Janssen Research & Development

Statistical Analysis Plan
Amendment 1

A Phase 3 Randomized Double-blind Controlled Study to Evaluate the Immunogenicity, Safety, and Reactogenicity of ExPEC9V and High-dose Quadrivalent Influenza Vaccine, With and Without Co-administration, in Adults Aged 65 Years or Older

E.ngage

Protocol VAC52416BAC3002; Phase 3

VAC52416 (JNJ-78901563) ExPEC9V

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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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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	11 September 2023	Not Applicable	Initial release
2.0	21 May 2024	(1) Added – MAAE to the safety analysis, – Non-inferiority testing based on MOPA functional titers at 29 days after the administration of ExPEC9V vaccine, – Description of the details and type of data to be reviewed by the IDMC.	(1) Requested by Health Authority.
		(2) Day 59 is removed from Table 6 (Visit Windows for HI Antibody Titers Immunogenicity Analysis).	(2) HI titer at Day 59 will not be available.
		(3) Data for the stratification factors, age and history of UTI will be obtained as collected from the eCRF; in addition, analysis using data from IWRS will be performed to support non-inferiority.	(3) Clarify the source of data for the stratification variables age and history of UTI, whether (as collected) from the eCRF or (as stratified) from IWRS.
		(4) Add ExPEC immunogenicity analysis stratified by baseline titer (titers <= LLOQ and titers > LLOQ).	(4) Interest in ExPEC immunogenicity analysis stratified by baseline immune status.
		(5) Minor changes (e.g., grammar, paragraph rearrangement) to the SAP for clarity.	

LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
AE	adverse event
AS	All Screened
BMI	body mass index
CI	confidence interval
CoAd	Coadministration
CSP	clinical study protocol
E. coli	*Escherichia coli*
ECL	Electrochemiluminescent
eCRF	electronic case report form
EPA	exotoxin A derived from *Pseudomonas aeruginosa*
ExPEC9V	9-valent extraintestinal pathogenic *Escherichia coli* vaccine
FAS	full analysis set
GMR	geometric mean ratio
GMT	geometric mean titer
HD	high dose
HI	hemagglutination inhibition
IDMC	Independent Data Monitoring Committee
IWRS	interactive web response system
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MOPA	multiplex opsonophagocytic killing assay
PPEI	per protocol ExPEC immunogenicity
PPII	per protocol influenza immunogenicity
SAE	serious adverse event
SAP	Statistical Analysis Plan
ULOQ	upper limit of quantification
UTI	urinary tract infection

1. INTRODUCTION

This SAP contains the definitions of analysis sets, derived variables, and statistical methods that will be used to evaluate the reactogenicity, safety and immunogenicity analysis of the VAC52416BAC3002 (E.ngage) study. The specifications of individual tables, listings and figures to be generated in each analysis will be described in the Data Presentation Specifications document.

This SAP is developed in line with the CSP Amendment 1 approved on 22 September 2023.

1.1. Objectives and Endpoints

Refer to Section 3 of the CSP. The statistical hypotheses are described in Section 2 of this SAP.

1.2. Study Design

Refer to Section 4.1 of the CSP for details on the study design. Refer to section 6.3 of the CSP for details on randomization and stratification and procedures for maintaining the blind. The target vaccination day for each intervention group is given in Table 2.

Table 2: Target Vaccination Days of the Study Intervention Groups

Group Number	Group Name	Day 1	Day 30
1	CoAd	ExPEC9V + Influenza vaccine	Placebo
2	Control	Placebo + Influenza vaccine	ExPEC9V

Group number and group name may be interchangeably used in the SAP.

2. STATISTICAL HYPOTHESES

To demonstrate the non-inferiority of the humoral immune response to the 4 influenza vaccine strains after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of a HD quadrivalent seasonal influenza vaccine administered alone

AND

to demonstrate the non-inferiority of the humoral immune response against the O-serotype antigens after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of ExPEC9V administered alone.

The following hypotheses will be tested:

Null Hypothesis:

For at least 1 of the 4 influenza vaccine strains: the GMT of HI antibody titers against the considered vaccine strain, 29 days after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine is inferior by at least 1.5-fold to the GMT 29 days after the administration of a HD quadrivalent seasonal influenza vaccine alone

OR

For at least 1 of the 9 O-serotype antigens: the GMT of antibody titers against the considered O serotype antigen 29 days after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine is inferior by at least 1.5-fold to the GMT 29 days after the administration of ExPEC9V alone.

