Janssen Research & Development*

Clinical Protocol

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Safety and Immunogenicity of the ExPEC4V (JNJ-63871860) Clinical Trial Material After a Single Intramuscular Dose and a Second Dose 6 Months Later in Healthy Subjects Aged 18 Years and Older

Protocol 63871860BAC2003; Phase 2

JNJ-63871860 ExPEC4V

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

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ExPEC4V (primary compound number: JNJ-63871860) is a 4-valent vaccine candidate in development for the prevention of invasive extraintestinal pathogenic *Escherichia coli* (ExPEC) disease. ExPEC4V consists of the O-antigen polysaccharides (PSs) of the ExPEC serotypes O1A, O2, O6A, and O25B separately conjugated to the carrier protein, a genetically detoxified form of exotoxin protein A (dEPA) derived from *Pseudomonas aeruginosa*.

During the ongoing Chemistry, Manufacturing and Controls (CMC) development of ExPEC4V, several changes have been introduced in the manufacturing process of ExPEC4V clinical trial material (CTM) which includes changes in the process, scale, manufacturing site, formulation buffer and introduction of the optimized strain (O1A). In support of the implemented changes, CMC will perform a physico-chemical comparability study and the results from this study will be available prior to the initiation of the clinical trial.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objectives

- To evaluate the safety/reactogenicity of the ExPEC4V CTM[a] after the first vaccination
- To evaluate the immunogenicity of the ExPEC4V CTM, as measured by the enzyme-linked immunosorbent assay (ELISA), 14 days after the first vaccination (on Day 15)

Secondary Objectives

- To evaluate the immunogenicity of the ExPEC4V CTM, as measured by the opsonophagocytic killing (OPK) assay, 14 days after the first vaccination (on Day 15)
- To evaluate the safety/reactogenicity of the ExPEC4V CTM after the second vaccination
- To evaluate the immunogenicity of the ExPEC4V CTM, as measured by the ELISA, 14 days after the second vaccination (on Day 195)
- To evaluate the immunogenicity of the ExPEC4V CTM, as measured by the OPK assay, 14 days after the second vaccination (on Day 195)

Endpoints

Primary Endpoints

- Solicited local and systemic adverse events (AEs) for 14 days after first vaccination (Day 1 to Day 15); unsolicited AEs for 29 days after first vaccination (Day 1 to Day 30); and serious adverse events (SAEs) until Day 180

[a] ExPEC4V CTM is the new CTM manufactured via a redesigned Chemistry, Manufacturing and Controls (CMC) process for future clinical studies.

- Antibody titers as determined by the ELISA on Day 1 pre-vaccination (prior to first vaccination) and Day 15 post-vaccination (14 days after first vaccination)

Secondary Endpoints

- Antibody titers as determined by the OPK assay on Day 1 pre-vaccination (prior to first vaccination) and Day 15 post-vaccination (14 days after first vaccination)
- Solicited local and systemic AEs for 14 days after second vaccination (Day 181 to Day 195); unsolicited AEs for 29 days after second vaccination (Day 181 to Day 210); and SAEs from Day 181 until Day 360
- Antibody titers as determined by the ELISA on Day 181 pre-vaccination (prior to second vaccination) and on Day 195 (14 days after second vaccination)
- Antibody titers as determined by the OPK assay on Day 181 pre-vaccination (prior to second vaccination) and on Day 195 (14 days after second vaccination)

Hypothesis

No statistical hypothesis testing will be performed. All analyses will be descriptive.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, interventional study to evaluate safety, reactogenicity and immunogenicity of the ExPEC4V CTM manufactured via a redesigned CMC process (hereafter referred as ExPEC4V CTM).

The study is planned to be conducted in approximately 100 male and female subjects aged ≥18 years with medically stable health. The subjects who fulfill all inclusion and exclusion criteria will be randomly assigned to receive a single dose of either ExPEC4V CTM or placebo on Day 1 in a ratio of 3:1, respectively. Subjects will receive a second dose of either ExPEC4V CTM or placebo on Day 181 (6 months after first vaccination).

Subjects will be closely observed by the study staff for at least 30 minutes after both vaccinations (on Day 1 and Day 181). Blood samples will be collected from all subjects on the day of vaccination (pre-vaccination; Day 1 and Day 181); and 14 days after each vaccination (on Day 15 and Day 195) for immunogenicity assessment by the ELISA and OPK assay.

The study duration will be approximately 1 year per participant; the end of the study will be the last subject's last visit (this will be a telephone contact). The study consists of randomization and first vaccination on Day 1 and second vaccination on Day 181 (6 months after first vaccination). Subjects will be followed until the end of the study at Day 360.

SUBJECT POPULATION

Subjects will be adult men and women, aged ≥18 years on the day of signing the informed consent form (ICF). All subjects will be in stable health (on the basis of physical examination, medical history and vital signs measurement performed on Day 1).

DOSAGE AND ADMINISTRATION

ExPEC4V (JNJ-63871860): *E. coli* bioconjugate vaccine in phosphate buffered solution containing O-antigen PS of ExPEC serotypes O1A, O2, O6A, O25B (4:4:4:8 µg PS/ExPEC4V serotypes) separately conjugated to the EPA carrier protein. The selected dose for further development of ExPEC4V is 4:4:4:8 µg PS/ExPEC serotype (O1A, O2, O6A and O25B), and the same dose will be used in this study.

- Single 0.5 mL intramuscular (IM; deltoid) injection of ExPEC4V CTM on Day 1 and on Day 181 (The second dose of study vaccination will be administered on the contralateral side of the first dose.)

Placebo: Tris-saline solution

- Single 0.5 mL IM (deltoid) injection on Day 1 and Day 181

The subjects, clinical staff, investigators, and sponsor personnel will be blinded to study vaccine group allocation, except for the designated pharmacist or qualified staff member with primary responsibility for study vaccine preparation.

SAFETY EVALUATIONS

Serious Adverse Events:

All SAEs will be collected for all subjects from the administration of the first dose of study vaccine until the end of the study (telephone call at Day 360). The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Solicited Adverse Events:

On a daily basis, for 14 days post-vaccination after each of the doses, the subjects will be asked to record symptoms of the following AEs via the electronic subject diary:

- Solicited local AEs: pain/tenderness, erythema, and induration/swelling at the injection site.
- Solicited systemic AEs: body temperature ≥38°C (100.4°F; fever), headache, fatigue, nausea, and myalgia.

Solicited (local and systemic) AEs will be collected for 14 days after each vaccination via the electronic subject diary to be completed by the subjects for both doses (Day 1 to Day 15 after the first dose, and from Day 181 to Day 195 after the second dose). If a solicited local or systemic adverse event is not resolved within 14 days after each vaccination (on Day 15 after first vaccination and Day 195 after second vaccination), the follow-up will be captured in a paper subject diary. The investigator will review each subject's diary at the subsequent in-clinic visit; diary information will be transcribed by the study personnel into the electronic case report form (eCRF). Fever will be recorded by the investigator for temperatures equal to or higher than 38.0°C (100.4°F). By definition, all solicited local AEs occurring at the vaccination site will be considered related to the study vaccine administration (injection-site reactions); relatedness of solicited systemic AEs should be determined by the investigator.

Unsolicited Adverse Events:

Unsolicited AEs will be collected from the administration of the first dose of study vaccine until 29 days after both vaccinations (Day 1 to Day 30 after the first dose and Day 181 to Day 210 after the second dose) in all subjects. Additionally, AEs that are related to the study procedures or that are related to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated ICF is obtained onwards. Relatedness of unsolicited AEs should be determined by the investigator.

Note: At the time of second vaccination (Day 181), if any AE of local origin will be observed in the contralateral arm (on the arm of first dose administration), that AE will be recorded as an unsolicited AE.

IMMUNOGENICITY EVALUATIONS

Blood samples will be collected from all subjects on the day of vaccination (pre-vaccination on Day 1 and prior to the second dose on Day 181), and 14 days after each vaccination (on Day 15 and on Day 195) to determine vaccine immunogenicity by the ELISA and OPK assay.

The following immunogenicity parameters will be assessed:

- Geometric mean titer (GMT)
- Proportion of subjects with at least a 2- and 4-fold increase in serotype-specific antibodies from baseline and from pre-second dose
- Geometric mean ratio (GMR): fold increase from baseline and fold increase from pre-second dose

STATISTICAL METHODS

Sample Size Determination

This is a descriptive study and no formal hypothesis is planned. The study will enroll approximately 100 subjects with 1 arm of 75 subjects with ExPEC4V CTM; and 1 arm of 25 subjects with placebo. While mild to moderate vaccine reactions (local site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated. With 75 subjects targeted in the ExPEC4V CTM group, the observation of 0 such reactions would be associated with a 95% confidence that the true rate is less than 3.9%.

With 75 subjects in the ExPEC4V CTM group, AEs with a true incidence of 2.5% will likely be observed in this study, ie, the probability of observing at least 1 AE is 85%.

Below is the table showing the probabilities of observing at least 1 AE in a group of N subjects.

True Probability of AE	Placebo	ExPEC4V Group
	N=25	N=75
0.1%	2.5%	7.2%
0.5%	11.8%	31.3%
1.0%	22.2%	52.9%
2.5%	46.9%	85.0%
5.0%	72.3%	97.9%

Analysis Populations

Vaccination assignment will follow the as treated principle.

Full Analysis Set (FAS): The full analysis set will include all randomized subjects with at least 1 vaccine administration documented.

Per-Protocol Immunogenicity Population (PPI): The per-protocol immunogenicity population will include all randomized and vaccinated subjects for whom immunogenicity data are available excluding the subject with major protocol deviations which might impact the immunogenicity outcomes.

In addition, the following samples will not be included in the PPI population: If subjects miss the second dose, but continue the planned visit schedule, samples taken after the planned but missed dose will not be taken into account.

Planned Analyses

The primary analysis will be performed when all subjects have completed the Day 30 visit or discontinued earlier, upon resolution of relevant queries and database lock. The primary analysis will include all available safety/reactogenicity data and immunogenicity data through Day 15. Sponsor personnel involved in the analysis of the data will be unblinded at the time of this primary analysis. The primary analysis data will be used by the sponsor for planning of future studies. At the time of the primary analysis, the subjects and investigator(s) or site staff will remain blinded to individual subjects' vaccine assignment.

