performed, including the excluded samples. To visualize excluded samples, participant profiles from several assays might be repeated, indicating the excluded samples.

2.4. Definition of Subgroups

The following subgroups will be investigated for safety: pre-existing neutralizing antibody response against the Ad26 vector at baseline, i.e., baseline titers >= the lower limit of quantification (LLOQ) versus baseline titers below the LLOQ.

3. DATA REVIEW COMMITTEE REVIEW

An internal data review 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 is one planned DRC meeting when the final participant in the initial safety cohort (Cohort 1) had his/her Day 8 visit. The DRC will review all safety data collected up to that point and provide their recommendation regarding the continuation of the study. The DRC will also convene to discuss any significant or unexpected safety issues. The investigator and SRP/SRS will inform the DRC of any AE of concern. If deemed necessary for safety review, the DRC may request the randomization codes and review unblinded data, if applicable. Moreover, the DRC may review unblinded immunogenicity data during the course of the study if this is deemed necessary for future vaccine development-related decisions. If this is the case, a biomarker representative (not involved in the conduct of the study) will be part of the DRC. Further information regarding the role of the DRC are included in the DRC Charter. Finally, in case additional analyses are requested this SAP will also serve as a guidance.

4. SUBJECT INFORMATION

Subject information will be shown for the full analysis set.

4.1. 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/m^2)

4.2. Disposition Information

The number and percentage of subjects screened, subjects in the FA, in the PPI, subjects vaccinated and not randomized, subjects randomized and not vaccinated and discontinued subjects (study discontinuation and vaccination discontinuation) with the reason of discontinuation will be tabulated per vaccine group and overall.

The number of subjects and percentage per phase will also be tabulated.

4.3. Protocol Deviations

Major protocol deviations will be summarized.

4.4. Concomitant Medications

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

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

If a concomitant therapy record missed components of its start and/or stop dates (time, 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. The same rule applies for identifying whether a concomitant therapy was administered during 8 days following a vaccination. For example, if the vaccination was administered on 30 December 2017 and the concomitant therapy start date is January 2018, then the concomitant therapy will be assumed to have started within 8 days of the vaccination.
- 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.

There will be special attention to any systemic use of analgesics/antipyretics that started during 8 days following each vaccination (00:00 of day of vaccination + 7 days). The following ATC/DD codes will be used for this: N02A (OPIOIDS) and N02B (OTHER ANALGESICS AND ANTIPYRETICS), M01A (ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS) and M01B (ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN

COMBINATION) (ATC/DD Index). The classes will be added in a footnote in all related tables and listings. For the use of analgesics/antipyretics which are taken on the day of vaccination, an exception is made in case the time is before vaccination. In this case, the concomitant medication is also allocated to the post-dose period.

Concomitant therapies will be tabulated per period.

5. SAFETY

Safety analyses will be performed on the FA set. 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 analysed by vaccine regimens as designed per protocol and data will be presented by period. Denominator for the percentages is the number of subjects with considered data in the considered population and period for a certain regimen (incidence per 100 subjects/period).

5.1. Adverse Events (AE)

5.1.1. Definitions

Solicited AEs shown in the tables and listings will be extracted from the SDTM CE domain which will be based on the diary pages and onsite assessment pages of the CRF (ATTACHMENT 2). When participants are given two injections in opposite arms at a given visit, then local solicited AEs will be collected and reported for both arms separately. For unsolicited AEs, only AEs with start date (grade and/or relation) within the 28-day period following vaccination will be presented in the safety tables except for SAEs, which will be captured and tabulated in the outputs covering the whole study period. All other unsolicited adverse events collected outside this 28-day period will be presented through listings. Any RTI recorded as an AE in the eCRF will be excluded from any AE analysis if the central laboratory RT-PCR is subsequently found to be positive for RSV.

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.

5.1.2. 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: 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 and discontinuation), all events, most frequent events, grade 3 events, events leading to permanent stop of vaccine, related events and SAEs. Potential adverse events of special interest (AESI) will be tabulated.

A summary of the solicited and unsolicited AEs will also be tabulated by subgroups of pre-existing Ad26 neutralizing antibody (<LLOQ, >=LLOQ). Refer to the subgroup definition in Section 2.4.

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.

5.1.3. Phase Allocation of Adverse Events

Solicited events are always allocated to the respective Post Dose period. Solicited events are allocated to the phases as described below. However, they are always allocated to the respective post-dose period and will never be attributed to a screening or follow-up phase. Time is not considered while attributing solicited AEs to phases.

For the phase allocation of unsolicited AEs, the following steps will also be followed:

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 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.

