Janssen Research & Development

Statistical Analysis Plan, Amendment 3

A Randomized, Observer-blind, First-in-Human Phase 1/2a Study to Evaluate the Safety, Reactogenicity and Immunogenicity of Three Different Doses of VAC52416 (ExPEC10V) in Adults Aged 60 to 85 Years in Stable Health

Protocol VAC52416BAC1001; Phase 1/2a Amendment 6

VAC52416, JNJ-69968054 (ExPEC10V)

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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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DOCUMENT HISTORY

Document	Date
Amendment 3	8 December 2020
Amendment 2	26 August 2020
Amendment 1	12 March 2020
Original SAP	28 August 2019

AMENDMENT HISTORY

Amendment 3 (8 December 2020)
Overall Rationale for the Amendment: To update the planned number of participants in Cohort 2 from 600 to approximately 420. To add that the use of oral licensed *E. coli* vaccines (e.g., Uro-Vaxom [OM-89] or Uromune) is allowed for the duration of the study, including long-term follow-up and is recorded as concomitant therapy (applicable to European Union countries only).

Amendment 2 (26 August 2020)
Overall Rationale for the Amendment: To update SAP to include methods for statistical analysis of safety and immunogenicity data collected from Cohort 2 participants. To add COVID-19 (Coronavirus Disease 2019) pandemic related analysis into the SAP following the FDA (Food and Drug Administration) and EMA (European Medicines Agency) guidance on the conduct of clinical trials during pandemic. To make editorial changes.

Amendment 1 (12 March 2020)
Overall Rationale for the Amendment: "ELISA" is replaced by "multiplex ECL-based immunoassay" and "OPA" by "MOPA". The handling of immunogenicity titers above the upper limit of quantification (ULOQ) is added to section 7.3 (Handling of Missing and/or Unquantifiable Immune Response Data). Minor abbreviation or grammatical changes are made.

ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
CI	(95% CI) Confidence Interval
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
DPS	Data Presentation Specifications
DRC	Data Review Committee
ECL	Electrochemiluminescence
EMA	European Medicines Agency
GMR	Geometric Mean of Ratios
GMT	Geometric Mean of Antibody Titers
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
ICF	Informed Consent Form
IgG	Immunoglobulin G
IU/ml	International Units per Milliliter
LLOQ	Lower Limit of Quantification
LTFU	Long-term Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MOPA	Multiplex Opsonophagocytic Killing Assay
PPI	Per-Protocol Immunogenicity
Q1, Q3	First and Third Quartiles
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TLF	Tables, Listings and Figures
ULOQ	Upper Limit of Quantification
U.S.	United States
UTI	Urinary Tract Infection
WHO	World Health Organization

1. INTRODUCTION

This amended statistical analysis plan (SAP) is based on amendment 6 of the global protocol approved on 24 November 2020. It describes the primary, the final (end of observer-blind period) and the three yearly follow-up analyses of Cohort 1 and Cohort 2. In both cohorts, the primary analysis occurs when all participants have completed the Day 30 visit or have discontinued earlier, the final analysis when all participants have completed the Day 181 visit or have discontinued earlier and the yearly long-term follow-up (LTFU) analysis occurs at Year 1 (Day 366), Year 2 (Day 731) and Year 3 (Day 1096) for participants in the selected dose group.

The study design was updated to add Cohort 2 consisting of approximately 420 participants ≥60 years of age in stable health with a history of urinary tract infection (UTI) in the past 5 years. Cohort 2 is aimed to expand the dataset supporting the short- and long-term safety and immunogenicity of the optimal dose of ExPEC10V, selected from the primary analysis results of Cohort 1. Cohort 2 is double-blind throughout the duration of the study.

Data from the two cohorts will not be pooled. Unless otherwise specified, safety and immunogenicity analyses are the same in both cohorts.

Sponsor personnel who were involved in the primary analysis will be unblinded at the participant level at the time of the primary analysis. The Clinical Read-outs Team, Bacterial Vaccines, Janssen will remain blinded until the database lock date for the final analysis in Cohort 1 and end of study analysis at Year 3 in Cohort 2.

1.1. Trial Objectives and Endpoints

1.1.1. Cohort 1

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of different doses of ExPEC10V in participants ≥60 to ≤85 years of age	• Solicited local and systemic AEs collected for 14 days post-vaccination (from Day 1 to Day 15) • Unsolicited AEs collected from the administration of the study intervention until 29 days post-vaccination (from Day 1 to Day 30) • Serious AEs (SAEs) collected from the administration of the study intervention until Day 181
• To evaluate the dose dependent immunogenicity of ExPEC10V on Day 15 in participants ≥60 to ≤85 years of age	• Antibody titers for ExPEC10V, as determined by multiplex electrochemiluminescent (ECL)-based immunoassay and multiplex opsonophagocytic assay (MOPA) on Day 15

Objectives	Endpoints
Secondary	
• To evaluate the correlation between multipex ECL-based immunoassay (total antibody) and MOPA (functional antibody) serum titers on Day 15	• Antibody titers for ExPEC10V, as determined by multiplex ECL-based immunoassay and MOPA on Day 15
• To evaluate the dose-dependent immunogenicity of ExPEC10V on Days 30 and 181 in participants ≥60 to ≤85 years of age	• Antibody titers for ExPEC10V, as determined by multiplex ECL-based immunoassay and MOPA on Days 30 and 181
• To evaluate, in the LTFU period, the safety of the ExPEC10V dose selected for further clinical development based on Day 30 primary analysis in participants ≥60 to ≤85 years of age	• SAEs related to the study intervention or study procedures collected from Day 182 until the end of the study
• To evaluate, in the LTFU period, the immunogenicity of the ExPEC10V dose selected for further clinical development based on the Day 30 primary analysis	• Antibody titers for ExPEC10V, as determined by multiplex ECL-based immunoassay and MOPA on Year 1 (Day 366), Year 2 (Day 731) and Year 3 (Day 1096)