The final analysis will be performed for safety/reactogenicity and immunogenicity, when all subjects have completed the Day 360 visit at the end of the study or discontinued earlier.

Safety Analyses

No formal statistical testing of safety data is planned. The safety analysis will include the descriptive summary (including 95% confidence intervals) of solicited local AEs, solicited systemic AEs, unsolicited AEs, and SAEs. The overall frequencies per study vaccine group as well as frequencies per severity and duration will be calculated for solicited (local and systemic) and unsolicited AEs.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by study vaccine group.

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

Immunogenicity Analyses

For serum antibodies to O-antigen serotypes as measured by ELISA and OPK assay; or to EPA as measured by ELISA only, the following measures of immunogenicity will be evaluated and tabulated by study vaccine group (ExPEC4V CTM and placebo, as applicable):

- GMT on Day 1 (pre-vaccination), Day 15, Day 181 (pre-second vaccination) and Day 195 (14 days after the second dose).
- Proportion of subjects with a ≥2-fold, or ≥4-fold increase in serum antibody titers (Day 15 compared to Day 1 and Day 195 compared to Day 181).
- GMR: fold change from baseline, calculated from the Day 15/Day 1 values and fold change from pre-second dose, calculated from Day 195/Day 181 values.

The analyses will be descriptive in manner and there will be no formal statistical comparisons. Graphical representations of immunological parameters will be made as applicable.

TIME AND EVENTS SCHEDULE

Study Phase	Vaccination[a]	Safety and Immunogenicity Follow-up		Vaccination	Safety and Immunogenicity Follow-up		Safety Follow-up	Early Exit[c]
Visit Timing	**VACC 1**	**VACC 1 + 14 days**	**VACC 1 + 29 days**	**VACC 2**	**VACC 2 + 14 days[b]**	**VACC 2 + 29 days[b]**	**VACC 2 + 179 days[b]**	
Day	**1**	**15 ± 2**	**30 ± 3**	**181 ± 7**	**195 ± 2**	**210 ± 3**	**360 ± 7**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7 (Telephone Contact)**	
Study Procedures								
Pre-vaccination								
Informed consent[d]	X							
Eligibility criteria	X							
Demographics	X							
Medical history	X							
Physical examination	X	X[e]	X[e]	X[e]	X[e]	X[e]		X[e]
Body weight and height	X[f]							
Vital signs including body temperature[g]	X			X				
Urine pregnancy test in all women of childbearing potential	X			X				
Blood sampling for immunogenicity	X	X		X	X			
Vaccination								
Randomization[h]	X							
Dispense/administer study vaccine[i]	X			X				
Post-vaccination								
Post-vaccination observation (30 minutes)	X			X				
Distribution of subject diary[j]	X			X				
Review of subject diary		X			X			
Solicited adverse events[k]	X	X		X	X			X[m]
Unsolicited adverse events[l]	X	X	X	X	X	X		X[n]
Serious adverse events[l]	X	X	X	X	X	X	X	X
Concomitant medication[o] (including vaccination history)	X[p]	X	X	X	X	X	X	X[q]

VACC 1: First dose of ExPEC4V or placebo on Day 1; **VACC 2**: Second dose of ExPEC4V or placebo on Day 181.

Footnotes:

a. Subject screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination on Day 1 (before the first dose vaccination).

b. The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.
c. For those subjects who are unable to continue participation in the study, but who do not withdraw consent, an Early exit visit will be conducted. This can be a telephone contact visit and will include only safety follow-up (recording of AEs/SAEs and concomitant medications related to SAEs).
d. Signing of the informed consent form (ICF) needs to be done before the first study-related activity.
e. Targeted physical examination only (based on complaints/symptomatology and health status of subject).
f. Subject's body mass index (BMI) should be ≤35.0 kg/m^2 (calculated before first vaccination at Day 1).
g. Vital signs (systolic and diastolic supine blood pressure and pulse/heart rate) including body temperature will be measured both before vaccination and at the end of the 30-minute observation period after vaccination (measurements should be done after 5 minutes of seated rest). Investigator must check for body temperature ≥38.0 °C at the time of vaccination.
h. Randomization of 3:1 to ExPEC4V clinical trial material (CTM) and placebo on Day 1.
i. The subjects will receive a single dose of either ExPEC4V CTM or placebo IM in the deltoid muscle on Day 1 in a ratio of 3:1, respectively. Subjects will receive a second dose of either ExPEC4V CTM or placebo IM in the deltoid muscle on the contralateral side of the first dose on Day 181 (6 months after first vaccination).
j. Subjects will be provided with an electronic subject diary (to record solicited local and systemic AEs), a thermometer (to measure body temperature), and a ruler (to measure diameter of any erythema and induration/swelling), and will be instructed to measure and record solicited local and systemic AEs and body temperature daily for 15 days post-vaccination (day of vaccination and the subsequent 14 days). The subjects will also be handed wallet cards.
k. Solicited local and systemic adverse events will be collected in an electronic subject diary for 14 days after each vaccination. If a solicited local or systemic adverse event is not resolved within 14 days after each vaccination (on Day 15 after first vaccination and Day 195 after second vaccination), the subject will be provided with a paper subject diary on Day 15 (after first vaccination) or Day 195 (after second vaccination) visit to capture the follow-up information. The subject will be instructed to record the date of last symptoms and maximum severity until resolution in the diary.
l. All adverse events and special reporting situations, whether serious or non-serious, that are related to study-related procedures or that are related to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated ICF is obtained onwards. All other AEs and special reporting situations, whether serious or non-serious, will be reported from the day of first vaccination onwards.
m. Only if the Early exit visit is conducted on or before Day 15 for the first dose, and, on or before Day 195 for the second dose.
n. Only if the Early exit visit is conducted on or before Day 30 for the first dose, and, on or before Day 210 for the second dose.
o. After Day 30 until pre-dose Day 181 and after Day 210 until Day 360, only medications in conjunction with serious adverse events should be recorded.
p. Prestudy specific therapies (non-steroidal anti-inflammatory drugs [NSAIDs], corticosteroids, antihistaminic, and vaccinations) administered up to 30 days before signing the ICF must be recorded at Day 1 pre-vaccination.
q. At Early exit visit, only concomitant medications related to the SAEs will be collected.

ABBREVIATIONS

AE	adverse event
BMI	body mass index
CMC	Chemistry, Manufacturing and Controls
CTM	clinical trial material
eCRF	electronic case report form(s)
eDC	electronic data capture
dEPA	detoxified form of exotoxin protein A
ELISA	enzyme-linked immunosorbent assay
EPA	exotoxin protein A
ExPEC	extraintestinal pathogenic Escherichia coli
FAS	full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMR	geometric mean ratio
HHS	Health and Human Services
ICF	informed consent form
ICH	International Conference on Harmonisation
IED	invasive ExPEC disease
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
IWRS	interactive web response system
LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	non-steroidal anti-inflammatory drugs
OHRP	Office for Human Research Protections
OPK	opsonophagocytic killing
PPI	per-Protocol Immunogenicity
PQC	product quality complaint
PS	polysaccharide
SAE	serious adverse events
SUSAR	suspected unexpected serious adverse reaction
UTI	urinary tract infections

DEFINITIONS OF TERMS

Sponsor	The term “sponsor” used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.
ExPEC4V CTM	The term “ExPEC4V CTM” used throughout the document refers to the new clinical trial material manufactured via a redesigned Chemistry, Manufacturing and Controls (CMC) process.

1. INTRODUCTION

ExPEC4V (primary compound number: JNJ-63871860) is a 4-valent vaccine candidate in development for the prevention of invasive extraintestinal pathogenic *Escherichia coli* (ExPEC) disease. ExPEC4V consists of the O-antigen polysaccharides (PSs) of the ExPEC serotypes O1A, O2, O6A, and O25B separately conjugated to the carrier protein, a genetically detoxified form of exotoxin protein A (dEPA) derived from *Pseudomonas aeruginosa*.

ExPEC are part of the *E. coli* flora in the human gut; however, in contrast to commensal *E. coli*, ExPEC strains possess virulence factors for the colonization and infection of sites outside the gastrointestinal tract. ExPEC can cause diverse and serious invasive diseases,[11,14] resulting in significant burden due to hospitalization and death.[8,19] ExPEC strains are the most common cause of urinary tract infection (UTI), and are a contributor to surgical site infections and neonatal meningitis.[11,19] These strains are associated with abdominal and pelvic infections and nosocomial pneumonia, and are occasionally involved in other extraintestinal infections such as osteomyelitis, cellulitis, and wound infections. All these primary sites of infection can lead to ExPEC bacteremia[19] which can evolve to sepsis and to septic shock with organ dysfunction and with underlying circulatory, cellular and metabolic abnormalities which are life-threatening conditions associated with a greater risk of admissions to intensive care units and increased mortality.

Invasive ExPEC disease (IED) is defined as an acute illness consistent with bacterial infection, and microbiologically confirmed either by the isolation and identification of *E. coli* from blood or other normally sterile body sites; or, by the isolation and identification of *E. coli* from urine in a patient with signs and symptoms of systemic inflammatory response syndrome and no other identifiable source of infection.

IED occurs in both community and healthcare populations. In the US, it is estimated that up to 40,000 patients die annually due to IED, in particular from *E. coli* sepsis.[1,19] Overall case-fatality rates for ExPEC bacteremia range from 13% to 19%, but may be much higher (up to 60%) in the elderly with healthcare-associated infections.[18] In a recent health care-associated infection (HCAI) US study by Weiner *et al*. (2016), *E. coli* surpassed *Staphylococcus aureus* as the most frequent cause of healthcare-associated infections.[21] Data over the last decade reveal a steady increase of IED likely linked to an aging population, increased rise of antimicrobial resistance and increased number of healthcare-associated procedures.[1]

Patients undergoing uro-genital or abdominal surgeries/procedures (e.g., transrectal ultrasound-guided prostate needle biopsy [TRUS-PNB], endoscopic cholangiopancreatography) are at increased risk to develop IED, regardless of prophylactic use of antibiotics, which is part of the standard of care. Consequently, healthcare-associated IED is often caused by drug resistant ExPEC. In the adult surgery population, the uro-genital and abdominal surgeries represent over one-third of all *E. coli* sepsis cases that occur in this population.[3]

Increasing resistance of ExPEC against first-line antibiotics including cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole has been observed worldwide.[6,16,20] The emergence and rapid global dissemination of ExPEC sequence type (ST) 131 is considered the

main driver of increased drug resistance, including multidrug resistance.[10,17] The ST131 clone comprises 12.5% to 30% of all ExPEC clinical isolates and shows high levels of fluoroquinolone resistance, which is often accompanied by trimethoprim/sulfamethoxazole resistance.[7,17] The ST131 clone mostly exhibits serotype O25B:H4 (O-serotype 25B and H4 flagellar antigen).

