Janssen Research & Development *

Clinical Protocol

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

E.ngage

Protocol VAC52416BAC3002; Phase 3

Version: Amendment 1

VAC52416 (JNJ-78901563) ExPEC9V

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency Identifier Number(s)

Registry	**ID**
EU TRIAL NUMBER	2023-504168-40-00

Status:	Approved
Document Date:	22 September 2023
Prepared by:	Janssen Vaccines & Prevention B.V.
EDMS Number:	EDMS-RIM-914860; 3.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Country/Territory Affected**	**Date**
Amendment 1	All	22 September 2023
Original Protocol	All	22 February 2023

Amendment 1 (22 September 2023)

Overall Rationale for the Amendment: The main purpose of this amendment is to add an Independent Data Monitoring Committee (IDMC) and mandate the collection of medically-attended adverse events (MAAEs) throughout the study.

The changes made to the clinical protocol VAC52416BAC3002 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	**Description of Change**	**Brief Rationale**
Title page 1.1 Synopsis	"EudraCT" was corrected to "EU TRIAL number".	Correction.
1.1 Synopsis 1.3 Schedule of Activities (SoA) 2.3.3 Benefit-risk Assessment of Study Participation 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 6.7 Treatment of Overdose 6.8 Concomitant Therapy 7.1 Discontinuation of Study Vaccination 8.2 Safety Assessments 8.3 Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, and Other Safety Reporting 9.4.4 Safety Analyses 10.2.10 Source Documents 10.3 Appendix 3: Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The assessment of MAAEs was added.	Added based on Health Authority request.
1.1 Synopsis 2.3.3 Benefit-risk Assessment of Study Participation 4.1 Overall Design 9.6 Independent Data Monitoring Committee 10.2.6 Committees Structure	Description of the details and type of data to be reviewed by the Independent Data Monitoring Committee (IDMC) was added.	Added based on Health Authority request.

Section number and Name	Description of Change	Brief Rationale
2.3 Benefit-risk Assessment 6.8 Concomitant Therapy	Updated the paragraphs on allowed vaccines.	For consistency in the ExPEC programs.
5.4 Screen Failures	The sentences "This study will use IWRS. The investigator will generate screening and enrollment logs directly from IWRS." were added.	Per Health Authority request.
10.2.10 Source Documents	"Respiratory rate" was added to the list of data to be recorded directly into the eCRF.	Correction, to align with overall vital signs assessments.
10.5 Appendix 5: Toxicity Grading Scale	Toxicity Grading Scale for Platelets Decreased were updated.	Clarification.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Registry	**ID**
EU TRIAL NUMBER	2023-504168-40-00

DESCRIPTION OF COMPOUND

ExPEC9V (primary compound number: VAC52416) is a 9-valent vaccine candidate in development for active immunization for the prevention of invasive extraintestinal pathogenic *Escherichia coli* (ExPEC) disease (IED) in adults 60 years of age and older. ExPEC9V consists of the O-antigen polysaccharides (PSs) of the ExPEC serotypes O1A, O2, O4, O6A, O15, O16, O18A, O25B, and O75 separately bioconjugated to the carrier protein, a genetically detoxified form of exotoxin A derived from *Pseudomonas aeruginosa* (EPA).

STUDY RATIONALE

ExPEC9V, which is currently in Phase 3 development for prevention of IED, is targeting the population aged ≥60 years in which seasonal influenza vaccination is also frequently recommended in different regions. To be able to deploy ExPEC9V as medically appropriate, data needs to be accrued that would allow concurrent administration of ExPEC9V and other vaccination interventions (such as influenza vaccination) that regularly target the population of interest. The current study will examine the immunogenicity and safety of ExPEC9V co-administered with a high-dose (HD) quadrivalent seasonal influenza vaccine (co-administration [CoAd] group) compared to administration of each vaccine separately (Control group). The aim of the study is to provide an indication of whether these vaccines can be administered concomitantly.

BENEFIT-RISK ASSESSMENT

Based on the available data and proposed safety measures, the overall benefit-risk assessment for this clinical study is considered acceptable.

All participants will receive vaccination with a seasonal influenza vaccine, which may provide protection against the influenza A subtype viruses and type B viruses contained in the vaccine during the season.

Safety measures are included in this protocol to minimize the potential risk to participants.

- Only participants who meet all inclusion criteria and none of the exclusion criteria will be allowed to participate in this study. The eligibility criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study.
  - In general, safety and tolerability assessments will be performed at scheduled visits during the study, as described in the Schedule of Activities (SoA).
  - After each vaccination, participants will closely be observed by study staff for at least 30 minutes.
  - Participants will use an eDiary to document solicited signs and symptoms. The investigator or designee will document unsolicited AEs. SAEs and MAAEs will be collected until 6 months after the last vaccination.

- All AEs, MAAEs, and SAEs will be followed by the investigator until clinical resolution or until a clinically stable condition is reached, or until the participant has been deemed lost to follow-up. An early exit visit will be conducted for those participants who withdraw from the study before Day 210, but who do not withdraw consent. Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent).
- Safety issues that arise from this study will be reviewed by an Independent Data Monitoring Committee (IDMC) on an ad hoc basis, including all related SAEs and all fatal cases.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To demonstrate the non-inferiority of the humoral immune response to the 4 influenza vaccine strains after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of a HD quadrivalent seasonal influenza vaccine administered alone.	• Antibody hemagglutination inhibition (HI) titers as measured by HI assay against each of the 4 influenza vaccine strains, 29 days after the administration of a HD quadrivalent seasonal influenza vaccine.
• To demonstrate the non-inferiority of the humoral immune response against the vaccine O-serotype antigens after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of ExPEC9V administered alone.	• Antibody titers to vaccine O-serotype antigens, as determined by multiplex ECL-based immunoassay 29 days after administration of ExPEC9V.
Secondary	
• To compare seroconversion rates against the 4 influenza vaccine strains after the concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of a HD quadrivalent seasonal influenza vaccine alone.	• Seroconversion is defined for each of the 4 influenza vaccine strains at 29 days after the administration of a HD quadrivalent seasonal influenza vaccine: – HI titer ≥1:40 in participants with a prevaccination HI titer of <1:10, or – a ≥4-fold HI titer increase in participants with a prevaccination HI titer of ≥1:10.
• To compare seroprotection rates against the 4 influenza vaccine strains after the concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of a HD quadrivalent seasonal influenza vaccine alone.	• Seroprotection is defined for each of the 4 influenza vaccine strains as HI titer ≥1:40 at 29 days after the administration of a HD quadrivalent seasonal influenza vaccine.

Objectives	Endpoints
• To assess the safety and reactogenicity of ExPEC9V when administered separately or concomitantly with a HD quadrivalent seasonal influenza vaccine	• Solicited local (injection site) and systemic AEs for 14 days post each vaccination. • Unsolicited AEs for 29 days post each vaccination. • MAAEs collected from administration of the first vaccination until 6 months post last vaccination. • SAEs collected from the administration of the first vaccination until 6 months post last vaccination.
• To evaluate the immunogenicity of ExPEC9V when administered separately or concomitantly with a HD quadrivalent seasonal influenza vaccine.	• Antibody titers to vaccine O-serotype antigens and EPA as determined by multiplex ECL-based immunoassay on Days 1, 30, and 59.
• To further evaluate the immunogenicity of ExPEC9V when administered separately or concomitantly with a HD quadrivalent seasonal influenza vaccine.	• Opsonophagocytic antibody titers to vaccine O-serotype antigens as determined by MOPA 29 days after administration of ExPEC9V.
• To evaluate the immunogenicity of ExPEC9V between participants with a history of UTI to those without a UTI history.	• Antibody titers to vaccine O-serotype antigens, in participants reporting a history of UTI at enrollment and participants without a UTI history at enrollment, as determined by multiplex ECL-based immunoassay 29 days after administration of ExPEC9V.
• To further evaluate the immunogenicity of ExPEC9V between participants with a history of UTI to those without a UTI history.	• Opsonophagocytic antibody titers to vaccine O-serotype antigens, in participants reporting a history of UTI at enrollment and participants without a UTI history at enrollment, as determined by MOPA 29 days after administration of ExPEC9V.

HYPOTHESES

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

AND

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

the following hypotheses will be tested:

Null Hypothesis:

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

OR

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

Alternative Hypothesis:

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

AND

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

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, parallel group, multicenter Phase 3 study in adult participants aged 65 years and older. A target of approximately 932 participants will be randomized in parallel in this study in a 1:1 ratio to 1 of 2 groups. Group 1 (CoAd group) will receive ExPEC9V on Day 1 administered at the same time as HD quadrivalent seasonal influenza vaccine, and placebo on Day 30. Group 2 (Control group) will receive placebo on Day 1 administered at the same time as HD quadrivalent seasonal influenza vaccine, and ExPEC9V on Day 30. All study vaccinations will be given by the IM route.

Group	N	Day 1	Day 30
1 (CoAd group)	~466	ExPEC9V + HD quadrivalent seasonal influenza vaccine	Placebo
2 (Control group)	~466	Placebo + HD quadrivalent seasonal influenza vaccine	ExPEC9V

N = number of participants

After each vaccination, participants will be observed for at least 30 minutes for presence of any acute reactions and solicited events. Any unsolicited AEs, solicited local (injection site) or systemic AEs, and vital signs (systolic and diastolic blood pressure [sitting], heart rate, respiratory rate, and body temperature) will be documented by study-site personnel following this observation period. In addition, participants will record solicited signs and symptoms in an eDiary beginning on the evening of the vaccination day and on a daily basis for 14 days post-vaccination.

Unsolicited AEs will be reported for 29 days post-vaccination. SAEs, MAAEs, and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure.

Blood will be collected from all participants to assess humoral immune responses on each vaccination day (prevaccination) and at 29 days after the second study vaccination.

The end of the study is defined as the last participant's last visit.

NUMBER OF PARTICIPANTS

Approximately 932 participants will be randomized in parallel in this study in a 1:1 ratio to 1 of 2 groups.

VACCINATION GROUPS AND DURATION

ExPEC9V (VAC52416): *Escherichia coli* (*E. coli*) bioconjugate vaccine in phosphate buffered solution containing O-antigen PSs of ExPEC serotypes O1A, O2, O4, O6A, O15, O16, O18A, O25B, and O75 separately bioconjugated to the EPA carrier protein. Participants will receive a single 0.5 mL IM (deltoid) injection of ExPEC9V on Day 1 (CoAd group) or Day 30 (Control group). ExPEC9V will be supplied in 2-R vials at a concentration of 176 µg PS/mL. The PS content of the dose to be tested in the present study is 88 µg/dose.