1.1.2. Cohort 2

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of the selected dose of ExPEC10V in participants ≥60 years of age with a history of UTI in the past 5 years	• Solicited local and systemic AEs collected for 14 days post-vaccination (from Day 1 to Day 15) • Unsolicited AEs collected from the administration of the study vaccine until 29 days post-vaccination (from Day 1 to Day 30) • SAEs collected from the administration of the study vaccine until Day 181
• To evaluate the immunogenicity of the selected dose of ExPEC10V on Day 30 in participants ≥60 years of age with a history of UTI in the past 5 years	• Antibody titers for ExPEC10V, as determined by multiplex ECL-based immunoassay and MOPA on Day 30
Secondary	
• To evaluate the correlation between multiplex ECL-based immunoassay (total antibody) and MOPA (functional antibody) serum titers on Day 30 in	• Antibody titers for ExPEC10V, as determined by multiplex ECL-based immunoassay and MOPA on Day 30

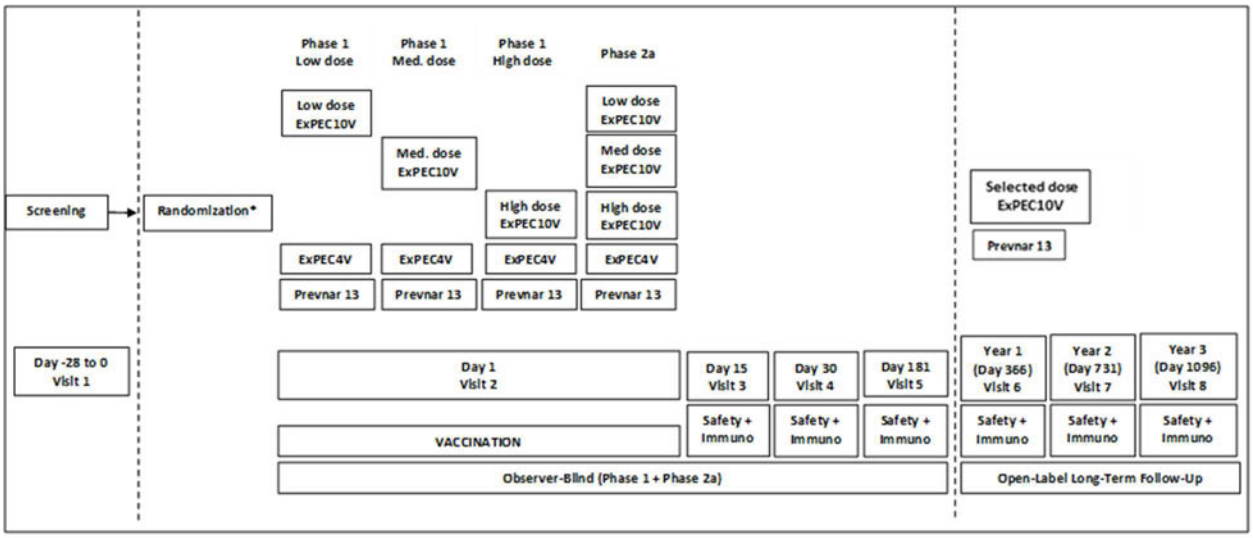
Objectives	Endpoints
participants ≥60 years of age with a history of UTI in the past 5 years	
• To evaluate the immunogenicity of the selected dose of ExPEC10V on Days 15 and 181 in participants ≥60 years of age with a history of UTI in the past 5 years	• Antibody titers for ExPEC10V, as determined by multiplex ECL-based immunoassay and MOPA on Days 15 and 181
• To evaluate, in the LTFU period, the safety of the selected dose of ExPEC10V in participants ≥60 years of age with a history of UTI in the past 5 years	• SAEs related to the study vaccine or study procedures collected from Day 182 until the end of the study
• To evaluate, in the LTFU period, the immunogenicity of the selected dose of ExPEC10V in participants ≥60 years of age with a history of UTI in the past 5 years	• Antibody titers for ExPEC10V, as determined by multiplex ECL-based immunoassay and MOPA at Year 1 (Day 366), Year 2 (Day 731), and Year 3 (Day 1096)

1.2. Trial Designs

For details, refer to section 4.1 of the clinical trial protocol (CTP).

1.2.1. Cohort 1

Figure 1: Cohort 1: Study Design



Immuno=Immunogenicity; Med= Medium

* For randomization schedule, refer to Table 1.

If any participant experiences any issue with the electronic diary (ediary) entry at any time in between vaccination (Day 1) and 14 days post-vaccination (Day 15) visit, an optional telephone contact(s) should be made to collect safety data.

In addition, all participants will be contacted by telephone 2 days post-vaccination (Day 3) to collect safety information and after the final analysis database lock to inform all participants whether that telephone contact will be their last study visit or if they will be progressing to the long-term follow-up (LTFU) period.

The dose selection for ExPEC10V will be based on the primary analysis (Day 30) results.

Table 1: Cohort 1: Vaccination Schedule

		Phase 1						Phase 2a	Total
		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	
Study Vaccination Group	Vaccination on Day 1	Sentinel participants (Low dose)	Additional participants (Low dose)	Sentinel participants (Medium dose)	Additional participants (Medium dose)	Sentinel participants (High dose)	Additional participants (High dose)	Additional Phase 2a Participants	
G1	Low dose ExPEC10V*	2	18					80	100
G2	Medium dose ExPEC10V*			2	18			80	100
G3	High dose ExPEC10V*					2	18	80	100
G4	ExPEC4V**	1	3	1	3	1	3	40	52
G5	Prevnar 13***	1	3	1	3	1	3	40	52
Total		4	24	4	24	4	24	320	404

G=Group

* ExPEC10V consists of the O-antigen polysaccharides (PSs) of the ExPEC serotypes O1A, O2, O4, O6A, O8, O15, O16, O18A, O25B and O75 separately bioconjugated to the carrier protein, a genetically detoxified form of exotoxin A (EPA) derived from *Pseudomonas aeruginosa*.

** ExPEC4V consists of the O-antigen polysaccharides (PSs) of the ExPEC serotypes O1A, O2, O6A, and O25B separately bioconjugated to the carrier protein, a genetically detoxified form of exotoxin A (EPA) derived from *Pseudomonas aeruginosa*.