ExPEC4V has the potential to prevent IED caused by serotypes O1A, O2, O6A and O25B. The ExPEC4V vaccine has been evaluated in 2 completed Phase 1 clinical trials (GVXN EC-4V and 63871860BAC1001) and one ongoing Phase 2 clinical trial (63871860BAC2001; primary analysis completed). A total of 1085 subjects were vaccinated so far in the ExPEC4V clinical development program: 892 subjects received different doses of ExPEC4V vaccine and 193 subjects received placebo. In each study, ExPEC4V was well-tolerated and no vaccine-related safety signals were observed. Also, the ExPEC4V vaccine was shown to be immunogenic in both studies, demonstrating a dose-dependent vaccine immune response, and O-antigen specific IgG (enzyme-linked immunosorbent assay [ELISA]) titer increases. Functional activity of the antibodies was demonstrated with an ExPEC4V-optimized opsonophagocytic killing (OPK) assay.

For the most comprehensive nonclinical and clinical information regarding ExPEC4V, refer to the latest version of the Investigator's Brochure for ExPEC4V.[2]

1.1. Background

1.1.1. Nonclinical Studies

The nonclinical safety of ExPEC4V was evaluated in 2 Good Laboratory Practice (GLP)-compliant repeated dose toxicology studies.

A repeated dose toxicity study was conducted in Sprague-Dawley rats which received 2 intramuscular (IM) injections of ExPEC4V at 4 µg PS per serotype (ie, 16 µg PS in total, equivalent to the highest dose tested in the Phase 1 clinical study GVXN EC-4V), the first on Day 1 and the second on Day 14. The vaccine was well-tolerated and no adverse vaccine-related effects were noted. Non-adverse inflammatory effects at the injection sites related to the IM administration were seen in vehicle- and vaccine-treated animals at the end of the treatment period. On Day 28 (2 weeks after the second injection), the Day 1-injection site was fully recovered while the recovery of the Day 14-injection site was ongoing. The vaccine was shown to be immunogenic in the animals, confirming the rat as a relevant toxicology species.

Another repeated dose toxicity study was conducted in New Zealand White rabbits which received 3 IM injections of ExPEC4V, given 2 weeks apart, at a maximum dose of 16 µg PS per serotype (ie, up to 64 µg PS in total, equivalent to the maximum human dose that is being evaluated in the Phase 2 clinical study 63871860BAC2001). The vaccine was well-tolerated and no adverse vaccine-related effects were noted. The vaccine was shown to be immunogenic in male and female rabbits, confirming the rabbit as a relevant toxicology species. Non-adverse, minimal changes were seen in red blood cell parameters and fibrinogen. Non-adverse inflammatory effects were seen at the injection sites at the end of the treatment period. Three weeks after the last (third) vaccination, injection sites had partially or fully recovered. In

addition, non-adverse findings were observed in the draining medial iliac lymph nodes and the spleen, which were considered related to the immune response induced by the vaccine administration.

1.1.2. Clinical Studies

To date, ExPEC4V has been tested in two completed Phase 1 clinical studies (GVXN EC-4V and 63871860BAC1001) and one ongoing Phase 2 clinical study (63871860BAC2001).

Study GVXN EC-4V

Study GVXN EC-4V was a Phase 1, randomized, placebo-controlled, single-blind, multicenter study to evaluate the safety, immunogenicity, and efficacy of 2 doses of ExPEC4V candidate vaccine (1:1:1:1 μg PS and 4:4:4:4 μg PS) in healthy women aged ≥18 to ≤70 years with a history of recurrent UTIs. After vaccination of the subjects with a single dose of ExPEC4V or placebo, each subject was followed-up for 9 months (Day 270). A total of 194 subjects were vaccinated (6 subjects in the 1:1:1:1 group, 93 in the 4:4:4:4 group and 95 in the placebo group).

Immunogenicity Results

Immunogenicity results showed a vaccine-specific immune response for all 4 vaccine antigens that is maintained over at least 270 days. The lack of relevant change in antibody titers for the majority of subjects in the placebo group suggests the antibody response in ExPEC4V recipients was vaccine-mediated, and was not due to environmental exposure to ExPEC bacteria. ExPEC4V was able to elicit a general increase in IgG titers in this recurrent UTI study population with heterogeneous pre-existing levels of vaccine-specific antibodies.

Efficacy Results

Efficacy analyses showed that the number of UTIs caused by vaccine-specific serotypes was similar in the 4 μg PS/serotype ExPEC4V and placebo group while the number of episodes caused by an *E. coli* of any serotype was lower in the ExPEC4V compared to the placebo group.

Safety Results

Most subjects in the study experienced at least 1 adverse event (AE) following injection; 78 (83.9%) in the 4 μg PS/serotype ExPEC4V group, 4 (66.7%) in the 1 μg PS/serotype ExPEC4V group and 81 (85.3%) in the placebo group. The number of subjects with serious adverse events (SAE) was higher in the 4 μg PS/serotype ExPEC4V group (9 [9.7%]) compared to the placebo group (3 [3.2%]). All SAEs were considered not related to the vaccine or placebo by the investigator. None of the subjects discontinued due to their respective SAEs. No deaths were reported in this study.

The number of subjects with at least 1 solicited local or systemic AE was 38 (41%) in the 4 μg PS/serotype ExPEC4V group, 2 (33%) in the 1 μg PS/serotype ExPEC4V group and 32 (34%) in the placebo group. The most frequently reported solicited local AEs in the 4 and 1 μg PS/serotype ExPEC4V group compared to the placebo group were injection-site pain (28%, 17% and 17%, respectively), injection-site erythema (25%, 17% and 21%, respectively), and injection-site swelling (15%, 0% and 13%, respectively).

The number of subjects with at least 1 frequently (≥3% of total subjects) reported unsolicited AE was 74 (80%) subjects in the 4 µg PS/serotype ExPEC4V group, 4 (66.7%) subjects in the 1 µg PS/serotype ExPEC4V group and 76 (80%) subjects in the placebo group. The most frequently reported unsolicited AE was headache, reported by 24 (25.8%) subjects in the 4 µg PS/serotype ExPEC4V group, 4 (66.7%) subjects in the 1 µg PS/serotype ExPEC4V group and 19 (20%) subjects in the placebo group.

Study 63871860BAC1001

Study 63871860BAC1001 was a Phase 1, randomized, double-blind, placebo-controlled, parallel-group, single center study in healthy Japanese subjects aged ≥20 years to evaluate the safety, tolerability and immunogenicity of 3 different ExPEC4V doses (4:4:4:4 µg PS, 8:8:8:8 µg PS and 16:16:16:16 µg PS). The study duration for each subject was approximately 38 days (inclusive of screening and post-vaccination follow-up periods). A total of 48 subjects were planned, randomized, and vaccinated (24 subjects each in the ≥20- to <50-years [younger] age group and ≥50 years [older] age group), and within each age group, 6 subjects each in the placebo group and in the 4:4:4:4, 8:8:8:8 and 16:16:16:16 groups).

Immunogenicity Results

The ExPEC4V vaccine yielded an immunogenic response for all dose groups, with an increase in ELISA (total IgG) and OPK (functional) antibody titers on Days 15 and 30 compared with baseline, within dose groups. There was a positive correlation observed between the ELISA and OPK antibody responses across all the study groups (3 ExPEC4V groups and placebo group), and serotypes (correlation coefficient ≥0.5940).

Safety Results

There were no deaths, other SAEs, or AEs leading to study discontinuation reported in the study. Overall, 23 of 48 subjects (47.9%) experienced at least 1 AE: 13 of 24 subjects (54.2%) in the younger age group and 10 of 24 subjects (41.7%) in the older age group. Solicited AEs were reported in 16 of 36 subjects (44.4%) in the combined ExPEC4V group and 6 of 12 subjects (50.0%) in the placebo group. Unsolicited AEs were reported in 3 of 36 subjects (8.3%) in the combined ExPEC4V group and 2 of 12 subjects (16.7%) in the placebo group.

The ExPEC4V 4, 8, and 16 µg PS/serotype doses were generally safe and well-tolerated in healthy Japanese subjects.

Study 63871860BAC2001

Study 63871860BAC2001 is a Phase 2, randomized, placebo-controlled, multicenter study conducted to evaluate the safety, tolerability, and the dose-dependent immunogenicity of 5 different ExPEC4V doses (4:4:4:4 µg PS, 4:4:4:8 µg PS, 8:8:8:8 µg PS, 8:8:8:16 µg PS and 16:16:16:16 µg PS) in men and women aged ≥18 years who are in stable health (primary analysis data through Day 30 was available at the time of protocol writing). A total of 848 subjects were randomized in the study, 275 in the ≥18 to <50 years age group and 573 in the ≥50 years age group. In the study, a total of 152 subjects were assigned to each of the 4:4:4:4, 8:8:8:8, 8:8:8:16 and 16:16:16:16 groups; 153 subjects to the 4:4:4:8 group, and 87 subjects to the placebo group.

Of the 848 randomized subjects, 843 subjects were vaccinated with either ExPEC4V or placebo. This study is being conducted in 2 phases: a double-blind phase from Day 1 to Day 360 and a single-blind long-term follow-up (LTFU) phase until Year 4 post-vaccination. The study is still ongoing and the data presented below is from the primary analysis (until Day 30) of the study.