Alternative Hypothesis:

For each of the 4 influenza vaccine strains: the GMT of HI antibody titers 29 days after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine is non-inferior to the GMT 29 days after the administration of a HD quadrivalent seasonal influenza vaccine alone, using a non-inferiority margin of 1.5, for the ratio $GMT_{\text{Control group}}/GMT_{\text{CoAd group}}$

AND

For each of the 9 O-serotype antigens: the GMT of antibody titers 29 days after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine is non-inferior to the GMT 29 days after the administration of ExPEC9V alone, using a non-inferiority margin of 1.5, for the ratio $GMT_{\text{Control group}}/GMT_{\text{CoAd group}}$.

3. SAMPLE SIZE DETERMINATION

Refer to Section 9.2 of the CSP.

4. PARTICIPANT ANALYSIS SETS

The study intervention assignment will follow the as-treated principle. The analysis sets that will be used in the analysis are shown in Table 3.

Table 3: Description of Analysis Sets

Analysis Sets	Description
AS Set	This analysis set will include all participants screened for the study regardless of whether they were screen failures or they were enrolled into the study. Rescreened participants are counted only once.
Randomized Set	This analysis set will include all participants who were randomized i.e., had a valid randomization issued by IWRS implemented in this study.
FAS	The analysis set will include all participants who received at least one study vaccination, regardless of the occurrence of protocol deviations and vaccine type (HD quadrivalent seasonal influenza vaccine, ExPEC9V, or placebo). All safety and participant information analyses will be based on the FAS.
PPII Set	This analysis set will include all randomized participants who received the first study vaccination (ExPEC9V in combination with a HD quadrivalent

Table 3: Description of Analysis Sets

Analysis Sets	Description
	seasonal influenza vaccine for the CoAd group and a HD quadrivalent seasonal influenza vaccine alone for the Control group), and for whom immunogenicity data are available for at least one of the influenza strains in the vaccine. Samples taken after a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from PPII analysis. The primary analysis set for analyses related to influenza immunogenicity is the PPII Set. As a sensitivity analysis, key tables may also be based on the FAS.
PPEI Set	This analysis set will include all randomized participants who received ExPEC9V in combination with a HD quadrivalent seasonal influenza vaccine for the CoAd group and ExPEC9V alone for the control group and for whom O-antigen immunogenicity data are available for at least one *E. coli* serotype. Samples taken after a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPEI analysis. The primary analysis set for analyses related to O-antigen immunogenicity is the PPEI Set. As a sensitivity analysis, key tables may also be based on the FAS.

The list of major protocol deviations that would lead to elimination from the immunogenicity analysis will be specified in the Major Protocol Violation Criteria Document, which is established before the study starts and will be finalized before database lock and unblinding. See Appendix 2 for more details.

5. STATISTICAL ANALYSES

5.1. General Considerations

The significance level (α) is 5% (2-sided). As both non-inferiority objectives should be demonstrated to have a successful study and as no interim analyses before the primary analysis are planned, no multiplicity adjustments are needed.

5.1.1. Study Phases

The immunogenicity baseline (or reference) value for the two groups is determined as follows. For CoAd group, the baseline value of the HI and ExPEC9V antibody titers will be the value of the last available assessment prior to the vaccination on Day 1. For the Control group, the baseline value for the HI and ExPEC9V antibody titers will be the value of the last available assessment prior to the vaccination on Day 1 and Day 30, respectively.

If a participant received at Day 1 both vaccinations but the start date-time of one of the vaccinations is not available in the clinical database, this date-time will be imputed with the date-time of the other vaccination.

The safety analysis will present all results by phase. Immunogenicity results will be presented per scheduled time point as appropriate. Listings may 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).

For ExPEC9V immunogenicity endpoints in the Control group, the day of the second vaccination will be considered as Day 1 in Post-dose 2.

5.1.2. Phase Definitions

The phases in the study will be constructed as follows (see Table 4).