*** Prevnar 13, Pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 protein) is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually linked to non-toxic diphtheria CRM197 protein.

The randomization ratio for the sentinel participants will be 2:1:1 (Steps 1, 3 and 5) and randomization ratio for the additional participants in Phase 1 will be 6:1:1 (Steps 2, 4 and 6).

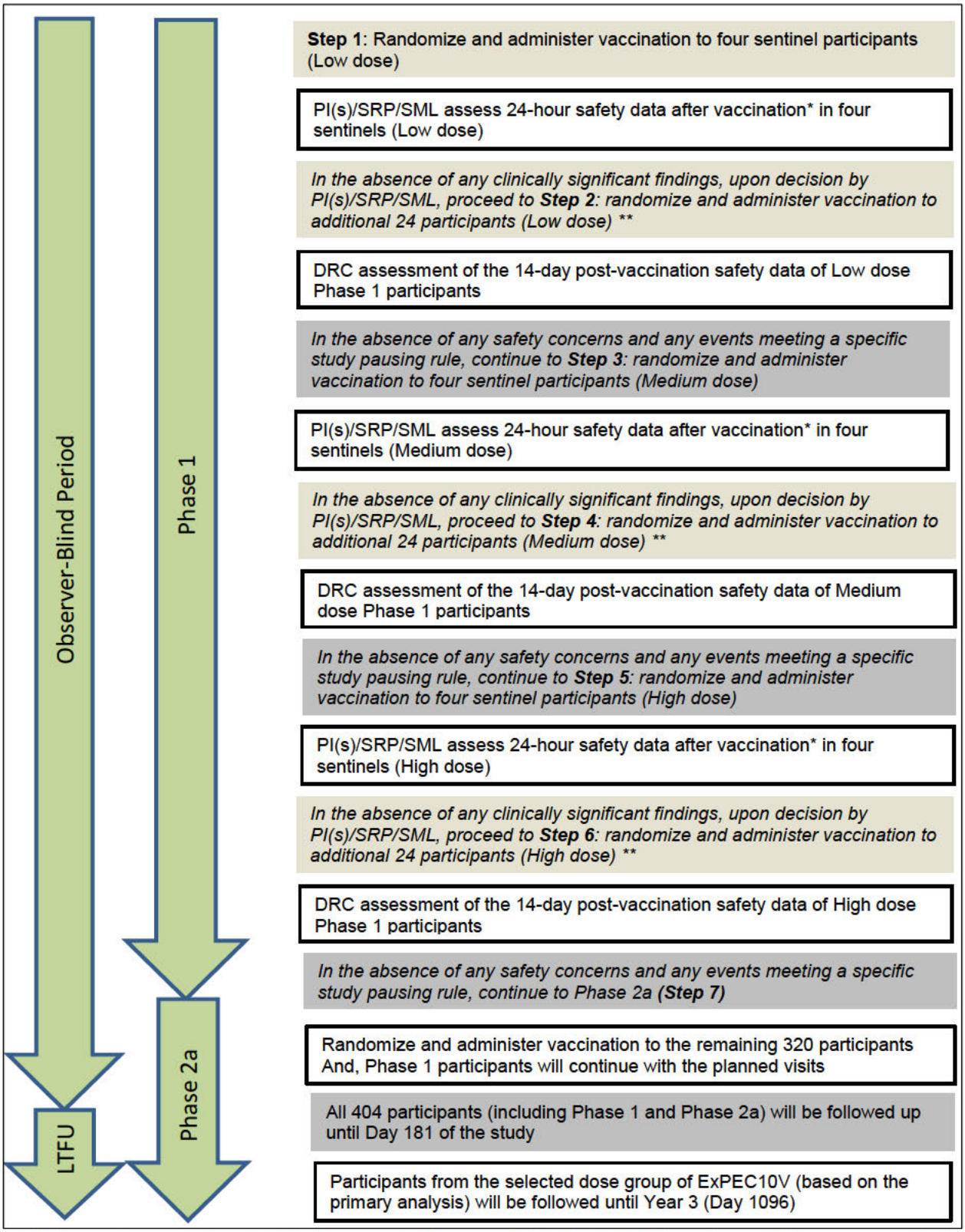
The 24-hour post-vaccination safety in sentinel participants will be monitored and reviewed by principal investigator (PI), study responsible physician (SRP) and sponsor medical lead (SML). Randomization of additional participants will be halted until this Day 2 sentinel safety evaluation is completed.

After dosing of 28 participants at each dose level, a Data Review Committee (DRC) review will be performed to evaluate the 14-day post-vaccination safety data before progressing to the next dose level or Phase 2a. (The double vertical lines indicate a DRC review)

The randomization ratio for the Phase 2a participants will be 2:2:2:1:1 (Step 7).

Total Phase 2a participants (404) include the 84 Phase 1 participants and additional 320 participants.

Figure 2: Cohort 1: Participant Enrollment and Vaccination Scheme



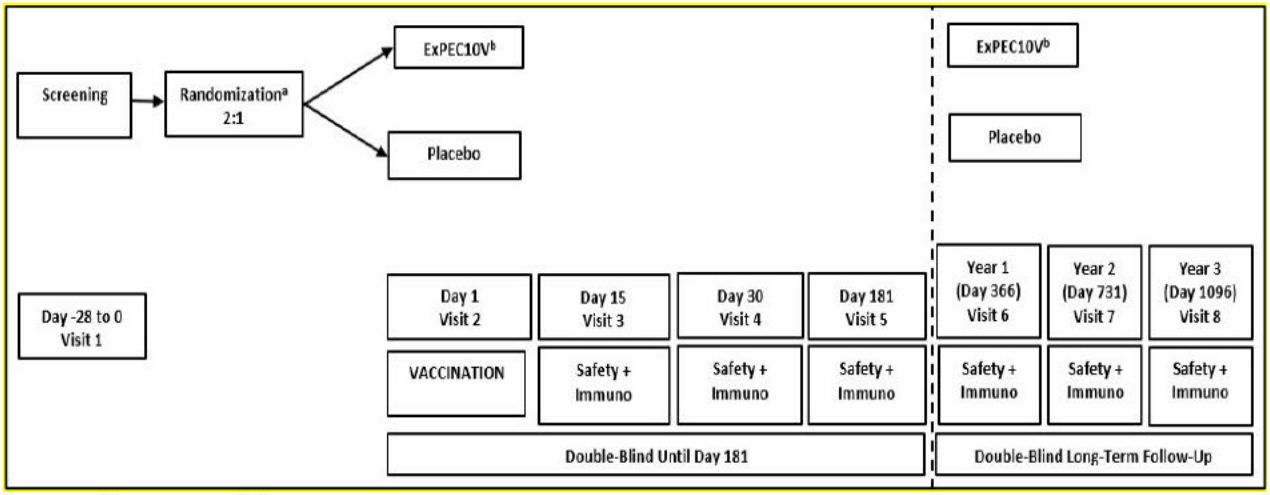
DRC=data review committee; LTFU=long-term follow-up period; PI=principal investigator; SML=sponsor medical lead; SRP=study responsible physician.
* Sentinel participants will be contacted by telephone 24 hours post-vaccination to collect safety information.
** Participants per dose level (28 participants for each dose level and 84 participants in total)