Immunogenicity Results

Immunogenicity results for both total ELISA and functional OPK antibodies showed that all doses were immunogenic. To provide guidance for dose selection from an immunogenicity perspective, an algorithm was used to identify the ExPEC4V dose generally exhibiting the highest ELISA or OPK antibody titer increase from baseline. Based on the immunogenicity dose selection algorithm and considering all dose groups, serotypes and age groups, the 16:16:16:16 dose generally yielded the highest vaccine-mediated immune response. A trend of increasing antibody titers with increasing ExPEC4V dose was observed for serotypes O1A, O2 and O6A, with maximum titers observed with the 16:16:16:16 dose (clinical relevance unknown), but maximum titers for O25B (a relevant serotype based on clinical prevalence and associated frequency of antibiotic resistance) were observed with 4:4:4:8 and 8:8:8:16 doses.

Based on the totality of the evidence, including safety, immunogenicity serotype prevalence, antibiotic resistance, antigen load and vaccine-mediated immune interference, the sponsor selected the 4:4:4:8 μg PS ExPEC4V dose for the LTFU and further clinical development.

Safety Results

Based on the primary analysis, all 5 doses of ExPEC4V were well-tolerated and no vaccine-related safety signals were observed in this Phase 2 study. A trend for higher frequency of local and systemic solicited AEs was observed with increasing ExPEC4V dose, however, the incidence of Grade 3 AEs remained low for all the ExPEC4V dose groups.

The incidence of at least one AE, whether solicited or unsolicited, was 63.2%, 55.3%, 62.3%, 61.3% and 67.1% in the 4:4:4:4, 4:4:4:8, 8:8:8:8, 8:8:8:16 and 16:16:16:16 ExPEC4V groups, respectively compared to 50.0% in the placebo group. The incidence of solicited AEs was 50.7%, 43.4%, 47.0%, 50.7% and 58.6% in the 4:4:4:4, 4:4:4:8, 8:8:8:8, 8:8:8:16 and 16:16:16:16 ExPEC4V groups, respectively; compared to 38.4% in the placebo group. The majority of solicited AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. The incidence of unsolicited AEs was 25.7%, 23.7%, 29.8%, 26.7% and 29.6% for the 4:4:4:4, 4:4:4:8, 8:8:8:8, 8:8:8:16 and 16:16:16:16 ExPEC4V groups, respectively, compared to 24.4% in the placebo group.

There was one death reported, the subject died due to homicide. The investigator considered the causality between death and study vaccine as not related. Besides one subject who died, no other subject discontinued from the study due to an AE/SAE. There were 9 (1.1%) subjects who experienced an SAE in the combined ExPEC4V groups and no SAEs were experienced in the placebo group. The incidence of SAEs was 0.7%, 1.3%, 1.3%, 0.7% and 2.0% in the 4:4:4:4, 4:4:4:8, 8:8:8:8, 8:8:8:16 and 16:16:16:16 ExPEC4V groups, respectively. There was 1 SAE

(trigeminal neuralgia) in the 16:16:16:16 group that was considered related to vaccine by the investigator.

1.2. Overall Rationale for the Study

As part of the Chemistry, Manufacturing and Controls (CMC) development activities for ExPEC4V, several changes have been introduced in the Drug Substance and Drug Product manufacturing process of ExPEC4V which include changes in the process, scale, manufacturing site, formulation buffer and introduction of the optimized strain (O1A). In support of the implemented changes, CMC performed a physico-chemical comparability study. The results from the physico-chemical comparability study will be available prior to initiation of the 63871860BAC2003 clinical trial and will be submitted as part of the Investigational New Drug (IND) Amendment.

In order to anticipate potential safety and immunogenicity risks, an initial assessment has been done based on:

- Evaluating the impact of the changes on the quality attributes through a risk analysis, and
- Physico-chemical comparability study in which data, from development material produced with the redesigned manufacturing process, have been compared to historical Phase1 & 2 data

and concluded as below:

- The safety profile of the clinical trial material (CTM) manufactured via the redesigned CMC process is expected to be comparable to the profile of the CTM used in the Phase 1 and Phase 2 clinical studies to date;
- Differences are expected in the molecular weight distribution due to a shift in the degree of glycosylation specifically for serotypes O1A and O25B.
  - The results complied with the pre-determined specifications.
  - The results of dose response studies in animals did not show any changes in the immune response with material produced via the redesigned CMC process.

In addition to the physico-chemical comparability study performed by CMC, this Phase 2 clinical study will be conducted to evaluate safety/reactogenicity and immunogenicity of the ExPEC4V CTM manufactured via the redesigned CMC process (hereafter referred as ExPEC4V CTM), and to expand the safety and immunogenicity database with the selected dose prior to using the new CTM in future clinical studies.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

- To evaluate the safety/reactogenicity of the ExPEC4V CTM after the first vaccination
- To evaluate the immunogenicity of the ExPEC4V CTM, as measured by the ELISA, 14 days after the first vaccination (on Day 15)

Secondary Objectives

- To evaluate the immunogenicity of the ExPEC4V CTM, as measured by the OPK assay, 14 days after the first vaccination (on Day 15)
- To evaluate the safety/reactogenicity of the ExPEC4V CTM after the second vaccination
- To evaluate the immunogenicity of the ExPEC4V CTM, as measured by the ELISA, 14 days after the second vaccination (on Day 195)
- To evaluate the immunogenicity of the ExPEC4V CTM, as measured by the OPK assay, 14 days after the second vaccination (on Day 195)

2.1.2. Endpoints

Primary Endpoints

- Solicited local and systemic AEs for 14 days after first vaccination (Day 1 to Day 15); unsolicited AEs for 29 days after first vaccination (Day 1 to Day 30); and SAEs until Day 180
- Antibody titers as determined by the ELISA on Day 1 pre-vaccination (prior to first vaccination) and Day 15 post-vaccination (14 days after first vaccination)

Secondary Endpoints

- Antibody titers as determined by the OPK assay on Day 1 pre-vaccination (prior to first vaccination) and Day 15 post-vaccination (14 days after first vaccination)
- Solicited local and systemic AEs for 14 days after second vaccination (Day 181 to Day 195); unsolicited AEs for 29 days after second vaccination (Day 181 to Day 210); and SAEs from Day 181 until Day 360
- Antibody titers as determined by the ELISA on Day 181 pre-vaccination (prior to second vaccination) and on Day 195 (14 days after second vaccination)
- Antibody titers as determined by the OPK assay on Day 181 pre-vaccination (prior to second vaccination) and on Day 195 (14 days after second vaccination)

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

No statistical hypothesis testing will be performed. All analyses will be descriptive.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, interventional study to evaluate safety, reactogenicity and immunogenicity of the ExPEC4V CTM.

The study is planned to be conducted in approximately 100 male and female subjects aged ≥18 years with medically stable health. The subjects who fulfill all inclusion and exclusion criteria will be randomly assigned to receive a single dose of either ExPEC4V CTM or placebo on Day 1 in a ratio of 3:1, respectively. Subjects will receive a second dose of either ExPEC4V CTM or placebo on Day 181 (6 months after first vaccination).

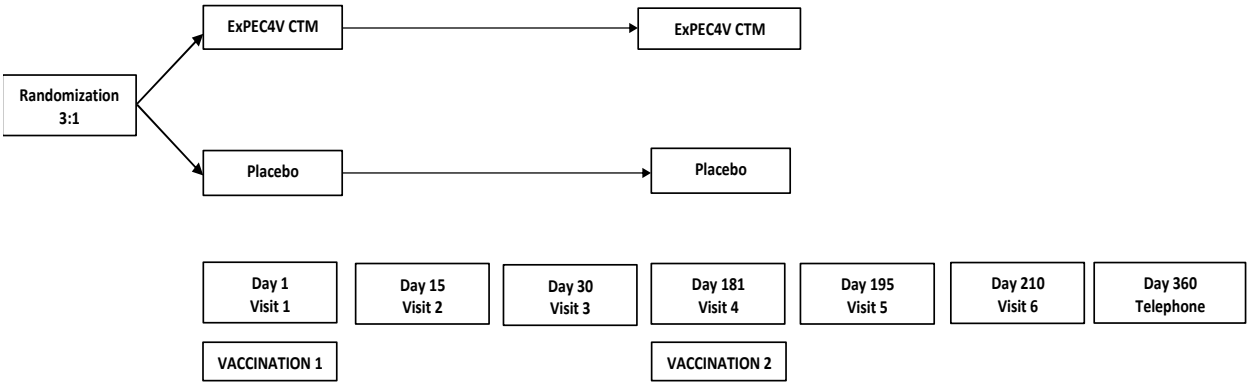
Subjects will be closely observed by the study staff for at least 30 minutes after both vaccinations (on Day 1 and Day 181). Blood samples will be collected from all subjects on the day of vaccination (pre-vaccination; Day 1 and Day 181); and 14 days after each vaccination (on Day 15 and Day 195) for immunogenicity assessment by the ELISA and OPK assay.

The study duration will be approximately 1 year per participant; the end of the study will be the last subject's last visit (this will be a telephone contact). The study consists of randomization and first vaccination on Day 1 and second vaccination on Day 181 (6 months after first vaccination) and subjects will be followed until the end of the study at Day 360.

The primary analysis is planned to evaluate all available safety/reactogenicity and immunogenicity data when all subjects have completed Day 30 visit or discontinued earlier. The final analysis will be performed when all subjects have completed the Day 360 visit at the end of the study or discontinued earlier.

A diagram of the study design is provided below in Figure 1.

Figure 1: Schematic Overview of the Study



ExPEC4V CTM=Clinical trial material manufactured via a redesigned CMC process

3.2. Study Design Rationale

Control, Study Vaccine Groups, Blinding

A placebo control will be used to establish the frequency and magnitude of changes in safety and immunogenicity endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of subjects to study vaccine groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across study vaccine groups, and to enhance the validity of statistical comparisons across study vaccine groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of safety and immunogenicity endpoints.

Rationale for ExPEC4V Dose Selection

The dose of study vaccine (4:4:4:8 µg PS/ExPEC4V serotypes) administered in this study was selected based on the primary analysis results from the ongoing Phase 2 study (63871860BAC2001) and totality of the available evidence, including safety, immunogenicity serotype prevalence, antibiotic resistance, antigen load and vaccine-mediated immune interference. Overall, safety data from studies with ExPEC4V vaccine is summarized in Section 1.1, Background.