Table 4: Phase Definitions

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 1 period
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 database cut-off date for analysis conducted before the final analysis c) For participant that discontinues from the second vaccination: the maximum of (29 days after the first vaccination at 23:59, scheduled visit completed 29 days after first vaccination at 23:59) is used d) For participant where the scheduled Day 30 visit = day of 2nd dose: one minute prior to Post-dose 2 e) For participant where the scheduled Day 30 visit < day of 2nd dose: scheduled visit 29 days after first vaccination at 23:59

Table 4: Phase Definitions

Phase	Phase #	Period	Period #	Interval	
				From	To
Follow-up 1	3			Only for participant where scheduled Day 30 visit < day of 2nd dose or participant who discontinues from 2nd vaccination: one minute after Post-dose 1 period end	Only for participant where the scheduled Day 30 visit < day of 2nd dose: one minute prior to Post-dose 2
					For participant that discontinues from the 2nd vaccination: Minimum of: a) 23:59 at the date of last contact (for early discontinuation or participants that completed the study) b) 23:59 at the date of database cut-off date for analyses conducted before the final analysis
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 for analysis conducted before the final analysis c) Maximum of (29 days after the 2nd vaccination at 23:59, scheduled visit completed 29 days after the 2nd vaccination at 23:59
Follow-up 2	4			One minute after Post-dose 2 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the database cut-off date for analysis conducted before the final analysis

5.1.3. Immunogenicity Visit Windows

For immunogenicity analysis, assessments will be allocated to an analysis visit based on the planned visit as captured in the eCRF. Visits that are out of the protocol-defined visit windows (see Table 5 for ExPEC9V and Table 6 for HI antibody titer immunogenicity analysis) will not be included in the PPII/PPEI immunogenicity analysis. However, they may be included in the sensitivity analyses based on FAS.

Table 5: Visit Windows for ExPEC9V Antibody Titers Immunogenicity Analysis

Group	Analysis time point label (relative to ExPEC9V vaccination)	Corresponding CSP visit day	Reference day	Target day (from reference day)	Window of target day (days)
CoAd group	Day 1	Day 1	Day of vaccination 1	1	(-8, 1]
	Day 30	Day 30	Day of vaccination 1	30	[23, 37]
	Day 59	Day 59	Day of vaccination 2	30	[23, 37]
Control group	Day 1	Day 30	Day of vaccination 2	1	(-8, 1]
	Day 30	Day 59	Day of vaccination 2	30	[23, 37]

Table 6: Visit Windows for HI Antibody Titers Immunogenicity Analysis

Analysis time point label (Relative to Flu vaccination)	Corresponding CSP visit day	Reference day	Target day (from reference day)	Window of target day (days)
Day 1	Day 1	Day of vaccination 1	1	(-8, 1]
Day 30	Day 30	Day of vaccination 1	30	[23, 37]

5.2. Participant Dispositions

Participant information will be shown in the appropriate analysis sets.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group or overall, as appropriate.

- participants in the AS set (overall only)
- participants in the Randomized set
- participants vaccinated and not randomized
- participants randomized and not vaccinated
- participants not randomized and not vaccinated (overall only)
- participants in the FAS
- participants in the PPII set at each visit after administration of flu vaccine
- participants in the PPEI set at each visit after administration of ExPEC9V vaccine
- participants who discontinued study
- participants who discontinued second vaccination
- reasons for premature termination of the study
- reasons for discontinuation of second vaccination

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

The number of participants in each of the stratification stratum in the IWRS (as stratified) will be compared to the number reported in the eCRF (as collected).

Other participant information variables: demographics and baseline characteristics, major protocol deviations, and concomitant medications will be analyzed as described in Appendix 1, Appendix 2 and Appendix 3, respectively. Medical history and concomitant diseases will be tabulated or presented in a listing, as appropriate.

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The primary endpoints are:

- HI titers against each of the 4 influenza vaccine strains at 29 days after the administration of a HD quadrivalent seasonal influenza vaccine and
- Multiplex ECL-based immunoassay antibody titers at 29 days after the administration of ExPEC9V vaccine.

5.3.2. Analysis Methods

The primary immunogenicity objectives will be assessed by calculating the following CI.

- The 2-sided 95% CIs for the difference in $\log_{10}$-transformed HI antibody titers against each of the 4 influenza vaccine strains at 29 days after the administration of the HD quadrivalent seasonal influenza vaccine between the Control and the CoAd groups.
- The 2-sided 95% CIs for the difference in $\log_{10}$-transformed O-serotype antibody titers against each of the 9 O-serotypes at 29 days after the administration of ExPEC9V vaccine between the Control and the CoAd group.