HD Quadrivalent Seasonal Influenza Vaccine: The influenza vaccine that will be used in this study is a suspension for IM injection supplied in a 0.7-mL single-dose prefilled syringe. Each dose of HD quadrivalent seasonal influenza vaccine contains 240 µg of hemagglutinin (HA): 60 µg of each of 4 influenza strains (2 influenza A strains and 2 influenza B strains), matched for the 2023-2024 season in the Northern Hemisphere.

Placebo: Sodium chloride 0.9% w/v. A single 0.5 mL IM (deltoid) injection of placebo will be administered on Day 1 (Control group) or Day 30 (CoAd group). The placebo for this study will be supplied by the sponsor as a commercially available injectable solution of 9 mg/mL Sodium Chloride (0.9% w/v).

On Day 1, each participant will receive 2 IM injections, 1 in each arm; on Day 30, each participant will receive 1 IM injection. The right arm should be used for seasonal influenza vaccination on Day 1; the left arm should be used for ExPEC9V or placebo on Days 1 and 30.

The study duration will be approximately 7 months per participant. The study comprises screening to be performed within 8 days of Day 1, vaccination for each participant on Days 1 and 30 with a 29-day follow-up period after each vaccination, and collection of SAEs and MAAEs until 6 months after the last study vaccination.

IMMUNOGENICITY EVALUATIONS

Venous blood samples of approximately 30 mL will be collected for the determination of humoral immune responses.

For assessment of immunogenicity, serum IgG antibody levels elicited by ExPEC9V against each of the 9 vaccine O-serotypes and the carrier protein EPA will be measured by a validated multiplex ECL-based immunoassay. Additionally, functional antibodies will be evaluated by a validated MOPA.

Antibody titers against influenza virus strains recommended by the WHO for use in 2023-2024 in the Northern Hemisphere season will be measured using validated HI assays.

SAFETY EVALUATIONS

Safety assessments will include the monitoring of AEs, MAAEs, physical examinations, and vital signs.

Solicited AEs, collected through a participant eDiary, will be recorded for each vaccination from the time of vaccination until 14 days post-vaccination. Unsolicited AEs and special reporting situations will be collected for each vaccination from the time of vaccination until 29 days post-vaccination. SAEs, MAAEs, and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) are to be reported from the moment of first study vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up. All AEs will be followed until resolution or until clinically stable.

AEs, MAAEs, and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal.

Safety issues that arise from this study will be reviewed by an IDMC on an ad hoc basis, including all related SAEs and all fatal cases.

STATISTICAL METHODS

Sample Size Determination

Sample size calculations are performed under the following assumptions:

- No effect of co-administration of ExPEC9V and seasonal influenza vaccine on the immune response against influenza as measured by HI antibody titers against the 4 influenza vaccine strains at 29 days after the administration of influenza vaccine.
- A standard deviation of 0.5 at the $\log_{10}$ scale for HI antibody titers against the 4 influenza vaccine strains at 29 days after the administration of influenza vaccine (with or without ExPEC9V).
- No effect of co-administration of ExPEC9V and seasonal influenza vaccine on the immune response against the O-serotype antigens as measured by antibody titers against the 9 O-serotype antigens at 29 days after the administration of ExPEC9V.
- A standard deviation of 0.6 at the $\log_{10}$ scale for ExPEC9V antibody titers at 29 days after the administration of ExPEC9V (with or without seasonal influenza vaccine).
- A non-inferiority margin of 1.5.
- 2-sided α of 5%.

A total of 419 evaluable participants per group are needed to have 99.91% power to show non-inferiority in HI antibody titers for 1 influenza vaccine strain and to have 98.88% power to show non-inferiority in antibody titers against 1 O-serotype antigen. With this sample size, the overall power to show non-inferiority in HI antibody titers against each of the 4 influenza vaccine strains at 29 days after the administration of seasonal influenza vaccine as well as non-inferiority in antibody titers against each of the 9 O-serotype antigens at 29 days after the administration of ExPEC9V is at least 90% (see table below).

	1 comparison	**All comparisons**
Flu NI (SD=0.5)	99.91%	99.64% (4 comparisons)
ExPEC9V NI (SD=0.6)	98.88%	90.36% (9 comparisons)
Total		> 90% power

To account for 10% exclusions from the per protocol set (see below for definitions of analysis sets), drop-outs and missing samples, approximately 466 participants per group should be enrolled, resulting in a total sample size of approximately 932 participants.

Participant Analysis Sets

Vaccination assignment will follow the as-treated principle.

The Full Analysis (FA) Set will include all participants who received at least 1 study vaccination, regardless of the occurrence of protocol deviations and vaccine type (seasonal influenza, ExPEC9V, or placebo). All safety and participant information analyses will be based on the FA Set.

The Per-protocol Influenza Immunogenicity (PPII) Set will include all randomized participants who received the first study vaccination (ExPEC9V in combination with seasonal influenza vaccine for the CoAd group and seasonal influenza vaccine alone for the Control group), and for whom immunogenicity data are available for at least one of the influenza strains in the vaccine. Samples taken after a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPII analysis.

The Per-protocol ExPEC9V Immunogenicity (PPEI) Set will include all randomized participants who received ExPEC9V in combination with seasonal influenza vaccine for the CoAd group and ExPEC9V alone for the Control group and for whom O-antigen immunogenicity data are available. Samples taken after a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPEI analysis.

The list of major protocol deviations that would lead to elimination from the immunogenicity analysis will be specified in the SAP or major protocol violation criteria document, which will be finalized before database lock and unblinding.

The primary analysis set for analyses related to influenza immunogenicity is the PPII Set, the primary analysis set for analyses related to O-antigen immunogenicity is the PPEI Set. As a sensitivity analysis, key tables may also be based on the FA Set.

Immunogenicity Analyses

The primary immunogenicity objectives will be assessed by calculating:

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

For HI antibody titers against each of the 4 influenza vaccine strains and for O-serotype antibody titers against each of the 9 O-serotypes, an ANOVA model will be fitted with the respective titers as dependent variable and group (Control or CoAd), age category, and history of UTI (as stratified) as independent variables. Based on these ANOVA models, the CIs around the difference will be calculated and will be back-transformed (by exponentiation) to CIs around a GMT ratio ($GMT_{Control\ group}/GMT_{CoAd\ group}$) and compared to the non-inferiority limit of 1.5.

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

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

Seroconversion is defined for each of the 4 influenza vaccine strains at 29 days after the administration of a seasonal influenza vaccine as:

- HI titer ≥1:40 in participants with a prevaccination HI titer of <1:10, or
- a ≥4-fold HI titer increase in participants with a prevaccination HI titer of ≥1:10

Seroprotection is defined for each of the 4 influenza vaccine strains as HI titer ≥1:40 at 29 days after the administration of a seasonal influenza vaccine.

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

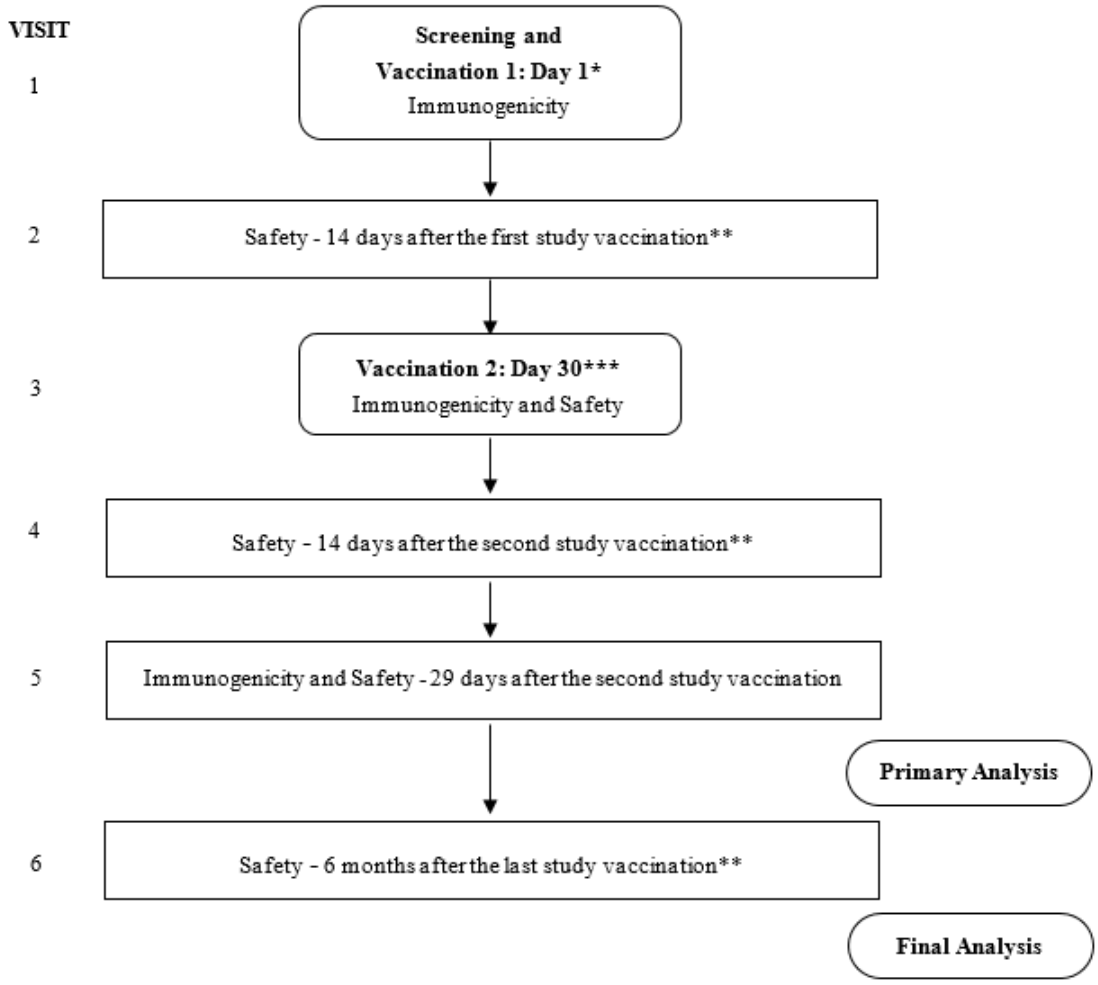
Additionally, HI antibody titers and O-serotype antibody titers will be summarized with descriptive statistics.