On 11 March 2020, United Nations' World Health Organization (WHO) declared COVID-19 a pandemic and the U.S. on 13 March declared the pandemic a national emergency. Between 19 March and 7 April, shelter-in-place was ordered in 45 U.S. states and the District of Columbia, either statewide or in parts of the state.

Of the 6 study sites, 3 remained open in Florida (1of 2 sites), Illinois and North Carolina during the pandemic and 3 sites in Florida, Kansas and New York were closed. As enrollment started on 24 June 2019 and completed in 9 December 2019, Day 181 (±14 days) visit was expected to be completed between December 2019 and June 2020. The following protocol-specified assessments and procedures are taken at Day 181: targeted physical examination, vital signs, SAEs, concomitant medications in conjunction with SAEs and blood samples for immunogenicity. Due to site closure, shelter-in-place restriction or self-isolation during the pandemic, the scheduled Day 181 visit cannot be conducted in person at the study site. In lieu of on-site visit, participants are contacted by telephone. Participants who completed the phone visit are asked to return to the site for post Day 181 blood draw after the shelter-in-place has been lifted.

1.2.2. Cohort 2

Figure 3: Cohort 2: Study Design



Immuno=Immunogenicity

[a] For randomization schedule, refer to Table 2

[b] The ExPEC10V dose used in Cohort 2 will be based on the primary analysis (Day 30) results of Cohort 1.
If any participant experiences any issue with the electronic diary (ediary) entry at any time in between vaccination (Day 1) and 14 days post-vaccination (Day 15) visit, an optional telephone contact(s) should be made to collect safety data. In addition, all participants will be contacted by telephone 2 days post-vaccination (Day 3) to collect safety information.
Stool samples will be collected from all participants on Day 1 and from a subset of 33% randomly selected participants on Days 30 and 181.

Table 2: Cohort 2: Vaccination Schedule

Study Vaccination Group	Vaccination on Day 1	Total[b]
G6	ExPEC10V[a]	280
G7	Placebo	140
Total		420

G=Group

[a] ExPEC10V consists of the O-antigen polysaccharides (PSs) of the ExPEC serotypes O1A, O2, O4, O6A, O8, O15, O16, O18A, O25B, and O75 separately bioconjugated to the carrier protein, a genetically detoxified form of exotoxin A (EPA) derived from *Pseudomonas aeruginosa*.
The randomization ratio for the participants enrolled in Cohort 2 of the study will be 2:1 (ExPEC10V:Placebo).
The ExPEC10V dose used in Cohort 2 will be based on the primary analysis (Day 30) results of Cohort 1.

[b] The total number of participants to be included in each study vaccination group is an approximation.

1.3. Statistical Hypotheses for Trial Objectives

No statistical hypothesis is pre-specified for both safety and immunogenicity. Hence, no formal hypothesis is tested. No formal comparisons between groups will be provided.

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.

2. GENERAL ANALYSIS DEFINITIONS

Continuous variables will be summarized using the following statistics, as appropriate: number of observations, arithmetic or geometric mean (mean), 95% CI for the mean (if applicable), standard deviation (SD), median, quartiles (Q1 and Q3), minimum and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized using tabulations (numbers, proportions). Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using the total number of participants with non-missing data as the denominator.

2.1. Study Phases and Visit Windows

A baseline (or reference) value will be defined as the value of the last available assessment prior to the single 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 $\geq$ date of Day 1 (date of vaccination).
Study Day = visit date – date of Day 1; if visit date < date of Day 1 (date of vaccination).

2.1.1. Study Phase Definitions

The safety analysis will present results by phase. The phases in the study will be constructed as shown in Table 3.

Table 3: Phase Definitions

Phase	Phase #	Interval	
		From	To
Screening	1	Date and time of signing the informed consent form (ICF)	One minute prior to start of Post-dose phase
Post-dose	2	Date and time of vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 on 29 days after the vaccination (23:59 of day of vaccination + 29 days)
Follow-up	3	One minute after Post-dose phase ends	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of Day 181 (6 Months) visit
Long-term Follow-up	4	One minute after date of Day 181 visit	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of Day 1096 (Year 3) visit

The analysis phases will be used primarily for safety and concomitant medication allocation. The Post-dose phase is considered an active phase. Screening and both follow-up phases are considered non-active phases.

2.1.2. Visit Windows

Immunogenicity results will be presented per scheduled time point. Protocol visits are scheduled at baseline (Day 1), Days 15, 30 and 181; for those on selected dose, at Days 366, 731 and 1096. Each protocol visit time window is specified in Table 4.