For HI antibody titers against each of the 4 influenza vaccine strains and for O-serotype antibody titers against each of the 9 O-serotypes, an analysis of variance (ANOVA) model will be fitted with the respective titers as dependent variable, and group (Control or CoAd), age category ($\geq$65 to <75 and $\geq$75 years) and history of UTI (yes/no) as independent variables. Based on these ANOVA models, the CIs around the difference will be calculated and will be back transformed (by exponentiation) to CIs around a GMT ratio ($GMT_{Control\ group}/GMT_{CoAd\ group}$) and compared to the non-inferiority margin of 1.5.

Only if the upper bound of the 2-sided 95% CI for the GMT ratio (Control group/CoAd group) of the HI antibody titers for each of the 4 vaccine strains and of the O-serotype antibody titers for each of the 9 O-serotype antigens lies below 1.5, non-inferiority of co-administration versus separate administration will be concluded for both vaccines (HD quadrivalent seasonal influenza vaccine and ExPEC9V). If 1 or more confidence limits for the GMT ratio exceed 1.5, non-inferiority cannot be concluded.

As a sensitivity analysis to assess the impact of baseline titers, the primary endpoint will also be evaluated adjusting for the respective baseline titers. For immunogenicity, baseline is considered as the last assessment prevaccination. In a second sensitivity analysis, different variances between the groups will be allowed. Therefore, the CIs will be calculated via Welch's ANOVA.

The primary analysis will be based on the stratification factors, age group and history of UTI reported in the database, as collected in the eCRF. Supportive analyses for non-inferiority will be performed by age group and history of UTI as stratified in IWRS.

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

Missing immune response data will not be imputed.

Data below the LLOQ will be treated differently according to the statistical analysis.

- For the calculation of GMT, data below LLOQ will be imputed with ½ of the LLOQ.
- For the calculation of geometric mean of fold change from prevaccination, data below LLOQ will be imputed with LLOQ.

Data above ULOQ will be imputed with the ULOQ.

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

5.4. Secondary Endpoint(s) Analysis

5.4.1. Non-inferiority Testing on MOPA

Analysis will be performed to evaluate the non-inferiority of MOPA functional antibody response against the vaccine O-serotype antigens after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of ExPEC9V administered alone. The endpoint is given by:

- Opsonophagocytic antibody titers to vaccine O-serotype antigens as determined by MOPA at 29 days after the administration of ExPEC9V vaccine.

5.4.2. Antibody HI Titers

- Seroconversion is defined for each of the 4 influenza vaccine strains at 29 days after the administration of a HD quadrivalent seasonal influenza vaccine
  - HI titer ≥1:40 in participant with a prevaccination HI titer of <1:10, or
  - a ≥4-fold HI titer increase in participant with a prevaccination HI titer of ≥1:10
- Seroprotection is defined for each of the 4 influenza vaccine strains as HI titer ≥1:40 at 29 days after the administration of a HD quadrivalent seasonal influenza vaccine

5.4.3. ExPEC9V O-serotype Antibody Titers

ExPEC9V serotype antibodies will be measured by multiplex ECL-based immunoassay and MOPA assays. The EPA is measured by multiplex ECL-based immunoassay only.

The immunogenicity endpoints are:

- Total serum immunoglobulin G antibody titers determined by multiplex ECL-based immunoassay
- Functional antibody titers determined by MOPA

The endpoints are evaluated between the two study vaccination groups at all immunogenicity time points, at Days 1, 30, and 59 for titers determined by multiplex ECL-based immunoassay and at Days 1 and 30 (relative to ExPEC9V vaccination, refer to Table 5) for titers determined by MOPA.

In addition, the two endpoints determined at 29 days after administration of ExPEC9V are evaluated between participants reporting a history and without history of UTI at enrolment.

5.4.4. Analysis Methods

As in the primary analysis, in all analyses that incorporate age group and history of UTI, the stratification factor data are obtained as collected from the eCRF. Supportive analyses for non-inferiority are performed by age group and history of UTI as stratified and recorded in IWRS.

A 2-sided 95% CIs for the difference in $\log_{10}$-transformed O-serotype opsonophagocytic antibody titers against each of the 9 O-serotypes at 29 days after the administration of ExPEC9V vaccine between the Control and the CoAd group will be evaluated to determine whether the immune response against O-serotype antigens after administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine is non-inferior compared to after the administration of ExPEC9V alone. As in the primary analysis method, an ANOVA model will be fitted with the respective titers as dependent variable and study intervention group, age group and history of UTI as independent variables. Based on these models, the CIs around the difference will be calculated and will be back transformed to CIs around a GMT ratio ($GMT_{Control\ group}/GMT_{CoAd\ group}$) and compared to the non-inferiority margin of 1.5.