Rationale for Administration of Second Dose

The subjects will be vaccinated twice in the study. Although it is not expected that a second vaccination with ExPEC4V would be needed to boost the immune response, in this study a second dose of ExPEC4V will be administered to evaluate its safety, reactogenicity and immunogenicity. Antibody titers will be assessed following the second dose to enhance the understanding of the immunological impact of ExPEC4V.

Rationale for Duration of Collection of Solicited Adverse Events

Based on 2 completed Phase 1 studies and the primary analysis results of the ongoing Phase 2 study (63871860BAC2001), most solicited (local and systemic) AEs started on Days 1 to 3 post-vaccination, however late onset solicited (mainly local) AEs were observed starting Days 6 to 8

post-vaccination. Pain/tenderness represented a majority of the late onset AEs and were Grade 1 in severity. There was a tendency for higher incidence of late onset AEs with higher ExPEC4V doses (observed in the Phase 1 Japanese study [63871860BAC1001] and the Phase 2 study [63871860BAC2001]). There is, so far, no explanation for this observation; but we hypothesize that it could be a T-cell mediated delayed hypersensitivity to the ExoProtein A (EPA) carrier protein or to the O-antigen. It is planned to further evaluate these late onset reactions in this study with the 4:4:4:8 µg PS/ExPEC serotype (O1A, O2, O6A and O25B) dose by following solicited local and systemic AEs until Day 15 (instead of Day 8) by means of the electronic subject diary to further evaluate the late onset reactogenicity.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.3, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Man or woman aged ≥18 years who provides written informed consent and signs the informed consent form (ICF) indicating that he or she understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study.

2. Subject is medically stable as confirmed by documented medical history, physical examination and vital signs. Subject may have underlying illnesses such as hypertension, diabetes, or ischemic heart disease, as long as their symptoms/signs are medically controlled. If he/she is on medication for a condition, the medication dose must have been stable for at least 12 weeks preceding vaccination.

3. Subject must have a body mass index (BMI) of ≤35.0 kg/m^2.

4. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol (Refer to Section 4.3).

5. Subject must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.

6. Subject agrees not to donate blood until 12 weeks after receiving the last dose of study vaccine.

7. Contraceptive (birth control) use by woman should be consistent with local regulations regarding the acceptable methods of contraception for subject participating in clinical studies.

   Before randomization, a woman must be either:

   a. Not of childbearing potential defined as:
      - premenarchal
        A premenarchal state is one in which menarche has not yet occurred.
      - postmenopausal
        A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
      - permanently sterile
        Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

   b. Of childbearing potential and
      - practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) Acceptable methods for this study include:
        a) Hormonal contraception;
        b) Intrauterine device (IUD);
        c) Intrauterine hormone-releasing system (IUS);
        d) Male or female condom with or without spermicide;
        e) Cap, diaphragm or sponge with a vaginal spermicide;
        f) Vasectomized partner (the vasectomized partner should be the sole partner for that subject);
        g) Sexual abstinence*.

        Sexual abstinence is considered an effective method **only if defined as refraining from heterosexual intercourse from signing the informed consent until 3 months after each study vaccination. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
      - agrees to remain on an effective method of contraception from signing the informed consent until 3 months after the last dose of study vaccine. Use of all contraception should start at least 28 days before the first administration of study vaccine.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active,) a woman must begin an acceptable effective method of contraception, as described throughout the inclusion criteria.

8. All females of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) at pregnancy test on Visit 1 (pre-vaccination) and Visit 4 (prior to the second vaccination).

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Subject with contraindication to intramuscular (IM) injections and blood draws, eg, bleeding disorders.

2. Subject with an acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0ºC (100.4ºF) within 24 hours prior to administration of study vaccine; enrollment at a later date is permitted.

3. Subject with known allergies, hypersensitivity, or intolerance to ExPEC4V or its excipients (refer to Investigator's Brochure).[2]

4. Subject with abnormal function of the immune system resulting from:

   - clinical conditions (eg, autoimmune disease or immunodeficiency).
   - chronic or recurrent use of systemic corticosteroids.

     Note: Ocular, topical or inhaled steroids are allowed.
   - administration of antineoplastic and immunomodulating agents or radiotherapy.

5. Subject has a history of neoplastic disease (excluding non-melanoma skin cancer or carcinoma *in situ* of the cervix that was successfully treated) within the past 1 year or a history of any hematological malignancy.

6. Subject with history of acute polyneuropathy (e.g. Guillain-Barré syndrome).

7. Subject who has received or plans to receive:

   - licensed live attenuated vaccines – within 28 days before or after each study vaccination.
   - other licensed (not live) vaccines - within 14 days before or after each study vaccination.

8. Subject who has received an investigational drug (including investigational vaccines) or

used an invasive investigational medical device within 90 days before vaccination in the study, is currently enrolled in an investigational study, or plans to enroll in an investigational study during this study.

9. Subject is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study.

10. Subject has received treatment with immunoglobulins in the 2 months or blood products in the 4 months before vaccination in the study or any plans to receive such treatment during the study.

11. Subject who has a history of an underlying clinically significant acute or [uncontrolled] chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

12. Subject who had a major surgery, (per the investigator's judgment) within 12 weeks before dosing, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 6 months after the last dose of study vaccine administration.

    Note: Subjects with planned surgical procedures to be conducted under local or locoregional anesthesia and not judged as major by the investigator may participate.

13. Subject who is an employee of the investigator or study-site, with direct involvement in the proposed study or other studies under the direction of that investigator or study-site, as well as family members of the employees or the investigator, or an employee of the sponsor.

14. Subject who has had major psychiatric illness and/or drug or alcohol abuse which in the investigator's opinion would compromise the subject's safety and/or compliance with the study procedures.

15. Subject who cannot communicate reliably with the investigator.

16. Subject who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or are unlikely to complete the full course of vaccination and observation.

NOTE: Investigators should ensure that all study enrollment criteria have been met before randomization. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after signing the ICF but before the first dose of study vaccine is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. The subject might be re-consented, re-screened, enrolled, and vaccinated at another visit, if he or she fulfills the enrollment criteria (provided the

enrollment will be ongoing). Similarly, if a subject's clinical status changes before the second vaccination on Day 181, while enrolled in the study, the subject may be re-checked and vaccinated within 1 week if the event(s) has resolved. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8, Prestudy and Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Live attenuated vaccines are prohibited within 28 days before and after each study vaccination. Other licensed (not live) vaccines (eg, tetanus, hepatitis A, hepatitis B, rabies) should not be given at least 14 days before or after each administration of the study vaccine in order to avoid potential confusion of adverse reactions and potential immune interference. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

5. STUDY VACCINE ALLOCATION AND BLINDING

Study Vaccine Allocation

Procedures for Randomization

Subjects will be randomly assigned to 1 of 2 study vaccine groups (ExPEC4V or placebo) in a ratio of 3:1 based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks.

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the study vaccine assignment. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

The subjects, clinical staff, investigators, and sponsor personnel will be blinded to study vaccine group allocation, except for an independent monitor and a designated pharmacist or qualified staff member with primary responsibility for study vaccine preparation.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the study vaccine group status of the subject. In such cases, the investigator may in an emergency determine the identity of the study vaccine group by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented by the IWRS, in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, for the primary analysis, the randomization codes and, if required, the translation of randomization codes into study vaccine and control groups will be disclosed to the authorized sponsor personnel involved in the analysis of the data. At the time of the primary analysis, the subjects, investigator(s) and site staff will remain blinded to individual subjects' vaccine assignment.

6. DOSAGE AND ADMINISTRATION

ExPEC4V (JNJ-63871860): *E. coli* bioconjugate vaccine in phosphate buffered solution containing O-antigen PS of ExPEC serotypes O1A, O2, O6A, O25B (4:4:4:8 µg PS/ExPEC4V serotypes) separately conjugated to the EPA carrier protein. The selected dose for further development of ExPEC4V is 4:4:4:8 µg PS/ExPEC serotype (O1A, O2, O6A and O25B), and the same dose will be used in this study.

Single 0.5 mL IM (deltoid) injection of ExPEC4V CTM on Day 1 and on Day 181 (The second dose of study vaccination will be administered on the contralateral side of the first dose.)

Placebo: Tris-saline solution

Single 0.5 mL IM (deltoid) injection on Day 1 and Day 181

The subjects, clinical staff, investigators, and sponsor personnel will be blinded to study vaccine group allocation, except for the designated pharmacist or qualified staff member with primary responsibility for study vaccine preparation.

7. INTERVENTION COMPLIANCE

Study vaccine will be administered IM by a blinded vaccine administrator at the study site who can be a trained and qualified study nurse, medical doctor, or otherwise qualified healthcare professional.

The date and time of each study vaccine administration will be recorded in the eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy specific therapies (non-steroidal anti-inflammatory drugs [NSAIDs], corticosteroids, antihistaminic, and vaccinations) administered up to 30 days before signing the ICF must be recorded at Day 1 pre-vaccination.

Concomitant therapies (NSAIDs, corticosteroids, antihistaminic, and vaccinations) must be recorded for all subjects until 29 days after the first vaccination (from Day 1 to Day 30) and from the second vaccination through the following 29 days (from Day 181 to Day 210), and additionally outside of these periods when associated with an SAE that meets the criteria outlined in Section 12.3.2. Serious Adverse Events. Information on concomitant use of herbal supplements or vitamins will not be collected.

Use of any investigational medication (including investigational vaccines other than the study vaccine) within 90 days before vaccination in the study or during the study is not allowed.

Receipt of licensed live attenuated vaccines within 28 days before or after, or any other licensed (not live) vaccine within 14 days before or after any of study vaccinations is not allowed. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Chronic or recurrent use of immunomodulators/suppressors, e.g. cancer chemotherapeutic agents, systemic corticosteroids is prohibited. *Note*: Ocular, topical or inhaled steroids are allowed.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of immunogenicity and safety/reactogenicity measurements applicable to this study.

Approximately 10 mL blood for immunogenicity will be drawn at each visit on Days 1, 15, 181 and 195 from all subjects. The total blood volume to be collected from each subject will be approximately 40 mL for the immunogenicity evaluations.

Additional unscheduled study visits may be required if in the investigator's opinion, further clinical or laboratory evaluation is needed. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Visit Windows

For the following visits, windows will be allowed as indicated below in Table 1.