- In case of a completely missing start date, the event is allocated to the first active phase (post dose 1 period), except if the end date of the AE falls before the start of the first active phase (post dose 1 period).

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 intermittent follow up (i.e. non-active periods) - followed by an AE in - post-dose 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. In case overlapping/consecutive events start in non-consecutive periods (regardless of active or non-active), they are allocated to their respective period and are considered as separate AEs.
5) In case a non-active period is followed by another non-active period, and the overlapping/consecutive events start in both periods, they are allocated to the first period and 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.

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.

AESI Analysis
Selection of potential AESIs (programmed definition):
Potential AESIs will be selected programmatically. Those will include all reported AEs that are identified by the selection rule:

- SMQ (Standardised MedDRA Queries) = “EMBOLIC AND THROMBOTIC EVENTS (SMQ)”
  or
- (SUB_SMQ1 = “HAEMATOPOIETIC THROMBOCYTOPENIA (SMQ)” and SCOPE in ('BROAD’,’NARROW’)) or HLT (higher level term) = “Thrombocytopenias”

Outputs:
Potential AESIs (programmed definition) will be summarized by Interest category and Preferred Term. The interest categories are:

- 'Embolic and thrombotic events (SMQ)'
- 'Haematopoietic Thrombocytopenias (SMQ) (broad) or HLT = Thrombocytopenias'.

Potential AESI determined programmatically, related to study vaccine (investigator assessment), will be tabulated similarly.
Those AESI analyses will be presented by phase as well as by time interval. The definition of the different time intervals can be found below.
For potential AESIs determined programmatically, attribution to the intervals will be done similarly to the unsolicited AEs as described in Section 5.1.3 above. For Step 2 of phase allocation of adverse events, the '0 - 28 days post-dose' intervals should be treated similar to 'active' periods and the rest as 'non- active' periods.

The Definition of the time intervals is shown in the table below. Additionally, in the tables a '0-56 days post-dose' interval and a '0-6 months post-dose' interval should also be shown. The '0-56 days post-dose' interval is the combination of the '0 - 28 days post-dose' interval and the '29 - 56 days post-dose' interval. The '0-6 months post-dose' interval is the combination of the '0 - 28 days post-dose' ,'29 - 56 days post-dose' and '57 days - 6 months post-dose' intervals.

Definition of intervals:

SR1004 cohort 1/2

Dose	Interval	From	to
Post-vaccination 1	0-28 days post dose	Date time of the 1st vaccination	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of Vaccination 1 + 28 days at 23:59, date of scheduled visit 4 weeks after 1st vaccination at 23:59)
	29-56 days post dose	One minute after the end of the interval 0-28 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • One minute prior to date time of vaccination 2
	57 days - 6 months post-dose #	One minute after the end of the interval 29-56 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses

			• Date of Vaccination 1 + 183 days at 23:59
	>6 months post-dose #	One minute after the end of the interval 57 days - 6 months post-dose	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at the date of DB cut-off for interim analyses • 1 minute prior to date time of Vaccination 3 *
Post-vaccination 2	0-28 days post dose	Date time of the 2nd vaccination	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of Vaccination 2 + 28 days at 23:59, date of scheduled visit 4 weeks after 2nd vaccination at 23:59)
	29-56 days post dose	One minute after the end of the interval 0-28 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Date of Vaccination 2 + 56 days at 23:59
	57 days - 6 months post-dose	One minute after the end of the interval 29-56 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Date of Vaccination 2 + 183 days at 23:59
	>6 months post-dose	One minute after the end of the interval 57 days - 6 months post-dose	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at the date of DB cut-off for interim analyses • 1 minute prior to date time of Vaccination 3 *
Post-vaccination M12*	0-28 days post dose	Date time of the 3rd vaccination	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of Vaccination 3 + 28 days at 23:59, scheduled visit 4

			weeks after **3rd** vaccination at 23:59)
	29-56 days post dose	One minute after the end of the interval 0-28 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Date Vaccination 3 + 56 days at 23:59
	57 days - 6 months post-dose	One minute after the end of the interval 29-56 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of Vaccination 3 + 183 days at 23:59 , day 547 visit at 23:59)
	>6 months post-dose	One minute after the end of the interval 57 days - 6 months post-dose	Min of: • 23:59 at date of last contact (for discontinuations/**completions**) • 23:59 at date of DB cut-off for interim analyses

Only for participants who did not receive the 2nd dose, but who received the 3rd one.
* only applicable for cohort 1, and for participant of cohort 2 who have received a 3rd dose

