Janssen Vaccines & Prevention B.V.

Statistical Analysis Plan (IDMC)

A Randomized, Controlled, Observer-blind, Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26.RSV.preF in RSV-seronegative Toddlers 12 to 24 Months of Age

Protocol VAC18194RSV2002; Phase 1/2a

VAC18194 (Ad26.RSV.preF)

Status:	Approved
Date:	25 June 2019
Prepared by:	Janssen Vaccines & Prevention B.V.
Document No.:	EDMS-ERI-165320895, v2.0

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

Table of Context

ABBREVIATIONS

Ad26	adenovirus serotype 26
ADaM	analysis data model
AE	adverse event
CEC	clinical endpoint committee
CTP	clinical trial protocol
CRF	case report form
DPS	data presentation specifications
EIA	enzyme immunoassay
ERD	enhanced respiratory disease
FA	full analysis
F protein	fusion protein
GCP	good clinical practice
ICS	intracellular cytokine staining
IDMC	independent data monitoring committee
IFNγ	interferon gamma
LRTI	lower respiratory tract infection
MA-RTIs	medically-attended RTIs
MedDRA	medical dictionary for regulatory activities
NSAID	non-steroidal anti-inflammatory drug
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
RTI	respiratory tract infection
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	standard data tabulation model
SE	standard error
SpO_2	peripheral capillary oxygen saturation
SSG	statistical support group
Th	T-helper (cell)
VNA	virus neutralizing antibody
vp	viral particles
WHO	world health organization

DEFINITION OF TERMS

Active vaccines	Ad26.RSV.preF
	Nimenrix
Study vaccine	Ad26.RSV.preF or Control

1. INTRODUCTION

An independent data monitoring committee (IDMC) will be established in the study VAC18194RSV2002 to review safety data and to ensure the continuing safety of the subjects enrolled in this study.

This statistical analysis plan (SAP) contains the derivations and statistical methods for the analysis to be conducted for the IDMC. There is one planned IDMC analysis in the current study, to be performed on Day 8, after the first dose in the first 12 toddlers (6 receiving the active vaccine and 6 receiving placebo). Snapshot data will be used—The database will be cleaned on an ongoing basis, there will be no formal data cleaning for the IDMC analyses.

The IDMC will review unblinded data. An external statistician (the statistical support group (SSG) statistician) independent of the sponsor and not involved in the interim, primary, and final analyses of the study will prepare the data and perform all analyses for review by the IDMC .

Details on each table, graph and listing to be generated for the IDMC is described in a separate data presentation specifications (DPS) document. However, the study team or IDMC may request additional deliverables, with this SAP serving as a guidance. Safety data from the interim (if applicable), primary and final analyses will also be shared with the IDMC.

1.1. Objectives of the IDMC

The primary purpose of this IDMC is to ensure the safety of subjects in this study by monitoring safety data collected in the clinical program and to provide recommendations to the study team. Special attention will be given to severe RSV-LRTI cases. The IDMC will make recommendations regarding the conduct of the study including changes to the informed consent. Details on the roles and responsibilities of the IDMC are described in Section 5 of the IDMC charter.

1.2. Trial Design

This is a multi-center, randomized, observer-blind, Phase 1/2a study, to be conducted in 48 male and female RSV-seronegative toddlers aged ≥12 to ≤24 months.

Each subject's RSV serostatus will be assessed by RSV enzyme immunoassay (EIA) at screening[a]. *Note*: serostatus may be assessed via this assay if available from a different study of the sponsor (VAC18194RSV2001). If done within 42 days of first dose, this assessment would not have to be repeated in the absence of a history of respiratory infection during that period. Additionally, the seronegative status will be confirmed by the absence of an anamnestic humoral immune response (which is usually observed 7-10 days post antigen re-exposure in RSV seropositive subjects) from blood samples taken on Day 8 after the first dose.

[a] The cut-off for seronegativity is a titer <1 EIA unit.

Subjects will be randomized 1:1 to receive either Ad26/Ad26/Ad26 (at 2.5×10^{10} vp) or placebo/placebo/Nimenrix®[a,b] (or placebo/placebo/placebo) (Table 1).

Table 1: Study Design VAC18194RSV2002

Group	N	Day 1	Day 29/Week 4	Day 57/Week 8
RSV-seronegative toddlers 12 to 24 months				
Group 1	24	Ad26.RSV.preF (2.5×10^{10} vp)	Ad26.RSV.preF (2.5×10^{10} vp)	Ad26.RSV.preF (2.5×10^{10} vp)
Group 2	24	Placebo (saline)	Placebo (saline)	Nimenrix or Placebo (saline)

N = number of subjects; vp = viral particles

Subjects will be followed up for safety up to 2 RSV seasons after the first dose. Immunogenicity samples will be taken at Day 1, Day 8, Day 85 and at the end of the first RSV season. For safety, solicited AEs will be checked up to Day 8 after each vaccination, unsolicited AEs up to Day 85 and SAEs throughout. All RTIs will be collected during the RSV season. Severe LRTIs and medically-attended RTIs (MA-RTIs) will be collected throughout the whole study.