Table 1: Visit Windows

VISIT	*Visit Day*	*Window*	*Primary Purpose*
Visit 1	Day 1 (VACC 1)	-	First vaccination
Visit 2	Day 15 (VACC 1 + 14 days)	± 2 days	14 days post-first vaccination safety and immunogenicity visit
Visit 3	Day 30 (VACC 1 + 29 days)	± 3 days	29 days post-first vaccination safety only visit
Visit 4	Day 181 (VACC 2)	± 7 days	Second vaccination (6 months post-first vaccination)
Visit 5	Day 195 (VACC 2 + 14 days*)	± 2 days	14 days post-second vaccination safety and immunogenicity visit
Visit 6	Day 210 (VACC 2 + 29 days*)	± 3 days	29 days post-second vaccination safety only visits
Visit 7	Day 360 (VACC 2 + 179 days*)	± 7 days	6 months post-second vaccination safety only visit (Telephone contact)

VACC 1: First dose of ExPEC4V or placebo on Day 1; **VACC 2**: Second dose of ExPEC4V or placebo on Day 181.
* The timings of visits after the second vaccination will be determined relative to the actual day of that vaccination.

9.1.3. Randomization and First Vaccination (Day 1, Visit 1)

Note: all eligibility criteria must be fulfilled prior to randomization and vaccination.

The following procedures will take place prior to vaccination:

- Written informed consent
- Screening for eligibility (inclusion/exclusion) criteria
- Demographic data (age, sex, race/ethnicity, smoking status)
- Medical history (clinically relevant medical events occurring between signing of ICF and time of first vaccination will be collected on the Medical History eCRF page as pre-existing conditions)
- Physical examination and body weight (including BMI) and height
- Vital signs (systolic and diastolic supine blood pressure and pulse/heart rate) including body temperature

- Urine pregnancy test for women of childbearing potential
- Recording of prestudy medication (including vaccination history)
- Recording of AEs or SAEs from the time a signed and dated ICF is obtained (all AEs and special reporting situations, whether serious or non-serious, that are related to study-related procedures or that are related to non-investigational (concomitant) Janssen products)
- Blood sampling for immunogenicity evaluation
- Randomization

All subjects will be administered 1 dose of the study vaccine (either ExPEC4V CTM or placebo) in the deltoid muscle.

The following procedures will take place after the vaccination:

- After vaccination, subjects will be observed for at least 30 minutes. Appropriate medical treatment should be readily available in case of any rare anaphylactic reaction. Vital signs (including systolic and diastolic supine blood pressure, pulse/heart rate and body temperature) will be measured at the end of the observation period.
- Subjects will be provided with an electronic subject diary (to record solicited local and systemic AEs), a thermometer (to measure body temperature), a ruler (to measure diameter of any erythema and induration/swelling), and a wallet card, and will be instructed to measure and record solicited local and systemic AEs and body temperature daily for 15 days post-vaccination (day of vaccination and the subsequent 14 days).
- Recording of unsolicited and solicited local or systemic AEs/SAEs
- Recording of concomitant medication
- Scheduling of next visit(s)

9.1.4. Visit 2 (Day 15 ± 2 days) & Visit 5 (Day 195 ± 2 days; 14 days After Second Dose)

The following procedures will take place at the Visit 2 and Visit 5:

- Targeted physical examination (based on complaints/symptomatology and health status of subject)
- Recording of unsolicited and solicited local or systemic AEs/SAEs
- Recording of concomitant medication
- Review of the electronic subject diary entries
- If a solicited local or systemic adverse event is not resolved within 14 days after each vaccination (on Day 15 after first vaccination and Day 195 after second vaccination), the subjects will be provided with a paper subject diary to capture the follow-up information. The subject will be instructed to record the date of last symptoms and maximum severity until resolution in the diary.

- Blood sampling for immunogenicity evaluation
- Scheduling of next visit(s)

9.1.5. Visit 3 (Day 30 ± 3 days) & Visit 6 (Day 210 ± 3 days; 29 days After Second Dose)

The following procedures will take place at the Visit 3 and Visit 6:

- Targeted physical examination (based on complaints/symptomatology and health status of subject)
- Recording of unsolicited AEs/SAEs
- Recording of concomitant medication
- Scheduling of next visit(s)

9.1.6. Second Vaccination (Day 181 ± 7 days, Visit 4)

The following procedures will take place prior to vaccination at the Visit 4:

- Targeted physical examination (based on complaints/symptomatology and health status of subject)
- Vital signs (systolic and diastolic supine blood pressure and pulse/heart rate) including body temperature
- Urine pregnancy test for women of childbearing potential
- Recording of concomitant medication (from Day 30 to Day 180 only in association with SAEs)
- Blood sampling for immunogenicity evaluation

All subjects will be administered second dose of the study vaccine on the contralateral side of the first dose in deltoid muscle (either ExPEC4V CTM or placebo).

The following procedures will take place after the vaccination:

- After vaccination, subjects will be observed for at least 30 minutes. Appropriate medical treatment should be readily available in case of any rare anaphylactic reaction. Vital signs (including systolic and diastolic supine blood pressure, pulse/heart rate and body temperature) will be measured at the end of the observation period.
- Subjects will be provided with an electronic subject diary, a thermometer, and a ruler, and will be instructed to measure and record solicited local and systemic AEs and body temperature daily for 15 days post-vaccination (day of vaccination and the subsequent 14 days).
- Recording of unsolicited and solicited local or systemic AEs/SAEs
- Recording of concomitant medication

- Scheduling of next visit(s).

9.1.7. Visit 7 (Day 360 ± 7 days, Telephone Contact)

The following information will be collected from the subject at the Visit 7 (safety follow-up, telephone call):

- Recording of SAEs and any associated concomitant medications

9.1.8. Early Withdrawal – Early Exit Visit

The following procedures will take place at the Early exit visit, for subjects who are unable to continue participation in the study, but who do not withdraw consent:

- Targeted physical examination (based on complaints/symptomatology and health status of subject)
- Recording of AEs/SAEs
  - Solicited (local and systemic) AEs if Early exit visit occur on or before Day 15 for the first dose or on or before Day 195 for the second dose
  - Unsolicited AE if Early exit visit occur on or before Day 30 for the first dose or on or before Day 210 for the second dose
- Recording of concomitant medication (only related to the SAEs)

This visit can be a telephone contact visit and will include only safety follow-up (recording of AEs/SAEs and concomitant medications related to SAEs).

9.2. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and reactogenicity according to the time points provided in the TIME AND EVENTS SCHEDULE:

9.2.1. Adverse Events

All AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study as specified in Section 12.3.1.

Solicited (local and systemic) AEs will be reported by the subject from the time of vaccination until 14 days after both doses of the study vaccine (Day 1 to Day 15 after the first dose, and from Day 181 to Day 195 after the second dose). Unsolicited AEs will be reported by the subject from when the first dose of study vaccine is administered until 29 days after the first vaccination (Day 1 to Day 30) and from the second vaccination until 29 days thereafter (Day 181 to Day 210), or

early discontinuation. Unsolicited AEs with the onset date outside the timeframe defined above (>29 days after both study vaccinations), which are ongoing on the day of the subsequent vaccination, should be recorded on the eCRF AE page. Relatedness of unsolicited AEs should be determined by the investigator. All SAEs will be collected for all subjects from the administration of the first dose of study vaccine until the end of the study at 6 months after the second dose of the study vaccine (telephone call at Day 360), or early discontinuation. Additionally, AEs or SAEs that are related to the study procedures or are related to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated ICF is obtained.

Note: At the time of second vaccination (Day 181), if any AE of local origin will be observed in the contralateral arm (on the arm of first dose administration), that AE will be recorded as an unsolicited AE.

Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Solicited (Local and Systemic) Adverse Events

Solicited (local and systemic) AEs are precisely defined events that subjects are specifically asked about and which are noted by subjects through the subject diary. The investigator will review each subject's diary at the subsequent in-clinic visit; diary information will be transcribed by the study personnel into the eCRF. In addition, after vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. By definition, all solicited local AEs occurring at the vaccination site will be considered related to the study vaccine administration (injection-site reactions); relatedness of solicited systemic AEs should be determined by the investigator.

Solicited Local AEs (Injection-Site Reactions)

Subjects will be instructed on how to note occurrences of pain/tenderness, erythema, and induration/swelling at the injection-site daily for 14 days after vaccination (day of vaccination and the subsequent 14 days) for both doses in the electronic subject diary. Subjects will be instructed on how to measure (using the ruler supplied) and record erythema and induration.

- **Injection-Site Pain/Tenderness**

  Injection-site pain (eg, stinging, burning) is an unpleasant sensory and emotional experience associated with actual or potential tissue damage and occurring at the immunization site (with or without involvement of surrounding tissue). Injection-site tenderness is a painful sensation localized at the injection site upon palpation and/or movement of the limb. Due to subjective nature of the reaction, the severity assessment of pain/tenderness is self-reported (if a subject is unable to provide self-report, other reporters include parent/care giver or health care provider).[9]

- **Injection-Site Erythema**

  Injection-site erythema is a redness of the skin caused by dilatation and congestion of the capillaries localized at the injection-site. It can best be described by looking and measuring.

- **Injection-Site Swelling/Induration**

  Injection-site swelling is a visible enlargement of an injected limb. It may be either soft (typically) or firm (less typical). Injection-site induration is a palpable thickening, firmness, or hardening of soft tissue, usually has well-demarcated palpable borders, can be visible (raised or sunken compared to surrounding skin), is often 'woody' to touch and has a flat shape. As differentiation between swelling and induration may be difficult without health care professional's assessment, both symptoms have been combined to allow self-assessment by the subjects. Both swelling and induration can best be described by looking and measuring.

  Note: any other injection-site events not meeting the above case definitions should be reported separately as unsolicited AEs.[12,13]

Solicited Systemic AEs

Subjects will be instructed on how to note daily symptoms in the electronic subject diary for 14 days after vaccination (day of vaccination and the subsequent 14 days), for both doses, of the following systemic events: headache, fatigue, nausea, and myalgia.