As a sensitivity analysis to assess the impact of baseline titers, this secondary endpoint will also be evaluated adjusting for the respective baseline titers. For immunogenicity, baseline is considered as the last assessment prevaccination. In a second sensitivity analysis, different variances between the groups will be allowed. Therefore, the CIs will be calculated via Welch's ANOVA.

The proportion of seroconverted and seroprotected participants will be tabulated. The difference in proportions of seroconverted and seroprotected participants between the Control and the CoAd group will be estimated together with the 2-sided 95% CIs (calculated using Wilson's score method).

The following measures of ExPEC9V O-serotype antibody titers (ECL and MOPA) and the EPA (ECL) will be evaluated and tabulated at the immunogenicity timepoints by study vaccination groups stratified by age (≥65 to <75 years, ≥75 years, and all) and by history of UTI. Analysis stratified by history of UTI in the combined study vaccination groups will also be performed.

- proportion of participants with a ≥2-fold and ≥4-fold increase in serum antibody titers from baseline (prevaccination)
- GMT
- geometric mean of fold change from baseline (GMR), calculated from the ratio of post baseline to baseline value (prevaccination)

Graphical representations of immunological parameters will be made as applicable.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

No tertiary and exploratory analyses are planned in this study.

5.6. Safety Analyses

Safety data will be summarized descriptively. No formal statistical testing of safety data is planned. If analysis by age group and by history of UTI is performed, stratification factor data are obtained as collected from the eCRF.

Safety endpoints (secondary endpoints):

- Solicited local (in each injection site for the first vaccination) and systemic AEs for 14 days post each vaccination
- Unsolicited AEs for 29 days post each vaccination
- MAAEs and SAEs collected from the administration of first vaccination until 6 months
- post last vaccination

Safety analyses will be performed on the FAS. Continuous variables will be summarized using the following statistics, as appropriate: number of observations, mean, 95% CI for the mean, median, quartiles (1st and 3rd), minimum, and maximum. Frequencies and percentages (one decimal place) will be generated for categorical variables. No formal comparisons between groups will be provided.

Safety data will be analyzed and presented by study intervention and phase, and across the entire study period where applicable. For solicited AEs, the denominator for the percentages is the number of participants with data assessed by the investigator in the considered population and phase for a certain regimen (incidence per 100 participants/phase). For unsolicited AE, the denominator for the percentages is the number of participants in the considered population and phase for a certain regimen (incidence per 100 participants/phase).

5.6.1. Adverse Events

5.6.1.1. Definitions

Solicited AEs shown in the tables are extracted from the investigator assessment pages (Clinical Events) of the eCRF. All solicited AEs at the injection site (local) are considered related to the study vaccine administration.

For unsolicited AEs, only the AEs within the 29-day period following each vaccination will be presented in the safety tables except for MAAE and SAE which will be captured and tabulated in the outputs covering the whole study period.

The severity of the AEs will be classified as Grade 1 to 4. Solicited or unsolicited events that are graded less than Grade 1, are not considered as AE.

5.6.1.2. Analysis of Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities.

Number and percentage of participants with at least one specific AE (solicited/unsolicited) will be tabulated. Solicited AEs will be summarized by class (local and systemic) and preferred term. Unsolicited AEs will be summarized by System Organ Class 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). 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 vaccination period.

For unsolicited AEs, the following tables will be provided as appropriate: summary, all events, most frequent, at least Grade 3, related AE, AE leading to study vaccine discontinuation, AE leading to study discontinuation, participants who died, MAAE, related MAAE, SAE and related SAE.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue vaccination due to an AE, who discontinue study due to an AE, MAAE or who experience a severe or a SAE.

Summaries and/or listings may be provided separately for AEs with onset outside the above defined timeframe (i.e., beyond 29 days post-vaccination).

5.6.1.3. Phase Allocation of Adverse Events

Step 1: Allocation of events to the periods:

As the analysis of solicited events will be based on the overall assessment of the investigators which is documented in the CE domain, the ADaM dataset will be based on the CE domain. 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 the screening phase. Time of day is not considered while attributing solicited AEs to phases.

Unsolicited adverse events 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 participants still ongoing in the study, and by the end date of the last period for participants who discontinued or completed the trial. In case of a completely missing start date, the event is allocated to the first active treatment phase (Post-dose 1 period), except if the end date of the AE falls before the start of the first active treatment phase (Post-dose 1 period).