SR1004 cohort 3

Dose	Interval	From	to
Post-vaccination 1	0-28 days post dose	Date time of the 1st vaccination	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of Vaccination 1 + 28 days at 23:59 , date of scheduled visit 4 weeks after 1st vaccination at 23:59)
	29-56 days post dose	One minute after the end of the interval 0-28 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Date of Vaccination 1 + 56 days at 23:59

	57 days - 6 months post-dose	One minute after the end of the interval 29-56 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum of (Date of Vaccination 1 + 183 days at 23:59 , date of scheduled visit 183 days post 1st vaccination at 23:59)
	>6 months post-dose	One minute after the end of the interval 57 days - 6 months post-dose	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at the date of DB cut-off for interim analyses • 1 min prior to date time of vaccination 2
Post-vaccination M12	0-28 days post dose	Date time of the 2nd vaccination	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of Vaccination 2 + 28 days at 23:59 , date of scheduled visit 4 weeks after 2nd vaccination at 23:59)
	29-56 days post dose	One minute after the end of the interval 0-28 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Date of Vaccination 2 + 56 days at 23:59
	57 days - 6 months post-dose	One minute after the end of the interval 29-56 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum (Date of Vaccination 2 + 183 days at 23:59 , day 547 visit at 23:59)
	>6 months post-dose	One minute after the end of the interval 57 days - 6 months post-dose	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at the date of DB cut-off for interim analyses

			• 1 min prior to date time of vaccination 3
Post-vaccination M24	0-28 days post dose	Date time of the 3rd vaccination	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of Vaccination 3 + 28 days at 23:59 , date of scheduled visit 4 weeks after 3rd vaccination at 23:59)
	29-56 days post dose	One minute after the end of the interval 0-28 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Date of Vaccination 3 + 56 days at 23:59
	57 days - 6 months post-dose	One minute after the end of the interval 29-56 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum of (Date of Vaccination 3 + 183 days at 23:59 , day 912 visit at 23:59)
	>6 months post-dose	One minute after the end of the interval 57 days - 6 months post-dose	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at the date of DB cut-off for interim analyses

5.1.4. 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.

5.1.5. Solicited Local (Injection Site) Reactions

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

- Erythema
- Induration/swelling
- Pain/tenderness

5.1.6. 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)

5.2. Clinical Laboratory Tests

For laboratory safety parameters, only abnormalities emerging will be tabulated by worst abnormality grade using the modified FDA table in ATTACHMENT 1.

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).

5.3. Vital Signs, Physical Examination Findings and Electrocardiogram (ECG)

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

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 5. 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 5: 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 – 160	>160
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, on-site assessments from day of vaccination and any on-site assessment performed between the vaccination visit and the visit 7 days post-vaccination (from 37.5° C until 40°C, in steps of half degree increments, e.g., <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.

Any abnormal physical examination result will be documented as AEs, by the investigator. For Cohorts 1 and 2, any abnormalities in ECG parameter (at screening) will be listed.

5.4. Respiratory Tract Infection (RTI) Forms

During the RSV season(s), participants should record any signs and symptoms of RTI (such as runny nose, fever, severe cough, rapid breathing, difficulty breathing), including measurement of body temperature, on a daily basis until symptoms have resolved using a specific RTI Symptoms Form.

The number of subjects with confirmed RSV infections (based on RT-PCR results or a serological assay) will be summarized per period and per group in case enough cases revealed, otherwise these data will be listed.

6. IMMUNOGENICITY ANALYSIS

The analysis of all secondary and exploratory immunogenicity endpoints related to RSV will be based on the PPI set.

6.1. Secondary and Exploratory Endpoints

The following humoral and cellular immune responses will be measured as part of the evaluation of secondary and exploratory objectives for both cohorts:

Immunogenicity against the insert:

Humoral immune response

- RSV A2 neutralizing titers of the vaccine-induced immune response
- Antibodies binding to RSV F protein in post-fusion (Post F) and pre-fusion (Pre F) form (RSV F-protein enzyme-linked immunosorbent assay [ELISA])

In addition, exploratory analyses may be performed to further investigate vaccine-elicited immune responses. These may include, but are not limited to, the following:

- RSV cross-neutralization of B strain
- Intranasal pre-F and Post-F antibody, from nasal wash samples
- Fc receptor function assays

Moreover, additional humoral immune responses may also be measured as part of further evaluation of exploratory objectives for both cohorts:

Humoral immune response

- RSV cross-neutralization of other A strain

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).

Moreover, additional cellular immune responses may also be measured as part of further evaluation of exploratory objectives for both cohorts:

- 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, TNFα, CD107a, Granzyme B, and CD154, if available.