Table 4: Visit Windows Definitions

Clinic Visit	Visit Day	Window	Primary Purpose
Visit 1	-28 to 0		Screening
Visit 2	Day 1 (VACC)		Vaccination
Visit 3	Day 15 (VACC + 14 days)	± 2 days	14 days post-vaccination safety and immunogenicity visit
Visit 4	Day 30 (VACC + 29 days)	± 3 days	29 days post-vaccination safety and immunogenicity visit
Visit 5	Day 181 (VACC + 6 months)	± 14 days	6 months post-vaccination safety and immunogenicity visit
Visit 6	Day 366 (VACC + 1 year)	± 14 days	1year post-vaccination safety and immunogenicity visit
Visit 7	Day 731 (VACC + 2 years)	± 28 days	2 years post-vaccination safety and immunogenicity visit
Visit 8	Day 1096 (VACC + 3 years)	± 28 days	3 years post-vaccination safety and immunogenicity visit

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

2.2. Pooling Algorithm for Analysis Centers

Data will be pooled across the different sites.

2.3. Analysis Sets

Vaccination assignment will follow the as-treated principle.

2.3.1. Full Analysis Set (FAS)

The full analysis set will include all participants with a study vaccine administration documented.

2.3.2. Per-Protocol Immunogenicity Analysis Set (PPI)

The per-protocol immunogenicity analysis set will include all randomized and vaccinated participants, for whom immunogenicity data are available excluding those samples with major protocol deviations expected to impact the immunogenicity outcomes. Participants in this analysis set should have at least a baseline antibody titer measurement.

Prior to interim or final database lock, the clinician will review the list of major deviations and determine which of these deviations is expected to impact the immunogenicity outcomes. For example, samples from blood draws outside the protocol visit window will be excluded from the per-protocol immunogenicity analysis.

2.4. Definition of Subgroups

Summary statistics will be presented for the following subgroups.

- Onset of solicited AE: no AE, early and late. Onset is early if the first solicited AE started on or before 5 days post-vaccination and late if the AE started after 5 days post-vaccination.
- Other subgroup analyses may be performed based on baseline characteristics and demographics. This will be further specified in the data presentation specifications (DPS).

3. DATA REVIEW COMMITTEE

An internal DRC is commissioned to ensure the safety and well-being of the participants enrolled in the study. A charter is available that details the roles and responsibilities of the DRC. It outlines what data are provided to the DRC, the process for disseminating study data and the communication plan. The DRC reviews blinded data first but is entitled to and has the right to require submission of unblinded data, if deemed necessary. A separate SAP is available for the DRC reviews.

4. PLANNED ANALYSES

For both cohorts, a primary analysis occurs when all participants have completed the Day 30 visit or have discontinued earlier. The analysis includes immunogenicity data up to Day 15 (Cohort 1) or Day 30 (Cohort 2) and all available safety data.

In Cohort 1, a dose from one of the three ExPEC10V doses is to be selected for further clinical development. A dose selection algorithm for immunogenicity is be implemented to guide the decision. The dose selection is based on the totality of evidence which includes safety, immunogenicity, serotype prevalence, antibiotic resistance, antigen load and vaccine-mediated immune interference available at the time of the analysis. This selected ExPEC10V dose safety and immunogenicity profile will be further evaluated in Cohort 2.

At the time of the primary analysis, the study will be unblinded for specific sponsor personnel. Participants, clinical staff, study-site personnel and the Clinical Read-outs Team, Bacterial Vaccines, Janssen will remain blinded to the study intervention allocation until the final analysis in Cohort 1 and the end of study analysis in Cohort 2.

A final analysis will occur when all participants have completed the Day 181 visit or have discontinued earlier.

For the LTFU phase, Cohort 1 study site will be informed after the final analysis which participants will continue into the open-label LTFU period and for which participants the Day 181 visit will be the last on-site visit. The open-label yearly LTFU analysis will include safety and immunogenicity data (multiplex ECL-based immunoassay and MOPA) collected at the time of the visit at Year 1 (Day 366), Year 2 (Day 731) and Year 3 (Day 1096) after vaccination and will be performed based on unblinded participant data.

In Cohort 2, the study remains double blind until the end of the study at Year 3.

5. PARTICIPANT INFORMATION

Participant information will be shown for the FAS. Data are presented by treatment group (in Cohort 1: low dose, medium dose, high dose, ExPEC10V, ExPEC4V, Prevnar and in Cohort 2: ExPEC10V high dose or simply, ExPEC10V dose, Placebo). If applicable, overall will be included in each of the 2 sets of treatment groups. ExPEC10V in Cohort 1 refers to the total for the 3 doses (low, medium and high).

5.1. Demographics and Baseline Characteristics

Demographic characteristics and screening/baseline characteristics will be tabulated and summarized with descriptive statistics by treatment group and over all participants.
The following demographic and baseline characteristics will be summarized.

- Sex (female/male)
- Age (years)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

5.2. Disposition Information

The number and percentage of participants for each of the following, if applicable will be tabulated. If study visit is affected by COVID-19, number of participants attending the on-site visit, phone visit or home (by health nurse) visit, whichever is applicable will be tabulated. COVID-19 related study discontinuation will be added to the list of reasons for study discontinuation.

- Screened
- In the FAS
- In the PPI
- Vaccinated and not randomized
- Randomized and not vaccinated
- Completed Day 30 visit
- Completed Day 181 visit
- Study discontinuations and reason of discontinuation
- Participants in each study phase
- Reconsented to participate in the LTFU
- Completed Year 1 visit
- Completed Year 2 visit
- Completed Year 3 visit

5.3. Protocol Deviations

Major protocol deviations including COVID-19 related deviations will be summarized and listed. Major protocol deviations which will have a potential impact on immunogenicity will be flagged in the listings.

5.4. Pre-study and Concomitant Medications

Pre-study and concomitant therapies will be tabulated. Except for vaccines, the analysis will be based on the WHO drug coded terms as provided in the clinical database. Vaccines will not be coded. If the coded term for a medication is missing, then the reported term will be used and noted in the table.

Details of pre-study specific therapies such as non-steroidal anti-inflammatory drugs, corticosteroids, antihistaminic and vaccinations administered up to 30 days before study vaccination will be collected at screening.

