Janssen Vaccines & Prevention B.V.*

Statistical Analysis Plan

A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate a Range of Dose Levels of an Ad26.RSV.preF-based Vaccine in Adults Aged 60 Years and Older

Protocol VAC18193RSV2005; Phase 2a

VAC18193 (JNJ-64400141/JNJ-64213175)

* 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.

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

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AMENDMENT HISTORY

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Document Type and File Name	**Issue Date**	**Amendment Type**	**Comments**
Initial Statistical Analysis Plan VAC18193RSV2005 SAP	09-June-2020	-	-

ABBREVIATIONS

Ad26	adenovirus serotype 26
ADaM	analysis data model
AE	adverse event
BMI	body mass index
CD	cluster of differentiation
CI	confidence interval
CTP	clinical trial protocol
DPS	data presentation specifications
DRC	data review committee
ELISA	enzyme-linked immunospot
ELISpot	enzyme-linked immunosorbent assay
FA	full analysis (analysis set)
F protein	fusion protein
FDA	Food and Drug Administration
GMT	geometric mean titer
ICS	intracellular cytokine staining
IFNγ	interferon gamma
Ig	immunoglobulin
IL	interleukin
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PPI	per-protocol immunogenicity (analysis set)
pre-F	pre-fusion
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDTM	standard data tabulation model
SE	standard error
Th	T-helper (cell)
TNFα	tumor necrosis factor alpha
ULOQ	upper limit of quantification
VNA	virus neutralization assay
vp	viral particles
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) contains information needed to perform the complete safety and immunogenicity analysis of the VAC18193RSV2005 trial. It applies to the primary and final analyses, as specified below:

- Cohort 1 primary analysis will include 14-day immunogenicity and 28-day safety data of all groups in Cohort 1. The sponsor will be unblinded for Cohort 1 at the time of the primary analysis of Cohort 1, and the blind will be maintained at the participant and study site level up to study end.
- Cohort 2 and 3 primary analysis will include 28-day safety data of all groups in Cohorts 2 and 3. If 14-day immunogenicity data are available at the time of the primary analysis, these will be included as well, otherwise these will be analyzed at a later timepoint. The sponsor will be unblinded for Cohorts 2 and 3 at the time of the primary analysis, and the blind will be maintained at the participant and study site level up to study end.
- Final analysis at the end of the study will include safety and immunogenicity data from all cohorts. Data collected up to the time of the last visit for the last participant will be included in the analysis. This analysis will be performed on unblinded data.

Note: The final analysis might be done per cohort, depending on the timing.

This document is based on the clinical trial protocol (CTP) version 2.0 (EDMS-ERI-201635401). The specifications of individual tables, listings and figures to be generated in each analysis will be described in a separate data presentation specifications (DPS) document.

1.1. Study Objectives

Refer to Section 3 of the CTP.

1.2. Study Design

Refer to Section 4 of the CTP.

1.3. Statistical Hypotheses for Study Objectives

No formal statistical testing is planned. The data will be analyzed descriptively.

1.4. Sample Size Justification

Refer to Section 9.2 of the CTP.

1.5. Randomization and Blinding

Refer to Section 6.3 of the CTP.

1.6. Changes to Planned Analysis

No changes from the planned analysis have been determined.

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 vaccination on Day 1.

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 the first year/season:

Table 1: Definitions of the Analysis Phases

Phase	Phase	Period	Period	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form	One minute prior to start of post dose period
Regimen	2	Post-dose	1	Date and time of first vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation from study) b) 23:59 at the date of database cut-off date for interim analyses c) Maximum (28 days after first vaccination at 23:59, scheduled visit 4 weeks after first vaccination at 23:59)
Follow-up	3			One minute after the end of the post-dose period	Minimum of: a) 23:59 at the date of last contact b) 23:59 at the date of database cut-off date for interim analyses

Adverse events and concomitant medications will be allocated to the above phases and period, see details in Section 6.1 and Section 4.4 respectively. The regimen phase (post-dose period) is considered the active phase, the screening and follow-up phase are considered non-active phases.