Safety Analyses

No formal statistical testing of safety data is planned. All safety data will be analyzed descriptively by group. All safety analyses will be based on the FA Set.

1.2. Schema

Figure 1: Schematic Overview of the Study



* Screening and vaccination may be split into 2 visits in consultation with the sponsor or its delegate, for example when a criterion for temporarily delaying study vaccine administration (see Section 5.5., Criteria for Temporarily Delaying Study Vaccine Administration) is met.
** By telephone.
*** In case any of the criteria for temporarily delaying study vaccine administration (see Section 5.5., Criteria for Temporarily Delaying Study Vaccine Administration) are met at Visit 3 (Day 30), the administration of the second study vaccination needs to be delayed (up to a maximum of 10 days on top of the allowed time window of Visit 3 [±7 days]). The immunogenicity and safety assessments of Visit 3 should still be performed on the actual Day 30 (±7 days).

1.3. Schedule of Activities (SoA)

Clinic Visit #	1 [a]	2 [b]☎	3 [a]	4 [b]☎	5 [a]	6 [b]☎	Exit [b,c]☎
Visit Timing	Vac 1	Vac 1 + 14 d	Vac 1 + 29 d	Vac 2 + 14 d	Vac 2 + 29 d	Vac 2 + 6 mo	
Visit Day	-8 to 1	15	30	44	59	210	
Visit Window		±2 d	±7 d	±7 d	±7 d	±42 d	
Visit Type	Screening and VACCINATION 1 [d]	Safety	VACCINATION 2	Safety	Immunogenicity and Safety	Safety	Early exit
Written informed consent [e]	❶						
Inclusion/exclusion criteria	❶						
Demographics	❶						
Medical history [f]/prestudy therapies [g]	❶						
Vital signs [h] incl. body temperature	❷		❷				
Physical examination	❶						
Height and weight	❶						
Randomization	❶						
Inclusion/exclusion criteria check [j]			❶				
Prevaccination symptoms [k]	❶		❶				
Humoral immunogenicity, mL	❶ 30		❶ 30		● 30		
Vaccination [k]	●		●				
30-minute post-vaccination observation [l]	●		●				
Solicited AE recording [m]	------ ❸ -----		------ ❸ -----				❹
Unsolicited AE recording [n]	---------- *continuous* ----------						❺
MAAE and SAE recording	---------- *continuous* ----------						●
Concomitant therapies [o]	---------- *continuous* ----------						●
Participant wallet card	---------- *continuous* ----------						
Issue participant eDiary [p,q]	●		●				
Participant eDiary review by site staff [q]		●	●	●	●		
Approximate daily blood draw, mL	30 [r]	–	30 [r]	–	30 [r]		–
Approximate cumulative blood draw, mL	30	30	60	60	90		–

Footnotes are provided on the next page

AE = adverse event; d = days; ICF = informed consent form; mo = months; MAAE = medically-attended adverse event; SAE = serious adverse event; vac = vaccination

☎ telephone contact or other means of communication; ❶ prevaccination; ❷ pre- and post-vaccination; ❸ solicited local (injection site) and systemic AEs will be collected via participant eDiary from vaccination until 14 days after each vaccination; ❹ if within 14 days of the previous vaccination; ❺ if within 29 days of the previous vaccination

Footnotes:

a. Visits that cannot be conducted in person at the study site may be conducted as home health visit after sponsor approval.
b. Safety visits and early exit visit will be by telephone.
c. An early exit visit will be conducted as soon as possible for those participants who are unable to continue participation in the study and withdraw from the study before Day 210, but who do not withdraw consent. Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent).
d. Screening and vaccination may be split into 2 visits in consultation with the sponsor or its delegate, for example when a criterion for temporarily delaying study vaccine administration (see Section 5.5. Criteria for Temporarily Delaying Study Vaccine Administration) is met. Every effort should be made for split visits to occur preferably within 3 to 5 days and no later than 10 days, and prevaccination vital signs should be repeated on the day of vaccination if this visit is split.
e. Signing of the ICF should be done before any study-related activity.
f. Information about planned surgeries and/or procedures should be reported. Medical history of all participants will be recorded in the eCRF. Participants will be specifically questioned regarding the medical history of UTI. This includes any uncomplicated, complicated, or recurrent UTIs that were diagnosed by a physician (or qualified healthcare provider) and that required antimicrobial therapy. The details will be collected in the eCRF. Note: a history of isolated male accessory gland infections will not be considered as a history of UTI.
g. Prestudy therapies administered up to 30 days before the first study vaccination must be recorded on Day 1.
h. Sitting systolic and diastolic blood pressure, heart rate, and respiratory rate after at least 5 minutes rest on Days 1 and 30. At non-vaccination visits, vital signs will be measured if deemed necessary by the investigator.
i. General physical examination; it is at the investigator's discretion how detailed the examination (which body systems are to be covered) is deemed needed. At any other visit, a targeted (abbreviated and symptom-directed) examination may be performed if deemed necessary by the investigator based on any clinically relevant issues, clinically relevant symptoms, and medical history.
j. Inclusion Criterion 2 and Exclusion Criteria 2, 4, 5, 6, 9, 10, 11 and 12.
k. Investigator must check for clinically significant acute illness at the time of vaccination, body temperature ≥38.0°C (≥100.4°F) within 24 hours prior to the planned time of vaccination, an illness which in the judgment of the investigator may interfere with reactogenicity or safety assessments, and whether the participant recently received a medically indicated vaccination. If any of these events occur at the scheduled time for the first vaccination, randomization at a later date within the screening period (allowed window up to 8 days) is permitted. If any of these events occur at the scheduled time for the second vaccination, the vaccination can be delayed up to 10 days on top of the allowed time window of Visit 3 (±7 days). The immunogenicity and safety assessments of Visit 3 should still be performed on the actual Day 30 (±7 days).
l. After each vaccination, participants will be observed for at least 30 minutes for presence of any acute reactions and solicited events. Any unsolicited AEs, solicited local (injection site) or systemic AEs, and vital signs (systolic and diastolic blood pressure [sitting], heart rate, respiratory rate, and body temperature) will be documented by study-site personnel following this observation period.
m. Includes the assessment of the severity of solicited AEs during the Visit 2 and Visit 4 phone calls.
n. Includes the assessment of the severity of unsolicited AEs and the occurrence of special reporting situations during all visits up to 29 days post-vaccination, including the Visit 2 and Visit 4 phone calls.

o. Concomitant therapies will be collected from the time of first study vaccination through 29 days after the last study vaccination when associated with an AE, and from ICF signature until 6 months after the last study vaccination when associated with an SAE. Concomitant therapies associated with solicited AEs will be collected by the participants in the participant eDiary from the time of study vaccination through 14 days after each vaccination.
p. Rulers and thermometers will be distributed at Visit 1 and at Visit 3, if applicable.
q. eDiary entries will be reviewed with the participant by a qualified and delegated study staff member (eg, investigator, sub-investigator, or study nurse). The delegated study staff member grades any signs or symptoms using the toxicity grading scale (Appendix 5: Toxicity Grading Scale) and will complete their assessment in the relevant sections of the eCRF. The eDiary review and grading of symptoms are done under the oversight of the investigator or a delegated physician.
r. Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request.

2. INTRODUCTION

ExPEC9V (primary compound number: VAC52416) is a 9-valent vaccine candidate in development for active immunization for the prevention of invasive extraintestinal pathogenic *Escherichia coli* (ExPEC) disease (IED) in adults 60 years of age and older. ExPEC9V consists of the O-antigen polysaccharides (PSs) of the ExPEC serotypes O1A, O2, O4, O6A, O15, O16, O18A, O25B, and O75 separately bioconjugated to the carrier protein, a genetically detoxified form of exotoxin A derived from *Pseudomonas aeruginosa* (EPA).

For the most comprehensive nonclinical and clinical information regarding VAC52416 (JNJ-78901563), refer to the latest version of the IB for VAC52416 (JNJ-78901563).

The term "study vaccination" throughout the protocol, refers to ExPEC9V, placebo, or the high-dose (HD) quadrivalent seasonal influenza vaccine as defined in Section 6.1., Study Vaccinations Administered.

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.

The non-inferiority criteria used in this study are based on guidance from regulatory authorities (for details, refer to Section 9.2., Sample Size Determination).

2.1. Study Rationale

ExPEC is a leading and increasing cause of bacteremia/bloodstream infections worldwide and comprises 17% to 37% of blood isolates (De Kraker 2013, Johnson 2003, Laupland 2014). In the US, the overall annual incidence of ExPEC bloodstream infections in adults ranges between 30 and 50/100,000 person-years (Laupland 2014, Williamson 2013). In Europe, the number of cases of ExPEC bacteremia annually increased by 8.1% between 2002 and 2008 (De Kraker 2013).

IED is defined as an acute illness consistent with systemic bacterial infection, which is microbiologically confirmed either by the isolation and identification of *E. coli* from blood or any other sterile body sites, or by the isolation and identification of *E. coli* from urine in a patient with urosepsis and no other identifiable source of infection. Although IED affects all ages, adults aged ≥60 years have an increased risk of developing IED, including bacteremia and sepsis. In a retrospective population-based study in the US from 1998 to 2007, the incidence of *E. coli* bloodstream infections was shown to increase markedly with age from 60 years onwards. The incidence rates in adults aged ≥60 years were estimated to be between 136 to 152/100,000 person-years; while by age stratum, incidence rates were estimated at 100/100,000 person-years in adults aged 60 to 79 years, and 300/100,000 person-years in adults aged ≥80 years. The urinary tract was found to be the most common primary source of infection (79.8%) (Al-Hasan 2009a, 2009b).

ExPEC9V, which is currently in Phase 3 development for prevention of IED, is targeting the population aged ≥60 years in which seasonal influenza vaccination is also frequently recommended in different regions. To be able to deploy ExPEC9V as medically appropriate, data needs to be accrued that would allow concurrent administration of ExPEC9V and other vaccination interventions (such as influenza vaccination) that regularly target the population of interest. The current study will examine the immunogenicity and safety of ExPEC9V co-administered with a

HD quadrivalent seasonal influenza vaccine (co-administration [CoAd] group) compared to administration of each vaccine separately (Control group). The aim is to provide an indication of whether these vaccines can be administered concomitantly.