For more details on the design, refer to the clinical trial protocol (CTP), section 3.1.

1.3. Statistical Hypotheses for Trial Objectives

No formal statistical hypothesis will be tested.

1.4. Sample Size Justification

See CTP, Section 11.2.

1.5. Randomization and Blinding

See CTP, Section 5.

[a] In countries where the commercial vaccine Nimenrix is licensed, placebo (0.9% saline) can be replaced with Nimenrix as the Day 57 vaccination for the study subjects in the control group, in accordance with the local label and local regulations, and unless contra-indicated. Nimenrix will be administered, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision). In the US, Nimenrix will not be used unless it has been licensed for use or an IND has been submitted. It should be recorded in the eCRF by the unblinded pharmacist whether the subject was vaccinated with either Nimenrix or placebo on Day 57.

[b] Nimenrix is a vaccine used to protect adults, adolescents, and children from the age of 6 weeks against invasive meningococcal disease caused by 4 groups of the bacterium *Neisseria meningitidis* (group A, C, W-135, and Y).

2. GENERAL ANALYSIS DEFINITIONS

A baseline (or reference) value will be defined as the value of the last available assessment performed prior to the first dose (active vaccine or placebo).

2.1. Study Phases

The phases and periods in the study will be constructed as follows:

Table 2: Analysis Phases and Periods

Phase	Phase #	Period	Period #	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form[a]	One minute prior to first vaccination
Regimen	2	Post-dose 1	1	Date and time of first vaccination	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 analysis c) One minute prior to second vaccination. If second vaccination was not administered, then use maximum of (Day 28 after the first vaccination at 23:59, scheduled visit 28 days after first vaccination at 23:59)
Regimen	2	Post-dose 2	2	Date and time of second vaccination	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 analysis c) One minute prior to third vaccination. If third vaccination was not administered, then use maximum of (Day 28 after the second vaccination at 23:59, scheduled visit 28 days after second vaccination at 23:59)
Regimen	2	Post-dose 3	3	Date and time of third vaccination	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 analysis c) Maximum (Day 28 after the third vaccination at 23:59, scheduled visit 28 days after third vaccination at 23:59)
Follow-up	3			One minute after the end of the last 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 in case of interim

[a] In case an earlier date is available (e.g. for vital signs), then use the very first date to include all data in the screening phase.

Adverse events will be allocated to the above phases and periods, see details in section 4.1. The regimen phase (post-dose 1, post-dose 2 and post-dose 3 periods) is considered the active phase, the screening and follow-up phase are considered non-active phases.

For descriptive statistics over time, assessments (regardless of the investigated parameter) will be allocated to an analysis visit based on the planned visit as captured in the database.

2.2. Pooling Algorithm for Analysis Centers

Data will be pooled across the different centers.

2.3. Analysis Sets

2.3.1. Full Analysis (FA) Set

The 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.

2.4. Definition of Subgroups

No subgroup analysis is planned for this study.

3. SUBJECT INFORMATION

Subject information will be analyzed based on the FA analysis set.

3.1. Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Sex (Female/Male)
- Age (months)
- Race
- Ethnicity
- Weight (will only be listed)
- Height (will only be listed)
- Weight for age percentile[3]
- Length for age percentile[3]
- Breastfeeding history
- Family members smoking history
- Number and age of siblings (will only be listed)

3.2. Disposition Information

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

- Screened
- randomized and vaccinated

- randomized not vaccinated
- not randomized but vaccinated
- not randomized, not vaccinated

Number and percentage of subjects who discontinued together with the reason(s) for discontinuation will be tabulated. This will be done separately for discontinuation of the study vaccine and for discontinuation of the trial.

3.3. Concomitant Medication

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 period based on their start and stop date. That is, a concomitant therapy will be allocated to each period in which it was taken.

If a concomitant therapy record has missing components of its start and/or stop dates (missing 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.

Concomitant therapies will be tabulated per period.

4. SAFETY

Continuous variables will be summarized using the following statistics, as appropriate: number of observations, arithmetic mean (mean), 95% 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 in each period of the active phase. Only SAEs will be tabulated for all phases, including the non-active phases. The analysis phases are defined in section 2.1. Denominator for the percentages is the number of subjects in the considered population and period for a certain regimen (incidence per 100 subjects/period).

Note: Safety data post-dose 3 in the control group will be presented separately for Nimenrix and placebo, unless otherwise specified (section 5.2).

4.1. Adverse Events

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

4.1.1. Definitions

The following safety and reactogenicity endpoints are the primary endpoints:

- Solicited local and systemic AEs for 7 days after each vaccination.
- Unsolicited AEs for 28 days after each vaccination.
- SAEs from first dose administration to the end of the study.