Details of concomitant therapies such as non-steroidal anti-inflammatory drugs, corticosteroids, antihistaminic and vaccinations will be collected from the signing of the ICF until 29 days after the study vaccination and additionally outside of these periods when associated with an SAE until

Day 181. The use of oral licensed *E. coli* vaccines (e.g., Uro-Vaxom [OM-89] or Uromune) is allowed for the duration of the study, including long-term follow-up and is recorded as concomitant therapy (applicable to European Union countries only). During the LTFU period, in addition to the oral *E. coli* vaccines, only medications in conjunction with SAEs thought to be related to study vaccine or study procedures are available for analysis. Attention will be given to all COVID-19 related concomitant therapy. Based on the start and stop date, concomitant therapies will be reported in each applicable study phase.

If a concomitant therapy misses components of its start and/or stop dates (day and/or month and/or year), the following allocation rules will be applied.

- In case of partial start or stop dates, the concomitant therapy records will be allocated to the 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 will be allocated to the phase(s) where these date parts match. This rule may lead to assignment to multiple phases.
- In case of a completely missing start date, the case report form (CRF) question "medication/therapy taken prior to the study" will be used to determine whether the concomitant therapy is considered as having started before the trial or not. In case the medication/therapy did not start prior to the study and accounting for the end date, it will be assigned to the Post-dose and all subsequent phases applicable.
- In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial.

6. SAFETY

Safety analyses will be performed on the FAS. The safety and reactogenicity endpoints are described in section 1.1 (solicited local and systemic AEs, unsolicited AEs, SAEs). The time window for Day 181 is widened to include participants contacted by telephone especially in study sites temporarily closed due to COVID-19.

6.1. Adverse Events (AEs)

All AEs and special reporting situations, whether serious or non-serious that are related to study procedures or non-investigational (concomitant) Janssen products will be reported from the time a signed and dated ICF is obtained onwards. All other AEs, SAEs and special reporting situations, will be reported starting from the day of the first vaccination onwards. Clinically relevant medical events, occurring between signing of the ICF and the time of vaccination will be reported on the medical history electronic CRF page as pre-existing conditions.

6.1.1. Definitions

Solicited AEs are extracted from the diary pages of the CRF. They are collected daily from the day of vaccination until 14 days post-vaccination.

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

covering the whole study period. All other collected unsolicited AEs will be presented through listings. COVID-19 related unsolicited AE and SAE are included in the tabulation.

The time to first onset of an AE is defined as (date of first onset – reference date + 1). The reference date is the date of vaccination. A solicited AE has a late onset if the time to first onset of the AE is more than 5 days, i.e., the AE occurs after Day 5 post-vaccination.

The duration of an AE is defined as the number of days from the start of the event until the resolution of the event, (AE end date – AE start date +1). Imputed dates are allowed. For ongoing AEs, the imputed date will be used (see Section 6.1.3 for more details); partial dates will not be used. If a participant experiences more than one event of the same AE, the duration of a single event having maximum duration will be used.

6.1.1.1. Solicited Injection Site (Local) AEs

The analysis of solicited local AEs or injection site reactions will include injection-site:

- pain/tenderness
- erythema
- swelling

6.1.1.2. Solicited Systemic AEs

The analysis of solicited systemic AEs will include:

- Fatigue
- Headache
- Nausea
- Myalgia
- Fever (i.e., body temperature > 38ºC)

6.1.1.3. Unsolicited and Serious AEs

Unsolicited AEs are all AEs for which the participant is not specifically questioned in the participant ediary.

Condition(s) on which a solicited or unsolicited AE is considered a SAE is described in the CTP. Unlike unsolicited AEs that are collected within 29 days period following vaccination, SAEs are collected throughout the study period following vaccination. During the LTFU period, SAEs thought to be related to the study vaccine or study procedures and COVID-19 related AEs will be available.

Unsolicited AE and SAE will include COVID-19 related AE.

6.1.1.4. Causality

Solicited local AEs are always considered related to the use of the study vaccine. Causality of the solicited systemic, unsolicited and SAEs will be considered as either related or not related to the study vaccine.

6.1.1.5. Severity Criteria

The severity of the AEs will be classified by the investigator as either one of grades 1 to 4. All AEs data will be graded for severity using the toxicity tables in ATTACHMENT 1. For AEs not identified in these toxicity tables, a guideline to determine severity grade is given in the CTP. If a participant has experienced the same event multiple times in the same period, the event with the worst severity is used.

6.1.2. Analysis of AEs

The number and percentage of participants with at least one AE (unsolicited/solicited) will be tabulated and will be presented by treatment groups (in Cohort 1: low dose, medium dose, high dose, ExPEC10V pooled, ExPEC4V, Prevnar and in Cohort 2: ExPEC10V dose and placebo). 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
- At least Grade 3
- Related (systemic only)
- Time to onset (in days) and duration (in days)
- Duration and severity of late onset AEs

For unsolicited AEs which will include COVID-19 related AEs, the following tables will be provided:

- Summary table (including SAE, fatal outcome and discontinuation)
- All events
- At least Grade 3
- Study discontinuation
- Related
- SAE

Listings and/or subject narratives will be provided as appropriate, for those participants who die or experience a severe or serious AE.

6.1.3. Study Phase Allocation of AEs

Solicited events are always allocated to the Post-dose phase.

In case of a missing end date (for the calculation of duration), the date is imputed by the cut-off date of the analysis for participants still ongoing in the study, and by the end date for participants who discontinued or completed the trial. The imputed end dates will not be shown in the data listings.

6.1.3.1. 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:

- If overlapping/consecutive events start in one of the following study phases - screening (non-active phase) - followed by an AE in - post-dose phase (active phase) - they are allocated to their respective phase and are considered as separate events.
- In case overlapping/consecutive events start within a single 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 should also be consistent with the new event.
- In case overlapping/consecutive events start in both an active phase followed by a non-active phase, they are allocated to the active phase 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 should also be consistent with the new event.
- In case a non-active phase is followed by another non-active phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate AEs.

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 study phase allocation), this date is also considered as a complete date.
- Time is not considered when determining overlap of events.

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 grade 3.

6.2. Clinical Laboratory Tests

There is no laboratory assessment in Cohort 2 participants.