Subjects will also be instructed on how to record daily temperature using a thermometer provided for home use. Subjects should record axillary temperature in the evening after vaccination (Day 1 and Day 181), and then daily for the next 14 days in the electronic subject diary for both doses. Temperature should be measured at the same time each day. If more than 1 measurement is made on any given day, the highest daily temperature will be used. Fever will be recorded by the investigator in the eCRF for temperatures equal to or higher than 38.0°C (100.4°F).

Fever is defined as endogenous elevation of body temperature ≥38°C, as recorded in at least one measurement.[15]

If a solicited local or systemic AE is not resolved within 14 days after each vaccination (on Day 15 after first vaccination and Day 195 after second vaccination), the follow-up will be captured in a paper subject diary. The subject will be instructed to record the date of last symptoms and maximum severity until resolution in the diary.

9.2.2. Vital Signs

The vital signs will be measured before vaccination and at the end of the 30-minute observation period after both doses of study vaccine on Day 1 and Day 181 (body temperature [axillary], pulse/heart rate, systolic and diastolic supine blood pressure).

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of seated rest in a quiet setting without distractions (eg, television, cell phones).

9.2.3. Physical Examination

A full physical examination will be performed at Day 1 (Visit 1) by the investigator or a designated medically trained clinical physician/associate. Height and body weight will be measured at Day 1 and used to calculate BMI.

A targeted physical examination may be performed at subsequent visits (except Day 360, which will be a telephone contact) based on the history of AEs or current symptoms and health status of the subject.

9.3. Immunogenicity

The immune response will be assessed in serum from blood samples taken at the following timepoints: Days 1 (pre-vaccination), 15, 181 (pre-vaccination) and 195.

The study will include the following immunogenicity evaluations according to the time points provided in the TIME AND EVENTS SCHEDULE.

9.3.1. Evaluations

Blood samples of approximately 10 mL will be collected for measurement of serum concentrations of ExPEC4V on the day of vaccination (pre-vaccination on Day 1 and prior to the second dose on Day 181), and 14 days after each vaccination (on Day 15 and on Day 195) to determine vaccine immunogenicity by the ELISA and OPK assay.

IgG antibody levels elicited by the vaccine against each of the 4 vaccine serotypes will be measured by ELISA and specific functional antibacterial antibodies will be measured by an OPK assay. The ELISA and OPK assay assessments will be performed by the sponsor and/or contract research organization.

Limits of assay variability will be defined within criteria described during assay qualification. Successful assay qualification will demonstrate designation of assays as fit for purpose. Operator training and adherence to defined Standard Operating Procedure and Good Clinical Practice (GCP) practices will be required to mitigate intra- and inter-operator assay variability. Procedural confounding factors that may influence assay results will be included in estimations of robustness during assay qualification. Factors to be evaluated will include: lot variability for

reagents, reagent stability, serum (antibody) freeze-thaw stability, antigen well-coating time (ELISA), and inter-operator variability. Confounding factors associated with serum sample integrity and clinical sample handling, including sample identity and stability will be addressed by Laboratory manual specifying sample handling, shipment and storage procedures.

Samples collected for analyses of ExPEC4V serum concentration may additionally be used to evaluate safety aspects that address concerns arising during or after the study period, for further characterization of immunogenicity. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.4. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples for immunogenicity assays are found in the Laboratory Manual that will be provided by the sponsor. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY INTERVENTION/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed Day 360 of the study. Subjects who prematurely discontinue the study for any reason before completion of the study duration (Day 360) will not be considered to have completed the study.

10.2. Discontinuation of Study Vaccine

A subject will not be automatically withdrawn from the study if he or she has to discontinue study vaccination before the second dose.

Subjects will be discontinued from study vaccine administration for the reasons listed below. These subjects must not receive any additional dose of study vaccine but should continue other study procedures, eg, safety follow-up:

- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- Any SAE considered related to the vaccine
- Any related AE, worsening of health status or intercurrent illness that, in the opinion of the investigator, requires study vaccine discontinuation

- The investigator believes that for safety reasons or tolerability reasons (eg, AEs) it is in the best interest of the subject to discontinue study vaccine
- The subject becomes pregnant
- The randomization code is broken by the investigator or the study-site personnel

10.3. Contraindications to Vaccination

The following events constitute a contraindication to vaccination on Days 1 and 181:

- Acute illness or acute infection at the time of vaccination (this does not include minor illnesses such as mild diarrhea or mild upper respiratory tract infection)
- Fever (temperature ≥38.0°C [100.4°F]) at the time of vaccination

If any of these events occur before the first vaccination on Day 1, but the subject fulfills all other inclusion and exclusion criteria (Section 4, Subject Population), the subject might be re-consented, re-screened, enrolled, and vaccinated after the event(s) has resolved (provided the enrollment will be ongoing). Similarly, if any of these events occur before the second vaccination on Day 181, while enrolled in the study, the subject may be re-checked and vaccinated within 1 week if the event(s) has resolved.

10.4. Withdrawal From the Study

Each subject has the right to withdraw from the study at any time for any reason without affecting the right to treatment by the investigator. Although the subject is not obliged to give reason(s) for withdrawing prematurely, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the subject's rights.

A subject will be automatically withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Noncompliance defined as failed to take both doses of the study vaccine
- Repeated failure to comply with protocol requirements
- Decision by the sponsor to stop or cancel the study
- Decision by the investigator to withdraw subjects
- Decision by local regulatory authorities and Institutional Review Board/Independent Ethics Committee (IRB/IEC) to stop or cancel the study

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal (if provided) is to be documented in the eCRF and in the source document. Study vaccine assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will be replaced only if they were not yet randomized. If a subject withdraws from the study before the end of the study, assessments of early withdrawal should be obtained (See Section 9.1.8, Early Withdrawal – Early Exit Visit). If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Subjects who wish to withdraw consent from participation in the study will be offered a single Early exit visit for safety follow-up (prior to formal withdrawal of consent). They have the right to refuse.

10.5. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the safety and immunogenicity data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

For all subjects, demographic characteristics (eg, age, BMI, race, and sex), and other baseline characteristics (eg, height, weight, physical examination findings, medical history including vaccination history) will be tabulated and summarized with descriptive statistics.

11.2. Analysis Sets

Vaccination assignment will follow the as-treated principle.

11.2.1. Full Analysis Set

The full analysis set (FAS) will include all randomized subjects with at least 1 vaccine administration documented.

11.2.2. Per-Protocol Immunogenicity Population

The per-protocol immunogenicity (PPI) population will include all randomized and vaccinated subjects for whom immunogenicity data are available excluding the subject with major protocol deviations expecting to impact the immunogenicity outcomes.

In addition, the following samples will not be included in the PPI population: If subjects miss the second dose, but continue the planned visit schedule, samples taken after the planned but missed dose will not be taken into account.

11.3. Sample Size Determination

This is a descriptive study and no formal hypothesis is planned. The study will enroll approximately 100 subjects with 1 arm of 75 subjects with ExPEC4V CTM; and 1 arm of 25 subjects with placebo. While mild to moderate vaccine reactions (local site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated. With 75 subjects targeted in the ExPEC4V CTM group, the observation of 0 such reactions would be associated with a 95% confidence that the true rate is less than 3.9%.

With 75 subjects in the ExPEC4V CTM group, AEs with a true incidence of 2.5% will likely be observed in this study, ie, the probability of observing at least 1 AE is 85%.

Table 2 shows the probabilities of observing at least 1 AE in a group of N subjects.

Table 2: Probabilities of Observing At Least One Adverse Event

True Probability of AE	Placebo	ExPEC4V Group
	N=25	N=75
0.1%	2.5%	7.2%
0.5%	11.8%	31.3%
1.0%	22.2%	52.9%
2.5%	46.9%	85.0%
5.0%	72.3%	97.9%

11.4. Safety Analyses

No formal statistical testing of safety data is planned. The safety analysis will include the descriptive summary (including 95% confidence intervals) of solicited local AEs, solicited systemic AEs, unsolicited AEs, and SAEs. The overall frequencies per study vaccine group as well as frequencies per severity and duration will be calculated for solicited (local and systemic) and unsolicited AEs.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by study vaccine group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue study early due to an AE, or who experience an SAE.

Vital Signs

Descriptive statistics of body temperature, pulse/heart rate, and blood pressure (systolic and diastolic [supine]) values and changes from baseline will be summarized at Day 1 and Day 181 pre- and post-vaccination.

Physical Examination

Abnormalities detected during physical examination at Day 1 will be summarized. Body weight and BMI results will be tabulated and summarized descriptively at Day 1. BMI will be calculated using the recording of height at Day 1.

11.5. Immunogenicity Analyses

For serum antibodies to O-antigen serotypes as measured by ELISA and OPK assay; or to EPA as measured by ELISA only, the following measures of immunogenicity will be evaluated and tabulated by study vaccine group (ExPEC4V CTM and placebo, as applicable):

- GMT on Day 1 (pre-vaccination), Day 15, Day 181 (pre-second vaccination) and Day 195 (14 days after the second dose).
- Proportion of subjects with a ≥2-fold and ≥4-fold increase in serum antibody titers (Day 15 compared to Day 1 and Day 195 compared to Day 181).
- GMR: fold change from baseline, calculated from the Day 15/Day 1 values and fold change from pre-second dose, calculated from Day 195/Day 181 values.

The analyses will be descriptive in manner and there will be no formal statistical comparisons. Graphical representations of immunological parameters will be made as applicable.

11.6. Planned Analyses

The primary analysis will be performed when all subjects have completed the Day 30 visit or discontinued earlier, upon resolution of relevant queries and after database lock. The primary analysis will include all available safety/reactogenicity data and immunogenicity data through Day 15. Sponsor personnel involved in the analysis of the data will be unblinded at the time of this primary analysis. The primary analysis data will be used by the sponsor for planning of future studies. At the time of the primary analysis, the subjects and investigator(s) or site staff will remain blinded to individual subjects' vaccine assignment.

The final analysis will be performed for safety/reactogenicity and immunogenicity, when all subjects have completed the Day 360 visit at the end of the study or discontinued earlier.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Solicited Adverse Events

Solicited (local and systemic) AEs are predefined local and systemic events for which the subject is specifically questioned and which are noted by subjects in their diary (see Section 9.2.1, Adverse Events).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the subject is specifically not questioned.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the study vaccine. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs, whether serious or non-serious, related to the study procedures or non-investigational (concomitant) Janssen products starting with the signing of the ICF; and all other AEs, whether serious or non-serious, starting with the administration of first dose of the study vaccine on the Adverse Event eCRF page (refer to Section 12.3.1, All Adverse Events, for time of last AE recording). Clinically relevant medical events, occurring between signing of ICF and time of first vaccination, are collected on the medical history eCRF page as pre-existing conditions.