2.1.2. 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 (Table 2 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

Analysis time point label (Relative to Day 1)	Target day	Window of target day (days)
Day 1	1	(-∞, 1]
Day 15	15	[12, 22]
Day 85	85	[71, 99]
Day 183	183	[169, 197]

2.2. Pooling Algorithm for Analysis Centers

Data will be pooled across the different centers.

2.3. Analysis Sets

Vaccination assignment will follow the as treated principle.

2.3.1. Full Analysis (FA) set

The FA set will include all participants who were randomized and received the study vaccine, regardless of the occurrence of protocol deviations. All safety and participant information analyses will be based on the FA set.

2.3.2. Per-Protocol Immunogenicity (PPI) set

The PPI set will include all participants who were randomized and received the study vaccine, and for whom immunogenicity data are available, excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes.

The analysis of all immunogenicity endpoints will be based on the PPI set. As a sensitivity analysis, key immunogenicity tables will also be based on the FA set.

2.4. Definition of Subgroups

No subgroup analysis is planned for this study.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An internal Data Review Committee (DRC) will be commissioned for this study to discuss any safety issues and any situation meeting a specific study vaccination pausing rule (CTP Sections 9.6 and 7.3). Planned data reviews of the DRC are specified in CTP Section 4.1. The role and responsibilities of the internal DRC are detailed in the DRC Charter. The DRC analyses will follow the same statistical methods described in this SAP. A separate DPS document has been provided to describe specifications of individual tables, listings and figures to be generated in each DRC analysis.

4. SUBJECT INFORMATION

Subject information will be analyzed based on the FA set. For each cohort, tables will be presented by vaccine group and overall. Categorical variables will be summarized in frequency tables and continuous variables with descriptive statistics.

4.1. Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

- Sex (Female/Male)
- Age (years)
- Age categories (years): 60-64, 65-74, 75-84, ≥85
- Race
- Ethnicity
- Risk level of severe RSV disease (Increased risk / Non-increased risk), as collected (CDC definition)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI categories (kg/m^2): <20, 20-<25, 25-<30, ≥30

4.2. Disposition Information

The number and percentage will be tabulated for subjects that were:

- Screened
- not randomized, not vaccinated
- not randomized but vaccinated
- randomized not vaccinated
- randomized and vaccinated (subjects in the FA set)
- in the PPI set

Number and percentage of subjects who discontinued the study together with the reason(s) for discontinuation will also be tabulated.

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

4.3. Protocol Deviations

Major protocol deviations will be tabulated.

4.4. Concomitant Medications

The analysis of concomitant therapies will be done using the World Health Organization (WHO) drug coded terms.

There will be special attention to any systemic use of analgesics/antipyretics, administered during 8 days following each vaccination (00:00 of day of vaccination + 7 days). The following CMCLASCD (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)[1]. The classes will be added in a footnote in all related tables and listings.

Concomitant therapies will be reported in each applicable study phase based on their start and stop date. That is, a concomitant therapy will be allocated to each study phase in which it was taken.

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

- In the event of a partial start or stop dates, the concomitant therapy records will be allocated to phases 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 phases, and the concomitant therapy record will be allocated to the phase(s) where these date parts match. This rule may lead to assignment to multiple phases. 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 the 30th of December 2017 and the concomitant therapy start date is January 2018 (missing day), then the concomitant therapy will be assumed to have started within 8 days of the vaccination.
- In the event of a completely missing start date, the concomitant therapy will be considered as having started before the study.
- In the event of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the study.

Concomitant therapies will be tabulated per study phase and period.

4.5. Medical History

Medical history and concomitant diseases will be listed.

5. IMMUNOGENICITY

5.1. Parameters

The immunogenicity endpoints (primary, secondary and exploratory endpoints) are described in CTP Section 3. The following immunogenicity assays are applicable for this study:

Immunogenicity against RSV:

Humoral Immune Response

- Pre-F protein binding antibodies using enzyme-linked immunosorbent assay (ELISA)
- RSV A2 neutralizing antibodies
- Post-F protein binding antibodies (ELISA)*
- RSV cross-neutralization of B and/or other A strain(s) *
- Anti-F protein antibody specificity characterization*
- Nasal immunoglobulin (Ig)A and/or IgG binding to RSV F protein in prefusion and/or postfusion form*

Cellular Immune Response

- Antigen-specific T-cell immune responses*
- Interferon (IFN)-γ enzyme-linked immunospot (ELISpot)

Immunogenicity against Ad26:

- Neutralizing antibodies to Ad26*

** This is an exploratory endpoint, it will only be analyzed if available.*

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

Missing immune response data will not be imputed.