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

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

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

- Worst grades/abnormalities are determined over the whole observational period for each trial period separately, including all post-baseline measurements of that period.
- The abnormalities 'abnormally low' and 'abnormally high' are considered equally important, i.e. if a participant has as well an abnormally low as an abnormally high value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)
- Note: as the grading scale for some parameters in the grading table has some gaps (zones where no toxicity grade definition exists), laboratory results falling in these zones will be allocated to the adjacent worst-case grade.
- If a lab 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 grades, no distinction will be made between test results of samples obtained under fasting and under non-fasting conditions: in case limits under fasting and non-fasting conditions differ, the limits of the conditions (fasting/non-fasting) of scheduled visits as planned in the CTP will always be used, also for samples obtained under a different condition (e.g. samples of withdrawal visits).

6.3. Vital Signs and Physical Examination Findings

In similar manner to the clinical laboratory tests performed, only vital signs abnormalities emerging after vaccination will be tabulated by worst abnormality grade in both cohorts.

Pulse or heart rate (beats per minutes), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths per minute) and body temperature will be collected. The respective vital signs abnormalities are defined in ATTACHMENT 1.

A listing of participants with fever according to the FDA grading table in ATTACHMENT 1 will also be provided.

A full physical examination is only conducted at baseline. At other visits, only targeted and symptom-directed examinations are performed at the investigator's discretion and any clinically significant abnormal findings are recorded as AEs and will be analyzed as such. Therefore, no separate analysis of physical examination findings will be performed.

7. IMMUNOGENICITY

7.1. Endpoints

Immunogenicity of all vaccine groups will be assessed by multiplex ECL-based immunoassay and MOPA that measures the level of serotype-specific antibodies (total Immunoglobulin G [IgG]) and their functionality. The immune response will be available for each of the following antigens: O1A, O2, O4, O6A, O8, O15, O16, O18A, O25B, O75 and Exoprotein A (EPA, multiplex ECL-based immunoassay only). The antigen-specific immune response will be assessed in serum from blood samples taken at the following timepoints: Days 1 (pre-vaccination), 15, 30, 181 and for the selected dose, on Year 1, 2 and 3.

The immunogenicity endpoints are

- Total IgG antibody titers determined by multiplex ECL-based immunoassay
- Functional antibody titers determined by MOPA

The primary endpoints are multiplex ECL-based immunoassay and MOPA antibody titers on Day 15 (Cohort 1) or on Day 30 (Cohort 2). Secondary endpoints will include multiplex ECL-based immunoassay and MOPA antibody titers on the other timepoints.

7.2. Parameters

The following summary measures will be evaluated.

- Geometric mean titer (GMT)
- Proportion of participants with a ≥2-fold and ≥4-fold increase in serum antibody titers from baseline.
- Geometric mean ratio (GMR) of fold changes from baseline

7.3. 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 treated differently according to the statistical analysis.

- For the calculation of GMT, titer values below LLOQ will be imputed to ½ of the LLOQ.
- For the calculation of GMR, titer values below LLOQ will be imputed to LLOQ.

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

Both LLOQ and ULOQ values will be available in the clinical immunogenicity database.

7.4. Analysis

The analysis of immunogenicity will use both the FAS and the PPI. PPI is the primary immunogenicity analysis set.

No formal hypothesis on immunogenicity will be tested. However, in Cohort 1 an immunogenicity dose selection algorithm will be used to guide the dose selection.

The analysis will be presented by timepoint and treatment group (in Cohort 1: three ExPEC10V doses, ExPEC4V, Prevnar and in Cohort 2: ExPEC10V dose and placebo).

The following results will be calculated: n, GM with the corresponding 95% confidence interval (CI) of the actual values and fold changes from baseline. The GM is obtained by taking the anti-$\log_{10}$ of the mean of the $\log_{10}$ transformed values. The CI is calculated as the back-transformed CI of the mean of the $\log_{10}$ transformed values. The CI is used to describe the precision of the geometric mean. The CI will be based on the t-distribution.

The proportion or percentage of participants reaching at least 2- and 4-fold increase in antibody titer from baseline will be presented. A 2-sided 95% Clopper-Pearson CI will be provided for each proportion or percentage.

The Pearson correlation between multiplex ECL-based immunoassay and MOPA measurements at each timepoint will be calculated.

The following immunogenicity plots will be presented. In each plot, the original values may be displayed on the log10 scale, as appropriate.

- GMT plots over time
- Reverse cumulative distribution curves of the actual values will be plotted for each treatment group and timepoint using step functions starting with 100% of participants going down to 0% of participants on the vertical (y-) axis and immunogenicity titers on the horizontal (x-) axis.

Other graphical representations of immunological parameters will be made as applicable.

7.4.1. COVID-19 Related Analysis of Cohort 1 at Day 181 Study Visit

Analysis will be based only on the FAS. Sensitivity analysis will be performed for antibody titers of blood samples in each of the ExPEC10V doses collected outside the Day 181 protocol specified window due to COVID-19. The sensitivity analysis will determine whether to widen the window for Day 181 or keep the out-of-window samples together in a separate group for immunogenicity analysis.

7.5. Dose Selection in Cohort 1

The dose selection will consider the totality of the evidence available at the time of the primary analysis, including a dose selection algorithm presented in Section 7.5.2 that will guide the decision.

7.5.1. Analysis of Covariance Model

Dose selection will be based on the analysis of covariance model. Let the $\log_{10}$ Fold Increase (FI) of antibody titer from baseline to Day 15 be the response variable. Including all 5 treatment groups, the analysis of covariance model is presented as follows.

$$Y_{ij} = \mu + \tau_j + \beta \times X_{ij} + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim IID, N(0, \sigma^2); \quad \sum_{j=1}^{j=5} \tau_j = 0$$

where

i: participant index ranging from 1 to n_j
j: treatment group index ranging from 1 to 5
n_j: number of participants in treatment group j, $\sum_{j=1}^{5} n_j = n$
Y_{ij}: $\log_{10}$ FI of titer from baseline to Day 15 of participant i vaccinated with treatment group j
X_{ij}: $\log_{10}$ baseline titer of participant i vaccinated with treatment group j
μ: overall mean of $\log_{10}$ FI of titers from baseline to Day 15 titers adjusted for baseline mean
τ_j: difference between overall mean and mean of treatment group j adjusted for baseline
β: regression coefficient of $\log_{10}$ baseline titer
ε_{ij}: error term attributed to participant i vaccinated with treatment group j

In SAS PROC GLM, the default constraint is to set $\tau_5 = 0$.