The present study also aims to include participants (aged ≥65 years) with and without a previous history of UTI to allow a comparison of vaccine-elicited immunogenicity between the 2 populations (ie, with a previous UTI history versus without a previous UTI history). Participants with a previous UTI history, particularly if some of the UTIs were attributable to *E.coli* infection, have been observed to elaborate higher baseline immune responses targeting *E.coli* O-antigens, as shown in the VAC52416BAC1001 study Cohort 2 (see Section 2.2., Background). This observation needs to be further investigated through a comparison of immunogenicity elicited by the vaccine for the 2 aforementioned populations.

2.2. Background

Nonclinical Studies

In a nonclinical immunogenicity study in NZW rabbits (TV-TEC-179827), 3 IM injections with ExPEC9V, 10-valent extraintestinal pathogenic *Escherichia coli* vaccine (ExPEC10V), or saline control were administered 2 weeks apart. ExPEC9V and ExPEC10V were shown to be immunogenic in this study.

A 4-week intermittent repeat-dose toxicity and local tolerance study (TOX13465, GLP study), with ExPEC10V was conducted in NZW rabbits. ExPEC10V was administered via IM injection once every 2 weeks, with a total of 3 IM injections. ExPEC10V was well tolerated in this study. All vaccine-related effects noted were consistent with a normal immunologic response to the vaccine and were not considered to be adverse.

For further details on the nonclinical immunogenicity and toxicology studies with ExPEC9V and/or ExPEC10V, refer to the latest version of the ExPEC9V IB.

Clinical Studies

ExPEC9V is a vaccine candidate for active immunization for the prevention of invasive *Escherichia coli* disease (IED), in adults 60 years of age and older. ExPEC9V is being developed based on the sponsor's preceding clinical experience with ExPEC10V and ExPEC4V, an earlier vaccine candidate which comprised 4 O-antigen conjugates (O1A, O2, O6A, and O25B).

The ExPEC4V vaccine has been evaluated in 2 completed Phase 1 clinical studies (GVXN EC-4V and 63871860BAC1001), and 2 completed Phase 2 clinical studies (63871860BAC2001 and 63871860BAC2003). ExPEC4V was well tolerated in these studies and no vaccine-related safety signals were observed at doses up to 16 µg PS per serotype. In each study, the ExPEC4V vaccine was shown to be immunogenic against all vaccine serotypes, demonstrating a dose-dependent vaccine immune response and O-antigen specific IgG titer increases, as measured by an ELISA. Functional activity of the antibodies was demonstrated with an ExPEC4V-optimized OPA. Immunogenicity analysis from study 63871860BAC2001 has demonstrated durability of the immune response through 3 years after vaccination with ExPEC4V (Synoptic Clinical Study Report 63871860BAC2001).

ExPEC10V is currently being investigated in the ongoing study VAC52416BAC1001. VAC52416BAC1001 is a randomized, multicenter, first-in-human Phase 1/2a study to evaluate the safety, reactogenicity, and immunogenicity of 3 different doses of ExPEC10V (serotypes O1A, O2, O4, O6A, O8, O15, O16, O18A, O25B, and O75) and to select an optimal dose of ExPEC10V for further clinical development. This study includes 2 cohorts. In Cohort 1, 416 participants aged ≥60 to ≤85 years in stable health received study vaccination (ExPEC10V [low, medium, or high dose], ExPEC4V, or Prevnar 13®). The 3 dose levels of ExPEC10V were evaluated in approximately 100 participants per dose level. Cohort 1 also included reference groups who received ExPEC4V or Prevnar 13® (approximately 52 participants per group). Results from Cohort 1 indicated that total IgG titers increased significantly for all ExPEC10V doses. A 2-fold or greater increase in IgG titers, for all serotypes except O8 and O75, was observed for at least 82% of participants who received the high dose. MOPA results were generally consistent with ECL data: increased functional antibody titers were observed on Day 15 for all ExPEC10V serotypes and dose groups, with the exception of serotype O8. The MOPA data for serotype O8 were further investigated and a functional antibody response for this serotype could not be demonstrated in the qualified MOPA assay used. This prompted the sponsor to investigate a new formulation (ExPEC9V), excluding the O8 serotype, in study VAC52416BAC3001, discussed below.

Safety results from study VAC52416BAC1001 (including preliminary results for Cohort 2) showed that the most frequent local solicited AE was pain/tenderness and the most frequently reported systemic AEs were myalgia, headache, and fatigue. While several of the observed solicited AEs occurred early, a trend towards late onset of local solicited AEs was observed in the VAC52416BAC1001 participants. Injection site erythema and swelling were the most common late onset events (time to first onset >5 days after vaccination) in participants from the combined ExPEC10V groups in both Cohorts 1 and 2. A trend towards increased local reactogenicity with higher doses of ExPEC10V was observed in Cohort 1. The most frequent unsolicited AE assessed as related to the vaccine was injection site pruritus, reported by <3% of the participants from the combined ExPEC10V groups in both Cohorts 1 and 2.

The ongoing Phase 3 study VAC52416BAC3001 was the first study in which ExPEC9V was administered to humans. The study is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, interventional Phase 3 study to investigate the efficacy, safety, reactogenicity, and immunogenicity of ExPEC9V in approximately 18,556 medically stable adults aged ≥60 years with a history of UTI in the past 2 years. Removal of the O8 serotype is expected to result in a change of ExPEC9V O-serotype coverage from approximately 70% (ExPEC10V) to approximately 65% of ExPEC associated bloodstream infections in adults aged ≥60 years. In May 2022, an IDMC meeting was held to review safety information from the first 500 randomized participants who had completed the Day 30 visit (or discontinued earlier). Following this safety review, the IDMC recommended that the study could continue unmodified until the next scheduled meeting.

The present Phase 3 study VAC52416BAC3002 will investigate the immunogenicity, safety, and reactogenicity of the selected dose of ExPEC9V and HD quadrivalent seasonal influenza vaccine, with and without co-administration, in medically stable adults aged ≥65 years.

2.2.1. Seasonal Influenza Vaccine

The HD quadrivalent seasonal influenza vaccine that will be used in this study is indicated for active immunization for prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in adults aged 65 years and older. The influenza strains contained in the vaccine are matched for the 2023-2024 Northern Hemisphere season. HD quadrivalent seasonal influenza vaccine is widely used in the United Kingdom and US.

For further information regarding HD quadrivalent seasonal influenza vaccine refer to the applicable product information sheet.

2.3. Benefit-risk Assessment

2.3.1. Risks Related to Study Participation

The following potential risks for ExPEC9V will be monitored during the study and are specified in the protocol:

Risks Related to ExPEC9V

Based on 2 completed Phase 1 studies and 2 completed Phase 2 studies in the ExPEC4V development program, most solicited (local and systemic) AEs started on Days 1 to 3 post-vaccination. Headache and fatigue/tiredness were the most frequent solicited AEs, reported as early onset events, with a median time of onset of 2 and 3 days, respectively. 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.

Late onset solicited AEs were also observed in ExPEC10V development program. The median time to first onset of local solicited AEs was 2 to 2.5 days after vaccination for those in the ExPEC10V dose groups. The most frequent solicited AEs, pain/tenderness, fatigue, myalgia, and headache occurred mostly as early onset events. Injection site erythema and swelling occurred as late onset events (time to first onset >5 days after vaccination) in the majority of participants from the combined ExPEC10V groups. In the combined ExPEC10V groups, 8 (2.6%) participants experienced late onset AEs with Grade 3 severity. A trend towards increased local reactogenicity with higher doses of ExPEC10V was observed.

Risks Related to HD Quadrivalent Seasonal Influenza Vaccine

HD quadrivalent seasonal influenza vaccine is indicated to be used for individuals aged 65 years or above in the countries participating to this study. HD quadrivalent seasonal influenza vaccine will be administered in the study following the approved prescribing information(s).

In adults, the most common (≥10%) solicited local adverse reaction after HD quadrivalent seasonal influenza vaccine administration was pain (41.3% to 42.6%), the most common solicited systemic adverse reactions were myalgia (22.7% to 23.8%), headache (14.4% to 17.3%), and malaise (13.2% to 15.6%). Overall, adverse reactions were generally less frequent in participants 65 years of age and older than in participants 60 to 64 years of age.

For further details, refer to the HD quadrivalent seasonal influenza vaccine package insert.

General Risks Related to Vaccination

In general, IM injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration, swelling, arm discomfort, or bruising of the skin. Participants may exhibit general signs and symptoms associated with IM injection of a vaccine and/or placebo, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue. These side effects will be monitored, but are generally short-term and do not require treatment.

Syncope 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. Fear of injection might lead to fainting and fast breathing.

Participants may have an allergic reaction to vaccination. An allergic reaction may cause a rash, urticaria or even anaphylaxis. Severe reactions are rare. Participants with a history of severe allergic reaction, anaphylaxis, or other serious adverse reactions to vaccines or vaccine excipients (specifically the excipients of the study vaccine) will be excluded from the study.

Polyneuropathy events (eg, Guillain-Barré Syndrome) have been reported with some vaccines.

Pregnancy and Birth Control

The effect of ExPEC9V on a fetus or nursing baby is unknown. Participants may therefore only participate if they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and not intending to conceive by any methods. Participants who are surgically sterile are also eligible for the study. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Because the effect on sperm is unknown, participants must inform the study-site personnel if their partner becomes pregnant during the study. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required upon the consent provided by the partner.

Risks Related to Concomitant Vaccination

Concomitant vaccination might have an influence on both the safety profile and immunogenicity of ExPEC9V. Likewise, ExPEC9V might have an influence on both the safety profile and immunogenicity of any concomitant vaccination.

In order to avoid misinterpretation of adverse reactions and potential immune interference, vaccination with licensed live attenuated vaccines is prohibited within 28 days before or after the administration of the study vaccination. Vaccination with other licensed vaccines (not live) (eg, COVID-19, tetanus, hepatitis A, hepatitis B, rabies) is prohibited within 14 days before or after the administration of the study vaccine. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Vaccination with a vaccine authorized for emergency use (eg, EUA, CMA, or a similar program) is permitted when given at least 28 days before or after administration of the study vaccine.

Participants with Immunosuppression/Reduced Immune Response

Participants with abnormal function of the immune system will be excluded from the study. Limited evidence indicates that inactivated vaccines (or nonreplicating viral vaccines) generally have the same safety profile in immunocompromised patients as in immunocompetent individuals. However, the magnitude, breadth, and persistence of the immune response to vaccination may be reduced or absent in immunocompromised persons.