Values below the lower limit of quantification (LLOQ) 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 increases, values below LLOQ will be imputed to LLOQ.

For ICS assays (if available), the LLOQ will be used if available and validated. In case no validated LLOQ is available then a provisional cut-off will be provided before database lock. Negative observations will be set to zero before calculating the total cytokine responses or other ICS parameters. For descriptive statistics or graphs on actual values, values below the LLOQ or cut-off will also be imputed to a value of LLOQ/2 or cut-off/2.

Values above the upper limit of quantification (ULOQ) will be imputed to ULOQ.

The LLOQ and ULOQ values per assay will be available in the database.

5.3. Immune Response Analysis

Immunogenicity data will be summarized per cohort, vaccine group and timepoint. For a selection of tables, data might be pooled over cohorts.

The primary analysis set for immunogenicity is the PPI set. As a sensitivity analysis, key tables will also be generated based on the FA set to explore the effect major protocol deviations. Depending on their occurrence, this factor might be further explored.

5.3.1. Immunogenicity Against RSV

5.3.1.1. Humoral Assays

For humoral assays, N, geometric mean (GMT)[§] and corresponding 95% CI of the actual values will be calculated. The fold increases from baseline will be tabulated and graphically presented.
[§]The mean and corresponding 95%CI will be calculated on the log_2 -transformed values, and then back-transformed [i.e. 2^mean] and CI [i.e. 2^CI].

Actual values and fold changes from baseline will be summarized in tables and 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 ratios 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 will be provided for selected time points. In the graphs, original values will be displayed on the log_2 scale.

A scatterplot of the virus neutralization assay **(**VNA) versus ELISA will 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.

To explore the dose-response relationship between pre-F ELISA and different dose levels of the study vaccine, a linear regression model will be fitted for each timepoint separately, using data of the active groups of Cohort 1, with the log transformed pre-F ELISA titers at the considered timepoint as dependent variable, the number of titration steps as independent variable, and the GMT of pre-F ELISA of the Ad26/protein pre-F RSV vaccine ($1x10^{11}$ vp/150 µg) at the considered timepoint as a fixed intercept. The regression slope and 95% one-sided lower confidence limit for the slope will be calculated.

The following linear model will initially be fitted for the active groups of Cohort 1 but may be extended in a later stage with data of the active groups of Cohorts 2 and 3. A similar model may be fitted as well for other assays:

$$log_2(\text{pre-F ELISA}_{timepoint}) = GMT\ \text{pre-F ELISA}_{Ad26/protein\ (1x10^{11}\ vp/150\ \mu g),timepoint} + slope.\#titration\ steps + error$$

Depending on the model fit, other models (such as, log-linear models or EMAX models) may be explored as well.

Other exploratory immunogenicity parameters maybe analyzed at the discretion of the sponsor.

5.3.1.2. Cellular Assays

For IFNγ enzyme-linked immunospot (ELISpot), N, median, quartiles and minimum and maximum of the actual values will be presented in tables and graphs. Subject profiles of the actual values over time will also be graphically presented.

Actual values will be shown as boxplots with the corresponding median and interquartile range per time point, including dots representing the individual subject values. In addition, boxplots over time will also be created with all the vaccine groups combined in one graph (without the individual subject dots). For the graphs, original values will be displayed on the $\log_{10}$ scale.

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

For ICS and PBMC secreted cytokines (if available) analyses may include:

Total Cytokine response: the % of subsets expressing at least IFNγ, TNFα or IL2 will be calculated for $CD4^+$ and $CD8^+$. Tables with the corresponding descriptive statistics will be provided. Subject profiles of the actual values over time will be graphically presented.

Actual values will be shown as boxplots with the corresponding median and interquartile range per time point for each assay, including dots representing the individual subject values. In addition, boxplots over time will also be created with all the vaccine groups combined in one graph (without the individual subject dots). For the graphs, original values will be displayed on the $\log_{10}$ scale

For all cytokine combinations (IFNγ and/or TNFα and/or IL2), bar charts reflecting the median magnitude of each combination of $CD4^+$ and $CD8^+$ T-cells will be graphically presented. Tables with the corresponding descriptive statistics will be provided.