Step 2: Combination of Events:

Overlapping/consecutive events are defined as events of the same participant 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 phases/periods - Screening or Follow-up (defined as non-active periods) - followed by an AE in - Post-dose period (defined as active period) - they are allocated to their respective phases/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 consecutive 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.

5.6.1.4. Missing Data

Missing data will not be imputed. Participants who do not report an event will be considered as participants without an event. An AE with a missing severity or relationship will be considered as an AE reported but will be considered as not reported for the severity 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 at least Grade 3.

5.6.2. Vital Signs

Vital signs (systolic and diastolic blood pressure [while sitting], heart rate, respiratory rate, and body temperature) will be measured both before vaccination and after the end of the 30-minute observation period. At non-vaccination visits, vital signs may be measured if deemed necessary by the investigator.

Baseline and emerging vital signs abnormalities after vaccination will be listed based on the abnormality gradings in Appendix 4 (Section 6.4). An abnormality 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.

Any clinically significant changes in vital signs will be reported as an AE. Any clinically significant changes in vital signs that are observed prior to the first vaccination will be reported as medical history.

5.6.3. Physical Examinations

A full physical examination will be carried out at screening. At all other visits, a targeted (abbreviated and symptom-directed) examination will be performed at the discretion of the investigator, based on clinically relevant issues, clinically relevant symptoms and medical history.

Physical examination findings, including body weight, height, and BMI, will be summarized at baseline using descriptive statistics.

Any clinically significant abnormal findings are recorded as AE and will be analyzed as such.

5.7. Other Analyses

5.7.1. Definition of Subgroups

Immunogenicity is evaluated in the following subgroups.

- Age: ≥65 to <75 years and ≥75 years
- UTI: whether reported a history of UTI at enrolment (Yes/No)

5.8. Interim Analyses

No formal interim analysis is planned for this study.

The primary analysis will take place when all participants have performed their Day 59 visit or are discontinued earlier. The primary analysis will include all available safety data and immunogenicity results up to Day 59. The analysis will be performed based on sponsor unblinded data.

The final analysis will include MAAE and SAE data up to the end of the study and will be performed on unblinded data.

5.9. Independent Data Monitoring Committee

An IDMC, will be established as noted in Committees Structure in the CSP Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations. All IDMC members will be external and independent of the sponsor, including at least one medical expert in the relevant therapeutic area and at least one statistician. Safety issues that arise from this study will be reviewed by an IDMC on an ad hoc basis, including all related SAEs and all fatal cases. The IDMC responsibilities, authorities, and procedures will be provided in its charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

Table 7 presents a list of the demographic variables that will be summarized by study intervention and overall for the FAS.

Table 7: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
BMI (kg/m^2)	
Categorical Variables	
Age (≥65 to <75 years, ≥75 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or another Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2])	
Reported history of urinary tract infection at baseline (yes/no)	
Reported history of hospitalization in prior 2 years (yes/no)	

[a]If multiple race categories are indicated, the Race is recorded as “Multiple”.

6.2. Appendix 2: Protocol Deviations

Major protocol deviations will be summarized.

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

Protocol deviations that influence immunogenicity will be flagged in a listing.

In addition, major protocol deviations and eligibility violations will also be summarized by study intervention group. Protocol deviations for this study include, but are not limited to, the following (see also the Major Protocol Deviation Criteria Form for this study for more details):

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication/vaccination
- Any other deviation that presents significant risk or safety concerns to the patient

6.3. Appendix 3: Prior and 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 misses 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.
- 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, started during 14 days following each vaccination (00:00 of day of vaccination + 14 days). Following ATC/DDD 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). 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.

6.4. Appendix 4: Toxicity Grading Scale for Vital Signs

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

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 - 40.0 102.1 - 104.0	> 40 > 104.0
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	Hospitalization for arrhythmia[#]
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	Hospitalization for arrhythmia[#]
Hypertension (systolic) - mm Hg	141 – 150	151 – 160[#]	> 160[#]	Hospitalization for malignant hypertension[#]
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension[#]
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock[#]
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** For oral temperature: no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
[#] Revised by the sponsor.

For the vital signs analysis in Section 5.6.2, only values will be used to assign abnormalities, no clinical interpretations will be used. Therefore, Grade 3 and 4 will be combined because Grade 4 always requires clinical interpretation.

7. REFERENCES

None