Risks from Blood Draws

Blood draws may cause pain, tenderness, bruising, bleeding, dizziness, vaso-vagal response, syncope, and, rarely, infection at the site where the blood is taken.

Unknown Risks

There may be other risks that are not known. If any significant new risks are identified, the investigators and participants will be informed.

2.3.2. Benefits of Study Participation

Participants may benefit from clinical testing and physical examination.

The clinical benefits of ExPEC9V have yet to be established.

Currently, there are no effective vaccines for the prevention of IED and no efficacy can be concluded from current data. The overall benefit and risk balance for individual participants thus cannot be ascertained. Participants must be informed that this vaccine has not yet been proven to be effective, and it should be assumed that it is not the case until clinical studies are conducted that demonstrate its effectiveness.

Vaccination with a seasonal influenza vaccine may provide protection against the influenza A subtype viruses and type B viruses contained in the vaccine during the season.

2.3.3. Benefit-risk Assessment of Study Participation

Based on the available data and proposed safety measures, the overall benefit-risk assessment for this clinical study is considered acceptable for the following reasons:

- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5., Study Population) will be allowed to participate in this study. The eligibility criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:
  - In general, safety and tolerability assessments will be performed at scheduled visits during the study, as described in the Schedule of Activities (SoA).
  - After each vaccination, participants will closely be observed by study staff for at least 30 minutes. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use an electronic diary (eDiary) to document solicited signs and symptoms. Details are provided in Section 8.2., Safety Assessments and Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting.

- The investigator or the designee will document unsolicited AEs, as indicated in Section 8.2., Safety Assessments, Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 3: Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.
- After the last vaccination, participants will enter a 6-month safety follow-up period for collection of SAEs and MAAEs.
- All AEs, MAAEs, and SAEs will be followed by the investigator until clinical resolution or until a clinically stable condition is reached, or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts. An early exit visit will be conducted for those participants who are unable to continue participation in the study and withdraw from the study before Day 210, but who do not withdraw consent. Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent) (Section 7.2., Participant Discontinuation/Withdrawal From the Study).
- Safety issues that arise from this study will be reviewed by an IDMC on an ad hoc basis, including all related SAEs and all fatal cases.

- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:
  - Study vaccinations will be discontinued in participants for the reasons included in Section 7., Discontinuation of Study Vaccination and Participant Discontinuation/ Withdrawal From the Study.
  - Contraindications to vaccination are included in Section 5.5., Criteria for Temporarily Delaying Study Vaccine Administration.

More detailed information about the known and expected benefits and risks of VAC52416 (JNJ-78901563) may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To demonstrate the non-inferiority of the humoral immune response to the 4 influenza vaccine strains after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of a HD quadrivalent seasonal influenza vaccine administered alone.	• Antibody hemagglutination inhibition (HI) titers as measured by HI assay against each of the 4 influenza vaccine strains, 29 days after the administration of a HD quadrivalent seasonal influenza vaccine.

Objectives	Endpoints
• To demonstrate the non-inferiority of the humoral immune response against the vaccine O-serotype antigens after concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of ExPEC9V administered alone.	• Antibody titers to vaccine O-serotype antigens, as determined by multiplex ECL-based immunoassay 29 days after administration of ExPEC9V.
Secondary	
• To compare seroconversion rates against the 4 influenza vaccine strains after the concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of a HD quadrivalent seasonal influenza vaccine alone.	• Seroconversion is defined for each of the 4 influenza vaccine strains at 29 days after the administration of a HD quadrivalent seasonal influenza vaccine: – HI titer ≥1:40 in participants with a prevaccination HI titer of <1:10, or – a ≥4-fold HI titer increase in participants with a prevaccination HI titer of ≥1:10.
• To compare seroprotection rates against the 4 influenza vaccine strains after the concomitant administration of ExPEC9V and a HD quadrivalent seasonal influenza vaccine versus the administration of a HD quadrivalent seasonal influenza vaccine alone.	• Seroprotection is defined for each of the 4 influenza vaccine strains as HI titer ≥1:40 at 29 days after the administration of a HD quadrivalent seasonal influenza vaccine.
• To assess the safety and reactogenicity of ExPEC9V when administered separately or concomitantly with a HD quadrivalent seasonal influenza vaccine	• Solicited local (injection site) and systemic AEs for 14 days post each vaccination. • Unsolicited AEs for 29 days post each vaccination. • MAAEs collected from administration of the first vaccination until 6 months post last vaccination. • SAEs collected from the administration of the first vaccination until 6 months post last vaccination.
• To evaluate the immunogenicity of ExPEC9V when administered separately or concomitantly with a HD quadrivalent seasonal influenza vaccine.	• Antibody titers to vaccine O-serotype antigens and EPA as determined by multiplex ECL-based immunoassay on Days 1, 30, and 59.

Objectives	Endpoints
• To further evaluate the immunogenicity of ExPEC9V when administered separately or concomitantly with a HD quadrivalent seasonal influenza vaccine.	• Opsonophagocytic antibody titers to vaccine O-serotype antigens as determined by MOPA 29 days after administration of ExPEC9V.
• To evaluate the immunogenicity of ExPEC9V between participants with a history of UTI to those without a UTI history.	• Antibody titers to vaccine O-serotype antigens, in participants reporting a history of UTI at enrollment and participants without a UTI history at enrollment, as determined by multiplex ECL-based immunoassay 29 days after administration of ExPEC9V.
• To further evaluate the immunogenicity of ExPEC9V between participants with a history of UTI to those without a UTI history.	• Opsonophagocytic antibody titers to vaccine O-serotype antigens, in participants reporting a history of UTI at enrollment and participants without a UTI history at enrollment, as determined by MOPA 29 days after administration of ExPEC9V.

HYPOTHESES

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

AND

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

the following hypotheses will be tested:

Null Hypothesis:

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

OR

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

Alternative Hypothesis:

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

AND

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

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel group, multicenter, Phase 3 study in adult participants aged 65 years and older.

A target of approximately 932 participants will be randomized in parallel in this study in a 1:1 ratio to 1 of 2 vaccination groups (Table 1). The randomization will be stratified by age category (≥65 to <75 years, ≥75 years) and history of UTI (yes/no).

Group 1 (CoAd group) will receive ExPEC9V on Day 1 administered at the same time as HD quadrivalent seasonal influenza vaccine, and placebo on Day 30. Group 2 (Control group) will receive placebo on Day 1 administered at the same time as HD quadrivalent seasonal influenza vaccine, and ExPEC9V on Day 30. All study vaccinations will be given by the IM route.

Table 1: Overview of the Groups, Targeted Number of Participants, and Vaccinations

Group	N	Day 1	Day 30
1 (CoAd group)	~466	ExPEC9V + HD quadrivalent seasonal influenza vaccine	Placebo
2 (Control group)	~466	Placebo + HD quadrivalent seasonal influenza vaccine	ExPEC9V

N = number of participants.

After each vaccination, participants will be observed for at least 30 minutes for presence of any acute reactions and solicited events. Any unsolicited AEs, solicited local (injection site) or systemic AEs, and vital signs (systolic and diastolic blood pressure [sitting], heart rate, respiratory rate, and body temperature) will be documented by study-site personnel following this observation period. In addition, participants will record solicited signs and symptoms in an eDiary for 14 days post-vaccination.

Unsolicited AEs will be reported for 29 days post-vaccination. SAEs, MAAEs, and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure. More details are provided in Section 8.3.1., Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

The study duration will be approximately 7 months per participant. The study comprises screening to be performed within 8 days of Day 1, vaccination for each participant on Days 1 and 30 with a 29-day follow-up period after each vaccination, and collection of SAEs and MAAEs until 6 months after the last study vaccination.

Unscheduled study visits may be performed based on investigator's clinical judgment and may include further evaluations, as needed.

Blood will be collected from all participants to assess humoral immune responses on each vaccination day (prevaccination) and at 29 days after the second study vaccination. Over the entire study, the total blood volume to be collected from each participant will be approximately 90 mL.

A diagram of the study design is provided in Section 1.2, Schema (Figure 1).

An IDMC will be commissioned for this study. Refer to Committees Structure in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations for details.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Vaccination Groups

The study will examine the immunogenicity and safety of ExPEC9V co-administered with a HD quadrivalent seasonal influenza vaccine compared to administration of each vaccine separately. A placebo control will be used for ExPEC9V to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active vaccination. Randomization will be used to minimize bias in the assignment of participants to vaccination groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across vaccination groups, and to enhance the validity of statistical comparisons across vaccination groups. Blinded vaccination will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

4.2.1. Study-specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study, and during the study, participants 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 participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Written consent/assent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or participant preferences.

The primary ethical concern is that this study will be performed in adult participants who may receive no benefit from participation in the study, except for compensation for the time and inconveniences that may arise from participation in the study.

Vaccination with a seasonal influenza vaccine may provide protection against the influenza A subtype viruses and type B viruses contained in the vaccine. Note, interference of ExPEC9V on the immunogenicity of seasonal influenza vaccine cannot be ruled out.

See Section 2.3., for Benefit-Risk Assessment.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the US Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), and US FDA guidelines of 550 mL in any 8-week period (OHRP 1998; FDA 1998).

4.3. Justification for Dose

The dose of ExPEC9V to be administered in the present study is based on the primary analysis of Cohort 1 of the ongoing ExPEC10V Phase 1/2a study (VAC52416BAC1001) (see Section 2.2., Background).

The dose of HD quadrivalent seasonal influenza vaccine is based on its licensed posology for the population aged 65 years and older in the countries participating in the study, as described in the package insert.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit (Day 210) for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Participant Study Completion Definition

A participant will be considered to have completed the study if the participant has completed the Day 210 visit.

Participants who prematurely discontinue study vaccination for any reason before completion of the Day 210 visit will not be considered to have completed the study.

5. STUDY POPULATION

Screening for eligible participants will be performed within 8 days before administration of the study vaccination. Refer to Section 5.4., Screen Failures for conditions under which the repeat of any screening procedures is allowed.

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

For a discussion of the statistical considerations of participant selection, refer to Section 9.2., Sample Size Determination.

5.1. Inclusion Criteria

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

Age

1. ≥65 years of age, inclusive, on the day of signing the ICF.