Graphs may also be created to explore additional CD4+ and CD8+ cytokine responses included in the ICS panel (may include but not limited to IL4, IL17, CD17, CD45RA), based on data availability.

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

Scatterplots with humoral versus 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 DPS.

5.3.2. Immunogenicity Against Ad26

For Ad26-specific VNA, the following statistics will be calculated and presented in tables: N, geometric mean[§] and corresponding 95% CI of the actual values.

[§]The mean and corresponding 95%CI will be calculated on the log_{10}-transformed values, and then back-transformed.

Subject profiles of the assays against the insert will be repeated, highlighting subjects with pre-existing immunity at baseline against the vector (Ad26-specific VNA).

Scatterplots of the Ad26-specific VNA at baseline versus the assays against the inserts will 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. SAFETY

Continuous variables will be summarized using the following statistics, as appropriate: number of observations (N), arithmetic mean (mean), 95% confidence interval (CI) for the mean, standard deviation (SD), standard error (SE), median, quartiles (Q1 and Q3), minimum and maximum. Frequencies and percentages (to one decimal place) will be generated for categorical variables.

Safety data will be summarized per cohort, vaccine group and study phase. In addition, for a selection of tables, data of Cohorts 2 and 3 may be pooled over cohorts.

Safety data will be presented only for the active period or phase, except SAEs which will be presented in all phases in which they were reported. The analysis phases are defined in Section 2.1.1. Denominator for the percentages is the number of subjects in the considered analysis set and period/phase for a certain vaccine group (incidence per 100 subjects/period).

6.1. Adverse Events (AE)

The analysis of AEs will be based on the medical dictionary for regulatory activities (MedDRA) coded terms as provided in the clinical database.

The safety endpoints (primary and secondary endpoints) are described in CTP Section 3.

6.1.1. Definitions

The analysis of solicited AEs will be based on the overall assessment by the investigator. For unsolicited AEs, only the AEs starting within the 28-day period following vaccination will be presented in the safety tables, except for SAE, which will be captured and presented throughout the study. Unsolicited non-serious adverse events collected outside the 28-day period following the vaccination will be presented through listings.

By definition, all solicited AEs at the injection site (local) will be considered related to the study vaccine administration.

The severity of the AEs (solicited and unsolicited) will be classified as Mild (Grade 1), Moderate (Grade 2), Severe (grade 3) or Potentially Life Threatening (Grade 4). See CTP Section 10.2 and 10.3 for details on the criteria for the AE severity classification.

6.1.2. Analysis of Adverse Events

Number and percentage of subjects with at least one particular AE (unsolicited/solicited) will be tabulated. Unsolicited AEs and SAEs 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, at least grade 3, related (systemic only), time to onset (in days) and duration (in days) for most frequent events.

For solicited AEs, duration is defined as the number of days from the start of the event until resolution of the event. If the investigator reports multiple events of the same solicited AE in the reporting period (e.g., due to differences in their relationships to the study vaccine), duration will be derived from the onset date of the first event and the resolution date of the last event (date of resolution of last event – date of first onset + 1). 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, the following tables will be provided: summary table (including SAE, fatal outcome), all AEs, most frequent AEs, grade 3, AE related study vaccine, SAE.

Listings and/or subject narratives will be provided as appropriate, for subjects who died, or experienced a severe or serious AE.

6.1.3. Phase allocation of Adverse Events

As the analysis of solicited events will be based on the overall assessment of the investigator which is documented in the SDTM CE domain, ADaM datasets will be based on the CE domain. Solicited AEs will always be allocated to the post-dose period, they will not be attributed to the Screening Phase. Time is not considered while attributing solicited AEs to phases. For unsolicited AEs, the steps below will be followed.

Step 1: Allocation of AEs to the phases

Adverse events in the SDTM database are allocated to phases 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 phase, the AE is attributed to that phase (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 phases using the available partial information on start and/or end date; no imputation will be done. If, for instance, for the AE start date only month and year are available, these data are compared to the month and year information of the phases. 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 phase (post dose period), except if the end date of the AE falls before the start of the first active phase (post dose period).
- In case of a completely missing end date (for the calculation of duration), 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 phase for subjects who discontinued or completed the trial. The imputed end dates will not be shown in the data listings.