- Sequencing of B-cells
- Transcriptome analysis

Immunogenicity against the vector:

- Adenovirus neutralization assay

This assay assesses neutralizing antibody responses against the Ad26 vector.

Immunogenicity to assess RSV exposure

- N protein antibodies (ELISA)
- Ga and Gb protein antibodies (ELISA)

6.1.1. Secondary and Exploratory Immunogenicity Analysis

No formal hypothesis on the secondary and exploratory immunogenicity parameters will be tested.

6.1.1.1. Humoral Assays

For **VNA** and **ELISA** assays 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].*

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.

Scatterplots between humoral assays may be provided for the most important time points. In these scatterplots 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.

Moreover, subjects with a 4-fold increase in Ga or Gb ELISA will be considered as infected and the number of infected subjects will be summarized per period and regimen. The subject profiles of the assays against the insert will also be repeated, highlighting the infected infected subjects based on Ga or Gb ELISA

Other exploratory parameters may be analysed at the discretion of the sponsor.

6.1.1.2. Cellular Assays

For **ELISpot,** following results will be calculated: N, median, quartiles, minimum and maximum of the actual values will be tabulated and graphically presented.

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.

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

Total Cytokine response: the % of subsets expressing at least IFNγ, 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.

For cytokine combinations (for example, IFNγ and/or TNFa and/or IL2), bar charts reflecting the median magnitude of each combination may be graphically presented. In that case, tables with the corresponding descriptive statistics will also be provided.

Th1 and Th2:

Th1 is defined as %RSV-F specific CD4 T-cells IFNγ+ AND/OR IL2+.

Th2 is defined as %RSV-F specific CD4 T-cells IL4+ AND/OR IL13+ AND CD40L+.

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.

Scatterplot with humoral and cellular assays may be provided for the most important time points.

The technical details for the calculation of the ICS values to be used in the graphs will be outlined in the data presentation specifications (DPS) document.

6.1.1.3. 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 scatterplots the actual values will be shown, even if they are below the LLOQ.

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

Missing immune response data will not be imputed.
Depending on the assay, a 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: if no LLOQ is available for a certain ICS cytokine combination (e.g., total cytokine response, Th1/2, etc.) at the time of analysis, a provisional lower limit of 0.001% will be used to impute as described above

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

7. REGIMEN SELECTION RULE

7.1. Immunogenicity Analysis

The objective is to compare the RSV A2 neutralizing antibody levels of all regimens containing RSV preF protein (Groups 12 through 17) to the one-dose Ad26.RSV.preF regimen (Group 11). This will be based on the estimation of GMT ratios and corresponding 95% confidence intervals (CIs) of the VNA A2 levels of the regimens containing RSV preF protein on Day 29 for the one-dose regimens (Groups 12 through 16) and on Day 85 for the two-dose regimen (Group 17) versus the VNA A2 levels on Day 29 of the one-dose Ad26.RSV.preF regimen (Group 11).

Additional factors such as data from other assays, cost of goods, and ease of administration will be taken into account to select the regimen for the expanded safety phase.

ATTACHMENTS

ATTACHMENT 1: Toxicity Tables

Adapted from the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).

The grading scale used for laboratory assessments is based on the FDA Guidance document "Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". Any laboratory value shown as a "graded" value in the table that is within the central laboratory normal ranges will not be graded for severity or recorded as an AE. For hemoglobin, both the actual value and the change from reference will be graded. For the change from reference, the corresponding actual value should also be at least Grade 1

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)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
***" ULN" is the upper limit of the normal range.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 160	> 160	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

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

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

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

ATTACHMENT 2: Transforming Solicited AE data into Analysis Format

Solicited AEs diary and onsite data in the SDTM FA and SR domains will both be remapped to the SDTM CE domain. They will be recorded by event in the CE domain, like the format of unsolicited AEs. The reported start date of an AE in the CE domain will be the date of first occurrence of the solicited AE. The last reported date will be used as the end date of the AE, regardless of possible changes in grade or time gaps, and taking into account if the AE continues after Day 8. The grade of the solicited AE (in CE) will be the maximum grade over the duration of the AE reporting period.

The derivation of the solicited AE ADAM dataset from SDTM CE will follow a similar approach to the derivation of the unsolicited AE ADAM dataset from SDTM AE. For observed solicited AE(s), one record per AE type will be derived per participant per post-dose period, pooling both onsite and diary records in the SDTM CE data. The start date of an AE will be derived as the first occurrence of that AE type (pooling the onsite and diary record) for a participant. The end date will be derived as the last end date between the onsite and diary record. The duration of a solicited AE will be recalculated in the ADAM dataset as: the derived end date – derived onset date + 1.