The least squares mean for treatment group j (LSM_j) is given by the expected value of $\log_{10}$ FI of titer from baseline to Day 15 at the average value of the baseline titers.

$$\widehat{LSM_j} = \hat{\mu} + \hat{\tau_j} + \hat{\beta} \times \bar{x}$$

A 95% CI of the difference between the least squares means for treatment group j and treatment group k is given by

$$\hat{\tau_j} - \hat{\tau_k} \pm t(0.975, n-6) \times \sqrt{\widehat{Var}(\hat{\tau_j} - \hat{\tau_k})}$$

t(0.975, n-6) is defined as the 97.5% percentile of the t-distribution with *n-6* degrees of freedom. The standard error of the estimate is available in the same SAS procedure.

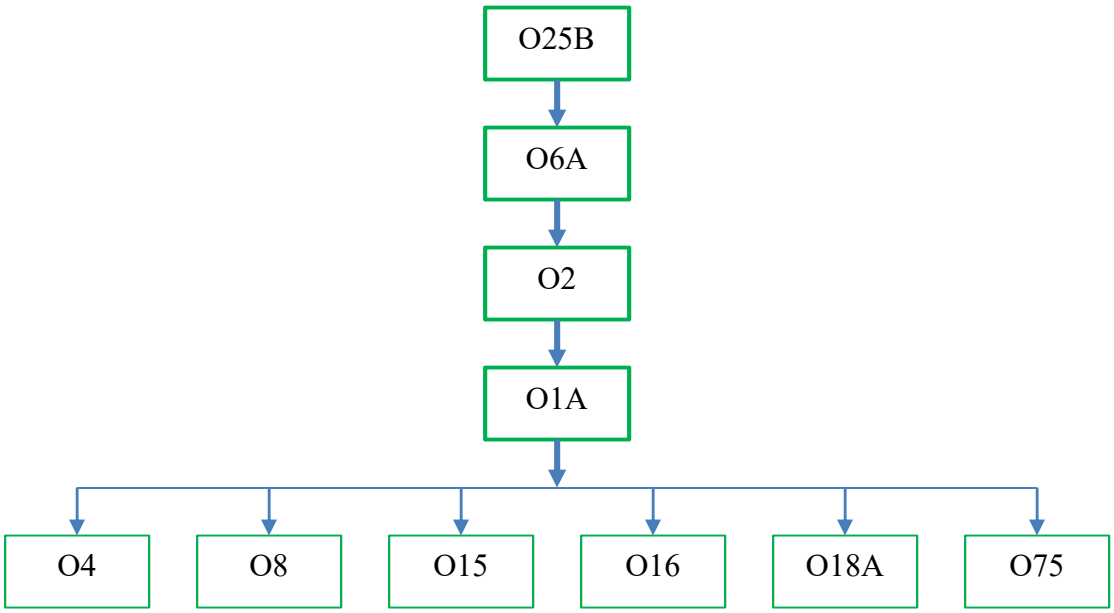
7.5.2. Algorithm

The algorithm will employ the following 2-step procedure.

1. Fit the analysis of covariance model for $\log_{10}$ FI on treatment groups and $\log_{10}$ baseline titer. The treatment group with highest least squares mean will be designated as THIGH.
2. Based on the same model, calculate the 95% CI of the difference between the least squares means of each of the other treatment groups and THIGH. The significance level of the CIs is not adjusted for multiplicity. Retain THIGH and those treatment groups which have nonnegative upper confidence limits, i.e., keep THIGH and those treatment groups which are non-inferior to THIGH.

Based on the model, there are 3 inputs to the 2-step procedure. For any given serotype, these are (1) $\log_{10}$ baseline titer, (2) $\log_{10}$ fold increase from baseline at Day 15 and (3) the treatment groups.

The dose selection immunogenicity algorithm is described as follows. It is mandatory that the first 4 steps are to be implemented with the same serotypes and in the same sequential order.



i. Start with O25B serotype. Keep only the treatment group(s) that have been retained by the 2-step procedure.

ii. Continue with O6A serotype. Use the treatment group(s) retained in step (1) as input and execute the 2-step procedure. Keep the treatment group(s) that have been retained by the procedure.

iii. Repeat step (2) for O2 and then O1A serotypes, separately and in that same order. Keep the treatment group(s) that have been retained by the last step of the procedure.

iv. Using the treatment group(s) retained in the step (3), execute the 2-step procedure separately in any order for the other 6 serotypes: O4, O8, O15, O16, O18A and O75.

v. At the end of the 2-step procedure applied to each serotype, at least one treatment group will be retained. By majority rule, the treatment group(s) that have been retained the most times will be the dose selected by the dose selection algorithm.

7.5.3. Decision Rules

Dose selection algorithm will be performed on 2 analysis sets for both multiplex ECL-based immunoassay and MOPA on Day 15.

1. PPI analysis set based on multiplex ECL-based immunoassay
2. FAS analysis set based on multiplex ECL-based immunoassay
3. PPI analysis set based on MOPA
4. FAS analysis set based on MOPA

At least one dose will be selected. A degenerate case happens when after the first step, only a single dose is kept which is the same as the treatment group with the highest least squares mean.

All the selected doses from the 4 combinations will be compared to come up with a single dose. It is noted that final selected dose my not be based solely on this immunogenicity dose selection algorithm. The clinical team and other stakeholders may consider other pertinent information in the decision process. Examples include, but may not be limited to manufacturing aspects, the Target Product Profile and the clinical implication of the selected dose.

REFERENCE

1. FDA Guidance document. "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", September, 2007.

ATTACHMENTS

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

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

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

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23-26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x	1.6 – 2.0 x	2.1 – 5.0 x	> 5.0 x ULN

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
	ULN	ULN	ULN	

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

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	ï€ 1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)
International Normalized Ratio (INR)***	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.
***: For INR, the values in the table are based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2014 (version 2.0)

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization forhyperglycemia
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 - 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.