Step 2: Combining overlapping/consecutive AEs

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 or may not be combined into one AE, according to the following rules:

1. If an overlapping/consecutive event starts in a non-active period (screening or follow up phase), and is followed by an AE in a post-dose period (active period), they are allocated to their respective phases/periods and are considered as separate events.
2. If the overlapping/consecutive events start within the same period/phase, 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. If the 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, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

Remarks:

- Events can only be combined into one and the same AE if their start and stop dates are known.
- In case the completely missing end date is imputed (for phase allocation), this date is also considered as a complete date.
- Time is not considered when determining overlap of events.

6.1.4. Handling of Missing AE Data

Missing data (severity grade, relationship) will not be imputed. Subjects for whom no event is reported by the investigator, will be considered as subjects without an event. An AE with a missing severity grade or relationship will be included in the tabulation of subjects with one or more AEs, but will be considered as 'not reported' for the tabulation of the severity grade or relationship. For example, an AE with missing severity will be considered as an AE reported for the analysis of any grade but will be considered as not reported for the analysis of grade 3.

6.2. Clinical Laboratory Tests (Cohorts 2 and 3 only)

Laboratory toxicity grades will be determined according to the FDA toxicity grading table (CTP Section 10.2). If toxicity grades are not defined for a test, the abnormalities (above/below normal range) will be determined according to the clinical laboratory normal ranges.

Emerging abnormalities will be tabulated by worst toxicity grade. 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. (i.e., for "<x", subtract 1 unit from x. For ">x" add 1 unit to x. E.g., <3.45 is imputed with 3.44).

In determining toxicity grades and abnormalities based on normal ranges, the following rules apply:

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

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

- The grading scale of some parameters in the grading table has 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.

- For the grading on hemoglobin changes from baseline, the corresponding actual value should be at least grade 1. Toxicity grades of the actual values and changes from baseline will be tabulated separately.
- Only the laboratory actual values will be used to determine the toxicity grades. For some parameters, extra clinical assessments are required to attribute a grade 4 toxicity (e.g., requiring hospitalization or dialysis), but these are not taken into account in this laboratory safety analysis.

For the grades, no distinction will be made between test results of samples obtained under fasting and under non-fasting conditions: if the normal range under fasting and non-fasting conditions differ, the normal range 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).

6.3. Vital Signs and Physical Examination Findings

The distribution of the body temperature data per half degree intervals (diary and onsite measurements from the time of vaccination until 7 days after vaccination) will be tabulated (intervals from 37.5° C until 40°C, in steps of half degree increments, e.g., <37.5, 37.5-<38, 38-<38.5, …, >40). The maximum temperature per subject for both diary and onsite assessments combined will be used for this tabulation. A listing of subjects with fever according to the FDA grading table will also be provided.

For heart rate, respiratory rate, systolic and diastolic blood pressure, the number and percentage of subjects with values beyond the following clinically relevant limits (Table 3) will be tabulated. Only the vital signs values will be used to assign abnormalities, no clinical interpretations will be used. Therefore, grade 3 and 4 are combined because grade 4 always requires clinical interpretation. Only vital signs abnormalities emerging after vaccination will be tabulated by worst abnormality grade. An abnormality (or grade) will be considered as emerging if it is worse than the baseline value. If the baseline is missing, the abnormality is always considered emerging.

Table 3: Vital Signs Abnormalities

Vital Signs	**Grade 1**	**Grade 2**	**Grade 3/4**
Tachycardia (beats per minute)	101 – 115	116 – 130	> 130
Bradycardia (beats per minute)	50 – 54	45 – 49	< 45
Systolic hypertension (mm Hg)	141 – 150	151 – 160	> 160
Diastolic hypertension (mm Hg)	91 – 95	96 – 100	> 100
Systolic hypotension (mm Hg)	85 – 89	80 – 84	< 80
Respiratory Rate (breaths per minute)	17 – 20	21 – 25	> 25

Abnormal vital signs results and abnormal physical examination findings will be listed.

REFERENCES

1. http://www.whocc no/atc_ddd_index/