Type of Participant and Disease Characteristics

2. must be medically stable at the time of vaccination such that, according to the judgment of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up. A stable medical condition is defined as disease not requiring significant change in therapy during the 6 weeks before enrollment and when hospitalization for worsening of the disease is not anticipated. Participants will be included on the basis of physical examination, medical history, and vital signs performed between ICF signature and vaccination.

Weight

Not applicable.

Sex and Contraceptive/Barrier Requirements

3. male or female.
4. before randomization, a participant must be:
   a. postmenopausal (postmenopausal state is defined as no menses for 12 months without an alternative medical cause); and
   b. not intending to conceive by any methods.

   Note: Surgically sterile participants are also eligible for the study.

Informed Consent

5. must sign an ICF indicating that the participant understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study.
6. willing and able to adhere to the lifestyle restrictions specified in this protocol.

Additional Inclusion Criteria

7. agrees to not donate blood from the time of vaccination until 3 months after receiving the last dose of study vaccine.
8. must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.
9. must be able to read, understand, and complete the eDiary.
10. must be able to work with smartphones/tablets/computers.

5.2. Exclusion Criteria

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

Medical Conditions

1. history of an underlying clinically significant acute or uncontrolled chronic medical condition or significant cognitive impairment or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
2. abnormal function of the immune system resulting from:
   a. clinical conditions or their treatments expected to have an impact on the immune response elicited by the study vaccine. Participants with clinical conditions that are stable under treatment without the use of prohibited therapies may be enrolled at the discretion of the investigator.
   b. chronic or recurrent use of systemic corticosteroids within 3 months before administration of study vaccine and during the study. A substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent.

      Note: Ocular, topical or inhaled steroids are allowed.
   c. administration of antineoplastic and immunomodulating agents (eg, cancer chemotherapeutic agents) or radiotherapy expected to have an impact on the immune response elicited by the study vaccine within 6 months before administration of study vaccine and during the study.
3. history of malignancy within 5 years before screening not in the following categories:
   a. participants with squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix may be enrolled at the discretion of the investigator.
   b. participants with a history of malignancy within 5 years before screening, with minimal risk of recurrence per investigator's judgment, can be enrolled.
   c. participants with a diagnosis of localized prostate cancer may be enrolled at the discretion of the investigator if they completed treatment (continuation of androgen deprivation therapy is allowed) or if they remain under observation or active surveillance. Participants who underwent radical prostatectomy or radiotherapy may be enrolled at the discretion of the investigator if treatment has been completed 6 months prior to the planned administration of the study vaccine.
4. known or suspected allergy or history of severe allergic reaction, anaphylaxis, or other serious adverse reactions to vaccines or vaccine excipients (specifically the excipients of the study vaccine) (refer to Investigator's Brochure).
5. history of severe allergic reactions (eg, anaphylaxis) to any component of the HD quadrivalent seasonal influenza vaccine, including egg protein, or following a previous dose of any influenza vaccine.
6. has had major surgery (per the investigator's judgment) within 4 weeks before administration of the first study vaccine or will not have recovered from surgery per the investigator's judgment at time of vaccination.

7. history of acute polyneuropathy (eg, Guillain-Barré syndrome) or chronic inflammatory demyelinating polyneuropathy.
8. has had major psychiatric illness or drug or alcohol abuse which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures.
9. contraindication to IM injections and blood draws (eg, bleeding disorders).

Prior/Concomitant Therapy

10. received hematopoietic stem cell transplant based on medical history, treatment with immunoglobulins in the 2 months, apheresis therapies in the 4 months, or blood products in the 3 months before the planned administration of the first dose of study vaccine or has any plans to receive such treatment during the study.

    Note: Given that not all immunoglobulins/monoclonal antibodies are expected to impact the vaccine-induced immune response, the investigator should contact the sponsor to discuss eligibility of participants on immunoglobulin treatment.

11. received or plans to receive:
    a. licensed live attenuated vaccines - within 28 days before or after planned administration of the first or subsequent study vaccinations.
    b. other licensed (not live) vaccines - within 14 days before or after planned administration of the first or subsequent study vaccinations.
    c. vaccination with a vaccine authorized for emergency use (eg, EUA, CMA, or a similar program) is permitted when given at least 28 days before or after planned administration of the first or subsequent study vaccinations.
12. received vaccination with seasonal influenza vaccine for the current influenza season in the Northern Hemisphere.
13. received any *E. coli*[1] or ExPEC vaccine.

Prior/Concurrent Clinical Study Experience

14. received an investigational drug or used an invasive investigational medical device within 90 days, or received an investigational vaccine within 90 days before the planned administration of the first dose of study vaccine, or is currently enrolled or plans to participate in another investigational study during the course of this study and before 6 months after administration of the study vaccine.

[1] *E. coli* vaccines include, and are not limited to, immunoactive agents used for rUTI prophylaxis and containing *E. coli* immunogens, eg, inactivated whole bacterial lysates of *E. coli* (eg, Uromune®) or lyophilized preparation of *E. coli* membrane proteins (eg, Uro-vaxom®).

Diagnostic Assessments

15. has uncontrolled HIV type 1 or type 2 infection.

    Note: a participant with a stable/well-controlled HIV infection is allowed.
    See Appendix 6: Specific Criteria for the Inclusion of Potential Participants with Chronic Stable HIV, HCV, or HBV Infection.

16. has a diagnosis of chronic active hepatitis B or hepatitis C infection that is not medically stable, based on judgment of the investigator.

    Note: a participant with a stable and virologically suppressed hepatitis B or hepatitis C infection is allowed.
    See Appendix 6: Specific Criteria for the Inclusion of Potential Participants with Chronic Stable HIV, HCV, or HBV Infection.

Other Exclusions

17. 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 or CRO.
18. cannot communicate reliably with the investigator.
19. who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or is unlikely to complete the full course of vaccination and observation.
20. who has significant scarring, tattoos, abrasions, cuts, or infections over the deltoid region of both arms that, in the investigator's opinion, could interfere with evaluation of injection site local reactions.

Note: Investigators must ensure that all study enrollment criteria have been met prior to the first vaccination. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first study vaccination is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Section 5.4., Screen Failures, describes options for retesting. The required documentation to support meeting the enrollment criteria is described in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. refer to Section 6.8., 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.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness. This study will use interactive web response system (IWRS). The investigator will generate screening and enrollment logs directly from IWRS.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreening is allowed only for resolution of an acute condition or meeting a time window (eg, for a prohibited medication). Only 1 rescreening per participant is permitted. Rescreened participants must be assigned new participant numbers, undergo the informed consent process, and then restart a new screening phase.

5.5. Criteria for Temporarily Delaying Study Vaccine Administration

The following events constitute a temporary contraindication to study vaccination:

- Clinically significant acute illness at the time of vaccination. This does not include minor illnesses, such as diarrhea or mild upper respiratory tract infection.
- Fever (body temperature ≥100.4°F [38.0°C]) within 24 hours prior to the planned time of vaccination.
- An illness which in the judgment of the investigator may interfere with reactogenicity or safety assessments.
- Medically indicated vaccinations, including SARS-COV-2 vaccine boosters, taking into account the restrictions outlined in Section 5.2., Exclusion Criteria, and Section 6.8., Concomitant Therapy.

If any of these events occur at the scheduled time for the first vaccination, randomization at a later date within the screening period (allowed window up to 8 days) is permitted at the discretion of the investigator and after consultation with the sponsor. If randomization cannot occur within the screening window, rescreening is required.

If any of these events occur at the scheduled time for one of the subsequent vaccinations, the vaccination can be delayed up to 10 days on top of the allowed time window of Visit 3 (±7 days). The immunogenicity and safety assessments of Visit 3 should still be performed on the actual Day 30 (±7 days).

Vaccination may be delayed for reasons other than acute illness at investigator's discretion. Vaccination must be completed within the specified window and upon approval of the sponsor. A check of eligibility criteria may be repeated as necessary.

If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

6. STUDY VACCINATIONS AND CONCOMITANT THERAPY

6.1. Study Vaccinations Administered

Participants will be vaccinated according to the schedule detailed in the Schedule of Activities (SoA). For description of the vaccinations, see below.

On Day 1, each participant will receive 2 IM injections, 1 in each arm; on Day 30, each participant will receive 1 IM injection. The right arm should be used for seasonal influenza vaccination on Day 1; the left arm should be used for ExPEC9V or placebo vaccination on Days 1 and 30. Two injections in the same deltoid are allowed only if medically indicated. If an injection cannot be given in the deltoids due to a medical condition or other contraindication (for example, due to the extent of tattoos which are felt to interfere with the examination of the injection site), use alternative locations such as the hip, thigh or buttocks (to be avoided in overweight participants). In all circumstances, IM injections in other locations than the upper arm are not considered protocol deviations.

For information on vaccination windows, see Section 8., Study Assessments and Procedures. If a participant cannot be vaccinated within the allowed window, the decision regarding vaccination will be assessed on a case-by-case basis, upon discussion between sponsor and investigator.

Study vaccination administration must be captured in the source documents and the eCRF.

VAC52416 (JNJ-78901563) will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Description of Vaccinations

Arm Name	CoAd group (Group 1)	Control group (Group 2)
Vaccination Name	ExPEC9V + high-dose quadrivalent influenza vaccine (Day 1) followed by placebo (normal saline) (Day 30)	Placebo (normal saline) + high-dose quadrivalent influenza vaccine (Day 1) followed by ExPEC9V (Day 30)
Type	Biological/Vaccine	Biological/Vaccine
Dose Formulation	Other Solution for injection	Other Solution for injection
Unit Dose Strength(s)	ExPEC9V: 176 µg PS/mL Quadrivalent influenza vaccine: 240 µg (ie, 60 µg per strain) of haemagglutinin (HA) Normal saline: 9 mg/mL Sodium Chloride (0.9% w/v).	ExPEC9V: 176 µg PS/mL Quadrivalent influenza vaccine: 240 µg (ie, 60 µg per strain) of haemagglutinin (HA) Normal saline: 9 mg/mL Sodium Chloride (0.9% w/v).
Dosage Level(s)	ExPEC9V - 0.5 mL single dose Quadrivalent influenza vaccine - 0.7 mL single dose Normal saline placebo - 0.5 mL single dose	ExPEC9V - 0.5 mL single dose Quadrivalent influenza vaccine - 0.7 mL single dose Normal saline placebo - 0.5 mL single dose
Route of Administration	IM	IM
Use	ExPEC9V: Experimental Quadrivalent influenza vaccine: Other Normal saline: Placebo comparator	ExPEC9V: Experimental Quadrivalent influenza vaccine: Other Normal saline: Placebo comparator
Investigational Medicinal Product (IMP)	Yes	Yes
Sourcing	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Study intervention will be provided in a kit. Each kit will be labeled as required per country requirement Not in child resistant packaging	Study intervention will be provided in a kit. Each kit will be labeled as required per country requirement Not in child resistant packaging

[a] Labels will contain information to meet the applicable regulatory requirements.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage of ExPEC9V and Placebo

All study vaccine must be stored at controlled temperatures in a secure location that can only be accessed by authorized individuals. The study refrigerator/freezer must be equipped with a continuous temperature monitor and alarm and should be equipped with back-up power systems. If study vaccine is exposed to temperatures outside the specified temperature range, all relevant data must be sent to the sponsor to determine if the affected supplies 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.