Solicited AEs are precisely defined events (local and systemic) that subjects are specifically asked about and which are noted by subjects in the diary. In each reporting period, the investigator will evaluate the solicited AEs (from diary) per subjects and will record the overall assessment in the CRF. These data will include whether a solicited AE was observed, its start and end date, maximum severity grade over the reporting period, causality and seriousness (Yes/No). The analysis of solicited AEs will be based on the overall assessment by the investigator, per subject per reporting period. By definition, all solicited AEs at the injection site (local) will be considered related to the study vaccine administration.

Unsolicited AEs are all AEs that a subject experienced but were not specifically asked about. For unsolicited AEs, only the AEs starting within the 28-day period following each vaccination will be presented in the safety tables, except for SAE, which will be captured and presented throughout the study.

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 12.1.3 for details on the criteria for the AE severity classification.

Phase Allocation of Adverse Events
Solicited AEs will always be allocated to their respective post-dose period, they will not be attributed to the Screening Phase..

The analysis of unsolicited AEs includes the following two steps:

1. AEs are allocated to phases;
2. Overlapping /consecutive AEs within a phase are combined.

STEP 1: Allocation of AEs to the phases (and respective periods)
Adverse events in the SDTM database will be 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/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 periods. In case of a completely missing start date, the event is allocated to the appropriate period (post-dose 1), except if the end date of the AE falls before the start of the post-dose 1 period. 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 (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 period 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 that have at least 1 day in 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) In case a non-active phase (e.g. Screening, Follow-up) is followed by an active phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate events.
2) In case overlapping/consecutive events start within a single phase, they are considered as one and the same AE. The individual events that contribute to this AE are retained as individual records in the ADAM database but are assigned the same onset, phase, and total duration.
3) In case an active phase is followed by a non-active phase (e.g. Follow-Up), and the overlapping/consecutive events start in both phases, they are allocated to the active phase and are considered as one and the same AE. The individual events that contribute to this AE are retained as individual records in the ADAM database but are assigned the same duration, onset and active phase.
4) In case an active phase is followed by an active phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate AEs. The same rule applies for 2 non-active phases.

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

2. In case the completely missing end date is imputed (for phase allocation), this date is also considered as a complete date.
3. Time during the day is not considered when determining overlap of events.

4.1.2. 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, the following tables will be provided: summary table, by worst severity grade, grade 3, related to study vaccine (systemic only). Note: for solicited AEs, duration is defined as 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 a 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 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, discontinuation), all AEs, most frequent AEs, grade 3, permanent stop of vaccine, AE related study vaccine, 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 AE or SAE.

4.1.3. Handling of Missing Data for Adverse Events

Missing data will not be imputed.

4.1.4. Solicited Local (Injection Site) Reactions

The analysis of local solicited adverse events will include:

- Erythema
- Induration/swelling
- Pain/tenderness

4.1.5. Solicited Systemic Adverse Events

The analysis of systemic solicited adverse events for pediatric subjects will include:

- Loss of appetite
- Vomiting
- Diarrhea
- Decreased activity/lethargy
- irritability/crying
- Fever (i.e., body temperature ≥ 38 °C)

4.2. Vital Signs and Physical Examination Findings

Heart rate, respiratory rates and oxygen saturation (SpO_2) will be summarized with descriptive statistics.

Body temperature (diary and onsite measurements during first 8 days) will be tabulated by half degree increments, in each analysis period. The number and percentage of subjects with values beyond the following clinically relevant limits will be tabulated:

- Respiratory rate >45 breaths/minute
- Pulse rate >140 beats/minute
- Oxygen saturation (SpO_2) <95%

A listing of a subject's narrative may be created in case a pausing rule is met. Vital signs results and abnormal physical examination findings will be included in the subject narratives. A mock layout of the subject narrative is provided in the DPS.

5. RSV INFECTIONS

5.1. Definitions

The secondary endpoint related to RSV infection:

- Severe RSV-LRTI as a preliminary indication of ERD
  Severe RSV-LRTI will be defined as the presence of severe LRTI as assessed by the CEC, and confirmation of RSV infection by nasal (mid-turbinate or nasopharyngeal) sample using independent RT-PCR by a central laboratory. If no central laboratory RT-PCR result is available, a positive test result (including commercial test results) for RSV from a local laboratory (if available) could be used to confirm RSV infection upon evaluation by the CEC.

5.2. Analysis of RSV infection

The number and percentage of subjects with RTI and RSV confirmed RTIs will be tabulated.

As soon as 3 or more events (regardless of group) of 'severe RSV-LRTI' have been observed, the proportions per group and the confidence limits for the difference in proportions (using Wilson score method[2]) between the Ad26.RSV.preF group and control group (pooling placebo/placebo/Nimenrix and placebo/placebo/placebo) will be constructed. The upper (one-sided) 95% confidence limit for the difference, the lower (one-sided) 95% confidence limit for the difference and the lower (one-sided) 80% confidence limit will be constructed.

REFERENCES

1. http://www.whocc no/atc_ddd_index/
2. Newcombe R. G. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med.; 1998;17:873-890
3. World Health Organization. WHO Child Growth Standards. Available at: http://www.who.int/childgrowth/standards/Technical_report.pdf?ua=1 (last accessed 16 March 2017)

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