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study vaccine and the event (eg, death from anaphylaxis), the event must be reported as a suspected unexpected serious adverse reaction (SUSAR).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ExPEC4V, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.[2]

Adverse Event Associated With the Use of the Vaccine

An adverse event is considered associated with the use of the vaccine if the attribution is related by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Every effort should be made by the investigator to explain any AE and assess its potential causal relationship, i.e. to administration of the study vaccine or to alternative causes (e.g. natural history of the underlying diseases, concomitant therapy). This applies to all AEs, whether serious or non-serious.

The investigator will use the following definitions to assess the causal relationship of an AE to study vaccine:

Related:

There is a suspicion that a relationship exists between study vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the study vaccine contributed to the AE.

Not Related

There is no suspicion of a relationship between study vaccine and the AE; there are other more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.

Note: By definition, all solicited local AEs occurring at the vaccination site will be considered related to the study vaccine administration (injection-site reactions); relatedness of solicited systemic AEs should be determined by the investigator.

12.1.3. Severity Criteria

The severity of solicited AEs will be graded in the diary by the subject based on the severity assessment criteria provided in the diary and then verified by the investigator using the scoring system shown in Table 3 and Table 4 as follows (Note: severity of the measured events - erythema, and induration/swelling – will be derived from the diameter):

Table 3: Severity Assessment: Solicited Local Events

Grade	Definition
0	No pain/tenderness; Diameter of erythema, swelling/induration <25mm.
1	Aware of symptoms but easily tolerated; Does not interfere with activity; Discomfort only to touch; Diameter of erythema, swelling/induration ≥25 mm and <50 mm.
2	Notable symptoms; Requires modification in activity or use of medications; Discomfort with movement; Diameter of erythema, swelling/induration ≥50 mm and <100 mm.
3	Incapacitating symptoms; Use of narcotic pain reliever; Inability to do work, school, or usual activities; Diameter of erythema, swelling/induration ≥100 mm.
4*	Emergency room (ER) visit or hospitalization; Pain/tenderness causing inability to perform basic self-care function; For erythema, swelling/induration: necrosis or exfoliative dermatitis.
* Note that AE leading to hospitalization or life-threatening experiences should be reported as SAE, see Section 12.3.2	

Table 4: Severity Assessment: Solicited Systemic Events

Grade	Definition
0	Absent
1	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities.
2	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities.
3	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever.
4*	Emergency room (ER) visit or hospitalization; Inability to perform basic self-care functions.
* Note that AE leading to hospitalization or life-threatening experiences should be reported as SAE, see Section 12.3.2	

All AEs data will be coded for severity using the grading tables in Attachment 1 (Toxicity Tables). For AEs not identified in these grading tables, the following guidelines will be used:

Mild (Grade 1): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate (Grade 2): Sufficient discomfort is present to cause interference with normal activity.

Severe (Grade 3): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Potentially Life-threatening (Grade 4): Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability.

12.2. Special Reporting Situations

Safety events of interest on a sponsor study vaccine that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study vaccine
- Suspected abuse/misuse of a sponsor study vaccine
- Accidental or occupational exposure to a sponsor study vaccine
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study vaccine, eg, name confusion)
- Exposure to a sponsor study vaccine from breastfeeding

Special reporting situations should be recorded in the eCRF accordingly. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

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

All unsolicited AEs and special reporting situations, whether serious or non-serious, will be reported from the time of vaccination until 29 days after both doses of study vaccine (Day 1 to Day 30 and Day 181 to Day 210). Solicited (local and systemic) AEs will be reported from the time of vaccination until 14 days after both doses of study vaccine (ExPEC4V and placebo) (day of vaccination and the subsequent 14 days). Serious adverse events (SAEs) must be reported to the sponsor during the entire study from the time of vaccination using the SAE Form until the

end of the study. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

The investigator will monitor and analyze study data including all AE data as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study vaccine. AEs will be deemed either related to study vaccine or not related to study vaccine, according to Section 12.1.2, Attribution Definitions. To ensure that all AEs are captured in a timely manner, eCRFs will be entered in real-time, and subjected to review to identify AEs that require expedited reporting as SAEs, invoke vaccination pausing rules or are other serious and unexpected events.

All AEs, regardless of seriousness, severity, or presumed relationship to study vaccine, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study vaccine or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study vaccine, is considered an SAE and must be reported.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any female subject who becomes pregnant during the study must stop further vaccination and continue participation in the study for safety follow-up.

Pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY VACCINE INFORMATION

14.1. Physical Description of Study Vaccine(s)

ExPEC4V

The ExPEC4V supplied for this study is a clear, slightly yellow to colorless solution for IM injection, formulated based on PS content. The administration dose consists of 0.5 mL of ExPEC4V. Each dose contains 4:4:4:8 µg of each PS O-antigen covalently linked to the protein carrier EPA, a genetically detoxified protein from *P. aeruginosa*. The amount of carrier protein depends on the degree of glycosylation which can be expressed by the PS-to-protein ratio, estimated to be between 0.1-0.5 depending on the O-antigen serotypes.

It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.[2]

Placebo

A diluent solution, supplied by the sponsor, will be used as a placebo. The diluent solution will contain Tris buffered solution of pH 7.4, comprising Tris (25 mM), NaCl (137 mM) and KCl (2.7 mM).

14.2. Packaging and Labeling

All study vaccine will be manufactured and packaged in in accordance with Current Good Manufacturing Practice. All study vaccines will be packaged and labeled under the responsibility of the sponsor. Study vaccine labels will contain information to meet the applicable regulatory requirements.

No study vaccine can be repacked or relabeled without prior approval from the sponsor.

Study vaccine labels will contain information to meet the applicable regulatory requirements.

Further details for study vaccine packaging and labeling can be found in the Study Site Investigational Product Manual.

14.3. Preparation, Handling, and Storage

ExPEC4V and placebo must be stored between +2 to +8°C (+35.6 to +46.4°F).

All study vaccine must be stored in a secured location with no access for unauthorized personnel. In the event that study vaccine is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected study vaccine can be used or will be replaced. The affected study vaccine must be quarantined and not used until further instruction from the sponsor is received.

The study vaccine will be prepared by the unblinded site pharmacist and administered by a blinded vaccine administrator.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study vaccine preparation, handling, and storage.

14.4. Vaccine Accountability

The investigator is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the subject must be documented on the study vaccine accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study vaccine containers.

The subjects, clinical staff, investigators, and sponsor personnel will be blinded to study vaccine group allocation, except for the designated pharmacist or qualified staff member with primary responsibility for study vaccine preparation.

Study vaccine must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study vaccine must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study vaccine will be documented on the vaccine return form. When the study site is an authorized destruction unit and study vaccine supplies are destroyed on-site, this must also be documented on the vaccine return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for study vaccine accountability purposes.

Study vaccine should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study vaccine will be supplied only to subjects participating in the study. Returned study vaccine must not be dispensed again, even to the same subject. Study vaccine may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study vaccine from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator’s Brochure
- Study Site Investigational Product Manual
- Laboratory manual
- Electronic Data Capture (eDC) Manual/ eCRF completion guidelines and randomization instructions
- IWRS Manual
- Sample ICF
- Subject Diaries
- Rulers, thermometers
- Subject wallet cards

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is the total blood volume to be collected from each subject will not exceed the US Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), and US Food and Drug Administration (FDA) guidelines of 550 mL in any 8-week period.[4,5]

Risks Related to Vaccines

Subjects may exhibit general signs and symptoms associated with administration of a vaccine, or vaccination with placebo, including fever, rash, aches and pains, nausea, headache, and fatigue. These side effects will be monitored, but are generally short-term and do not require treatment.

Subjects may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, hives or even difficulty breathing. Severe reactions are rare. Medications must be available in the clinic to treat serious allergic reactions.

Syncope (fainting) can occur in association with administration of injectable vaccines. Syncope can be accompanied by falls. Procedures should be in place to avoid falling injury. If syncope develops, participants should be observed until the symptoms resolve.

The effect of this vaccine on a fetus or nursing baby is unknown, so female subjects of childbearing potential will be required to agree to use birth control for sexual intercourse beginning prior to vaccination in the study and through 3 months after vaccination. Women who are pregnant or nursing will not be recruited into the study. Women who become pregnant during the study should remain in the study for safety follow-up.

Risks from Blood Draws

Blood drawing may cause pain, red small spots (petechiae), bruising, and, rarely, infection at the site where the blood is taken.

Potential Benefits

Although study subjects may benefit from clinical testing and physical examination, they may receive no direct benefit from participation. Others may benefit from knowledge gained in this study that may aid in the development of a vaccine for the prevention of IED.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects

- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study vaccine
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel

without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ExPEC4V, to understand IED, and to develop tests/assays related to ExPEC4V and IED. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.5, Withdrawal From the Use of Samples in Future Research.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study vaccine to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed

informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; vaccine receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or another equivalent document).

The subject diary will be considered a source document. Information from the subject diary provided to subjects to record symptoms of solicited local and systemic AEs for 15 days post-vaccination (day of vaccination and the subsequent 14 days), will be reviewed by the investigator or designee.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Electronic case report forms (eCRF) are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).

- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor or designee will use a combination of monitoring techniques (remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit (Day 360) for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the clinical trial agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator

- Discontinuation of further study vaccine development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding ExPEC4V or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ExPEC4V, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory and other analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee Of Medical Journal Editors (ICMJE) Recommendations for the conduct, reporting, editing and publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Toxicity Tables

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

A: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to Touch	Discomfort with Movement	Significant discomfort at rest	ER visit or Hospitalization
Erythema/redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever** (°C) Fever** (°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

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

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Systemic Illness	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study vaccine, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Patricia Ibarra de Palacios

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

SIGNATURES

Signed by	Date	Justification
Patricia Ibarra de Palacios	19Dec2017, 13:15:29 PM, UTC	Document Approval