Administration of study vaccine (ExPEC9V or placebo) on Days 1 and 30 will be blinded. An unblinded study-site pharmacist, or other qualified individual will prepare the appropriate vials and syringes, labeled with the participant's identification number, and provide the syringes for ExPEC9V and placebo in a blinded manner to the blinded vaccine administrator who will perform the injection. The left arm should be used for ExPEC9V or placebo vaccination on Days 1 and 30.

Refer to the study Site Investigational Product Procedures Manual and/or the Investigational Product Preparation and Administration Instructions for additional guidance on study vaccine preparation, handling, storage and stability.

Preparation/Handling/Storage of High-dose Quadrivalent Seasonal Influenza Vaccine

HD quadrivalent seasonal influenza vaccine should be stored, handled, and administered according to the instructions on the package insert. Administration of HD quadrivalent seasonal influenza vaccine on Day 1 will not be blinded. The right arm should be used for seasonal influenza vaccination on Day 1. The disposal of the vaccine will be according to local prescribing information. The study refrigerator/freezer must be equipped with a continuous temperature monitor and alarm and should be equipped with back-up power systems. If the vaccine is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected vaccine can be used or will be replaced. The affected vaccine must be quarantined and not used until further instruction from the sponsor is received.

Accountability

The investigator is responsible for ensuring that all study vaccination received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the participant must be documented on the vaccine accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions.

Study vaccination 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 vaccination 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 vaccination will be documented on the vaccination return form. When the study site is an authorized destruction unit and study vaccination supplies are destroyed on-site, this must also be documented on the vaccination return form.

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

Study vaccination 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 vaccination will be supplied only to participants participating in the study. Returned study vaccination must not be dispensed again, even to the same participant. Study vaccination may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study vaccination from, nor store it at, any site other than the study sites agreed upon with the sponsor.

Further guidance and information for the final disposition of unused study vaccinations are provided in the Investigational Product Preparation Instructions and Study Site Investigational Product and Procedures Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Vaccination Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned in a 1:1 ratio to 1 of 2 vaccination groups 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 and will be stratified by age category (≥65 to <75 years, ≥75 years) and history of UTI (yes/no).

The IWRS will assign a unique vaccination code, which will dictate the vaccination assignment and matching study vaccination kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Participants who withdraw will not be replaced.

Blinding

The investigator will not be provided with randomization codes until database lock of the final analysis. The participants remain blinded until database lock of the final analysis. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

For the sponsor, unblinding (at the participant level) will occur at the time of the primary analysis (Section 9.5., Interim Analysis). From the primary analysis onwards, group level results may be shared as needed; however, efforts will be made to preserve the blinding to the individual participant allocation.

Data that may potentially unblind the study vaccine assignment (eg, immunogenicity data, study vaccine preparation/accountability data, study vaccine allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

The investigator may, in an emergency, determine the identity of the study vaccine by contacting the IWRS. While the responsibility to break the study vaccine allocation code in emergency situations resides solely with the investigator, it is recommended that the investigator contacts 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, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

The study-site pharmacist or qualified individual with primary responsibility for study vaccine preparation and dispensing will be unblinded to study vaccine allocation.

Note: administration of HD quadrivalent seasonal influenza vaccine will not be blinded.

Participants who have had their study vaccine assignment unblinded should continue to return for scheduled evaluations.

6.4. Study Vaccination Compliance

Study vaccines will be administered IM by qualified study-site personnel. Details of each administration will be recorded in the eCRF (including date, time, and site of injection).

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Vaccination After the End of the Study

No continued access will be proposed for this study as all participants in this study will receive ExPEC9V and HD quadrivalent seasonal influenza vaccine, irrespective of the study group to which they are randomized. Therefore, there is no need to offer active study vaccine to placebo recipients after the end of the study.

Participants will be instructed that study vaccination will not be made available to them after they have completed/discontinued study vaccination.

6.7. Treatment of Overdose

For this study, any dose of ExPEC9V (VAC52416 (JNJ-78901563)) or HD quadrivalent seasonal influenza vaccine greater than the protocol-specified dose will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study vaccine should be interrupted.
- Closely monitor the participant for AEs/MAAEs/SAEs until resolution.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.
- Report as a special reporting situation.

6.8. Concomitant Therapy

Disallowed Medication

Refer to Section 5.2., Exclusion Criteria for details on which medication is disallowed before the first vaccination and during the study. If any of these medications are indicated in a disease or a post-exposure setting, these must take priority over the study vaccination.

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

Any use of disallowed medication is to be recorded in the eCRF.

Recording of Prestudy and Concomitant Medication

Prestudy specific therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, vaccinations, antivirals, and all antibacterials (including antibiotics and urinary tract antiseptics) administered within 30 days before the first study vaccination must be recorded at screening.

Concomitant therapies associated with solicited AEs will be collected by the participants in the participant eDiary from the time of study vaccination through 14 days after each vaccination. Concomitant therapies associated with unsolicited AEs will be collected and recorded in the eCRF from the time of study vaccination through 29 days after each vaccination. Concomitant therapies associated with SAEs and MAAEs will be collected and recorded in the eCRF from ICF signature until 6 months after the last study vaccination.

Analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs may be used post-vaccination only in cases of medical need (eg, fever or pain) and their use must be documented. Use of these medications as routine prophylaxis prior to study vaccination is discouraged.

Information on concomitant use of herbal supplements or vitamins will not be collected.

Use of any experimental medication (including experimental vaccines other than the study vaccine) during the study is not allowed.

In order to avoid misinterpretation of adverse reactions and potential immune interference, vaccination with licensed live attenuated vaccines is prohibited within 28 days before or after the administration of the study vaccination. Vaccination with other licensed vaccines (not live) (eg, COVID-19, tetanus, hepatitis A, hepatitis B, rabies) is prohibited within 14 days before or after the administration of the study vaccine. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Vaccination with a vaccine authorized for emergency use (eg, EUA, CMA, or a similar program) is permitted when given at least 28 days before or after administration of the study vaccine.

Use of systemic corticosteroids[2], antineoplastic agents, and immunomodulating agents must be documented until 29 days after the last study vaccination. Antineoplastic and immunomodulating agents, eg, cancer chemotherapeutic agents or systemic corticosteroids, or radiotherapy are prohibited until 29 days after the last study vaccination. If the use of systemic corticosteroids, antineoplastic or immunomodulating agents or any therapy described in Exclusion Criterion 2 becomes medically indicated during the study for any participant, the sponsor should be notified.

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

Study vaccinations will be withheld for the reasons listed below. These participants should not receive any further doses of study vaccine but should remain on study for follow-up with assessments of safety and immunogenicity, unless the participant withdraws consent for study participation. Additional unscheduled visits or telephone calls may be performed for safety/reactogenicity reasons, if needed. In case of questions, the investigator is encouraged to contact the sponsor.

- The participant withdraws consent to receive further study vaccination
- The investigator believes that for safety reasons or reactogenicity reasons (eg, AE/MAAE) it is in the best interest of the participant to discontinue study vaccination.
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- Anaphylactic reaction and/or severe hypersensitivity reaction following vaccination, not attributable to causes other than vaccination
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Disallowed use of systemic corticosteroids, antineoplastic and immunomodulating agents or radiotherapy as detailed in Section 5.2., Exclusion Criteria.

[2] Note: Ocular, topical, or inhaled steroids are allowed.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent for study participation
- Repeated failure to comply with protocol requirements
- Decision by the sponsor or the investigator to stop or cancel the study
- Decision by local regulatory authorities or IRB/IEC to stop or cancel the study
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

An early exit visit will be conducted for those participants who are unable to continue participation in the study and withdraw from the study before Day 210, but who do not withdraw consent (see Schedule of Activities (SoA)). Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent). They have the right to refuse.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal from the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations). 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.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (SoA) summarizes the frequency and timing of study visits and of immunogenicity and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: vital signs, other safety assessments, blood draws. If needed, assessments may be performed at another day within the applicable visit window. Actual dates and times of assessments will be recorded in the source document and/or in the eCRF.

At screening, participants will be specifically questioned regarding the medical history of UTI. This includes any uncomplicated, complicated, or recurrent UTIs that were diagnosed by a physician (or qualified healthcare provider) and that required antimicrobial therapy. The details will be collected in the eCRF. Note: a history of isolated male accessory gland infections will not be considered as a history of UTI.

Participants will be provided a thermometer (to measure body temperature), ruler (to measure local injection site reactions), and participant eDiary to record body temperature and solicited local (at injection site) and systemic signs and symptoms.

The eDiary includes instructions on how to capture the signs and symptoms and grading scales to assess severity. The study staff is responsible for providing appropriate training to the participant to avoid missing or incorrect data. The eDiary will be reviewed by study personnel at visits indicated in the Schedule of Activities (SoA). If the eDiary review is missed, the eDiary will be reviewed during the following visit. If a participant misses a vaccination, the eDiary covering the period after the missed vaccination does not have to be completed.

The total blood volume to be collected from each participant will be approximately 90 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Visit Windows

Visit windows are provided in the Schedules of Activities.

The timings of the post-vaccination visits will be determined relative to the actual day of the corresponding vaccination. If a participant misses a vaccination, the post-vaccination visits will be calculated from the imputative vaccination date according to protocol.

Note: In case any of the criteria for temporarily delaying study vaccine administration (see Section 7.1., Discontinuation of Study Vaccination) are met at Visit 3 (Day 30), this visit would need to be split into 2 visits. The administration of the second study vaccination can be delayed up to 10 days on top of the allowed time window of Visit 3 (±7 days). The immunogenicity and safety assessments of Visit 3 should still be performed on the actual Day 30 (±7 days).

Home Health Care and Telemedicine Visits

Home health care and telemedicine visits conducted via phone or video conference may be implemented by or with approval from the sponsor and per the clinical judgment of the investigator, where feasible and permissible by local policy, regulations (as applicable) for participants for whom there is no safety concern.

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 Schedule of Activities (SoA) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure
- SmPC Package Insert for HD Quadrivalent Seasonal Influenza Vaccine
- Participant eDiary and instructions for use
- Thermometer
- Ruler (to measure diameter of any erythema and swelling)
- Study Site Investigational Product and Procedures Manual
- Investigational Product Preparation Instructions
- Laboratory manual

- Laboratory kits
- Contact Information page(s)
- Study protocol
- IWRS manual
- electronic data capture (eDC) Manual/eCRF completion guidelines
- Wallet card
- Sample ICF

8.1. Immunogenicity Assessments

Venous blood samples of approximately 30 mL will be collected for the determination of humoral immune responses at the timepoints indicated in the Schedule of Activities (SoA). Sample collection and processing will be performed by the study-site personnel according to current versions of approved standard operating procedures.

For assessment of immunogenicity, serum IgG antibody levels elicited by ExPEC9V against each of the 9 vaccine O-serotypes and the carrier protein EPA will be measured by a validated multiplex ECL-based immunoassay. Additionally, functional antibodies will be evaluated by a validated MOPA.

Antibody titers against influenza virus strains recommended by the WHO for use in 2023-2024 in the Northern Hemisphere season will be measured using validated HI assays.

8.2. Safety Assessments

Safety assessments will include the monitoring of AEs, MAAEs, physical examinations, and vital signs.

AEs and MAAEs will be reported and followed by the investigator as specified in Section 8.3., Adverse Events, Medically-attended Adverse Events, Serious Adverse Events, and Other Safety Reporting and Appendix 3: Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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 condition is reached, or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up effort.

The study will include the following evaluations of safety and reactogenicity according to the time points provided in the Schedule of Activities (SoA).

8.2.1. Physical Examinations

A general physical examination including body weight and height will be performed at screening. It is at the investigator's discretion how detailed the examination (which body systems are to be covered) is deemed needed.

At any other visit, a targeted (abbreviated and symptom-directed) examination may be performed if deemed necessary by the investigator based on any clinically relevant issues, clinically relevant symptoms, and medical history.

Physical examinations will be performed by the investigator or appropriately trained delegate. Any clinically relevant abnormalities or changes in severity observed during the review of body systems should be documented in the eCRF as an AE or SAE if it meets the criteria for an AE or SAE according to the protocol reporting requirements. Any abnormalities or changes in severity that occurred after signing of the ICF until immediately before vaccination would be recorded if due to participation in the study.

8.2.2. Vital Signs

Vital signs will be measured pre- and postdose at each vaccination visit (Days 1 and 30). At non-vaccination visits, vital signs will be measured if deemed necessary by the investigator. Body temperature (oral route preferred), heart rate (beats per minute), respiratory rate (breaths per minute), and systolic and diastolic blood pressure (mmHg) will be assessed. Height and weight will be measured during screening.

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

Sitting systolic and diastolic blood pressure and heart and respiratory rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Confirmatory vital signs measurement can be performed if inconsistent with a prior measurement. Any abnormalities or changes in severity noted during the review of vital signs should be documented in the eCRF.

Participants will utilize an eDiary to record body temperature measurements post-vaccination (see Section 8., Study Assessments and Procedures).

8.3. Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, MAAEs, and PQCs, from clinical studies are crucial for the protection of participants, 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.

AEs and MAAEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, MAAEs, SAEs, and PQCs can be found in Appendix 3: Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event, Medically-attended Adverse Events, and Serious Adverse Event Information

AEs, MAAEs, and SAEs will be collected as indicated in the Schedule of Activities (SoA).

All Adverse Events

AEs and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal.

Clinically relevant medical events not meeting the above criteria and occurring between signing of ICF and moment of first vaccination will be collected on the Medical History eCRF page as pre-existing conditions.

Solicited AEs, collected through an eDiary, will be recorded for each vaccination from the time of vaccination until 14 days post-vaccination.

All unsolicited AEs and special reporting situations will be collected for each vaccination from the time of vaccination until 29 days post-vaccination. Unsolicited AEs with the onset date outside the timeframe defined above (>29 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded as such.

Serious Adverse Events and Adverse Events Leading to Discontinuation

All SAEs and AEs leading to discontinuation from the study/vaccination are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, but no later than 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax).

Medically-attended Adverse Events

MAAEs are defined as AEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Adverse events (eg, abnormal vitals) identified at a routine study visit will not be considered MAAEs. Routine medical visits for chronic comorbidities (or study visits) will not be considered medically-attended visits.

All MAAEs are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up.

8.3.2. Method of Detecting Adverse Events, Medically-attended Adverse Events, and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs, MAAEs, or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local (at injection site) and systemic events for which the participant is specifically questioned and which are noted by participants in their eDiary.

After each vaccination, participants will be observed for at least 30 minutes for presence of any acute reactions and solicited events.

In addition, participants will record solicited signs and symptoms in an eDiary for 14 days post-vaccination. All participants will be provided with an eDiary and instructions on how to complete the eDiary (see Overview in Section 8., Study Assessments and Procedures). Electronic diary information will be transferred from the eDiary source to the sponsor. Review of eDiary entries with participants and grading of symptoms must be done by a qualified and delegated study staff member under the oversight of the investigator or a delegated physician. Once a solicited sign or symptom from an eDiary is considered to be of severity Grade 1 or above, it will be recorded as a solicited AE.

Solicited Injection Site (Local) Adverse Events

Participants will be asked to note in the eDiary occurrences of injection site pain/tenderness, erythema and swelling at the study vaccine injection site daily for 14 days post-vaccination (day of vaccination and the subsequent 14 days). The extent (largest diameter) of any erythema and swelling should be measured (using the ruler supplied) and recorded daily. The case definitions for solicited injection site events can be found in the references (Gidudu 2012, Kohl 2007).

Solicited Systemic Adverse Events

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the temperature (oral route preferred) in the eDiary in the evening of the day of vaccination, and then daily for the next 14 days approximately at the same

time each day. If more than one measurement is made on any given day, the highest temperature of that day will be used in the eCRF.

Fever is defined as endogenous elevation of body temperature ≥100.4°F (38°C), as recorded in at least one measurement (Marcy 2004).

Participants will also be instructed on how to note signs and symptoms in the eDiary on a daily basis for 14 days post-vaccination (day of vaccination and the subsequent 14 days), for the following events: fatigue, headache, nausea, and myalgia.

Unsolicited Adverse Events

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

Medically-attended Adverse Events

MAAEs are AEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Adverse events (eg, abnormal vitals) identified at a routine study visit will not be considered MAAEs. Routine medical visits for chronic comorbidities (or study visits) will not be considered medically-attended visits.

8.3.3. Follow-up of Adverse Events, Medically-attended Adverse Events, and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, MAAE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

AEs and the special reporting situation of pregnancy will be followed by the investigator as specified in Appendix 3: Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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 suspected unexpected serious adverse reactions (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.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants 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 Serious Adverse Event form.

If a participant becomes pregnant during the study, a determination regarding study vaccination discontinuation must be made by the investigator in consultation with the sponsor. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. If the partner of a male participant becomes pregnant during the study, follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required upon the consent provided by the partner.

8.4. Pharmacokinetics

Not applicable.

8.5. Genetics and Pharmacogenomics

Not applicable.

8.6. Biomarkers

Not applicable.

8.7. Immunogenicity Assessments

See Section 8.1.

8.8. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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 immunogenicity and safety is outlined below. Specific details will be provided in the SAP.

9.1. Statistical Hypotheses

For a description of the hypotheses, see Section 3., Objectives and Endpoints.

The study is successful if both below objectives are demonstrated:

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

AND

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

Therefore, the following CIs will be calculated:

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

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

As both non-inferiority objectives should be demonstrated to have a successful study, no multiplicity adjustment is needed.

9.2. Sample Size Determination

Sample size calculations are performed under the following assumptions:

- No effect of co-administration of ExPEC9V and seasonal influenza vaccine on the immune response against influenza as measured by HI antibody titers against the 4 influenza vaccine strains at 29 days after the administration of influenza vaccine
- A standard deviation of 0.5 at the $\log_{10}$ scale for HI antibody titers against the 4 influenza vaccine strains at 29 days after the administration of influenza vaccine (with or without ExPEC9V)
- No effect of co-administration of ExPEC9V and seasonal influenza vaccine on the immune response against the O-serotype antigens as measured by antibody titers against the 9 O-serotype antigens at 29 days after the administration of ExPEC9V
- A standard deviation of 0.6 at the $\log_{10}$ scale for ExPEC9V antibody titers at 29 days after the administration of ExPEC9V (with or without seasonal influenza vaccine)
- A non-inferiority margin of 1.5[3]
- 2-sided α of 5%

[3] Non-inferiority criteria based on FDA guidance for influenza vaccines (FDA 2007b).

A total of 419 evaluable participants per group are needed to have 99.91% power to show non-inferiority in HI antibody titers for 1 influenza vaccine strain and to have 98.88% power to show non-inferiority in antibody titers against 1 O-serotype antigen. With this sample size, the overall power to show non-inferiority in HI antibody titers against each of the 4 influenza vaccine strains at 29 days after the administration of seasonal influenza vaccine as well as non-inferiority in antibody titers against each of the 9 O-serotype antigens at 29 days after the administration of ExPEC9V is at least 90% (see table below).

	1 comparison	**All comparisons**
Flu NI (SD=0.5)	99.91%	99.64% (4 comparisons)
ExPEC9V NI (SD=0.6)	98.88%	90.36% (9 comparisons)
Total		> 90% power

To account for 10% exclusions from the per protocol set (see below for definitions of analysis sets), drop-outs and missing samples, approximately 466 participants per group should be enrolled, resulting in a total sample size of approximately 932 participants.

9.3. Participant Analysis Sets

Vaccination assignment will follow the as-treated principle.

For purposes of analysis, the following analysis sets are defined:

The Full Analysis (FA) Set will include all participants who received at least 1 study vaccination, regardless of the occurrence of protocol deviations and vaccine type (seasonal influenza, ExPEC9 vaccine, or placebo). All safety and participant information analyses will be based on the FA Set.

The Per-protocol Influenza Immunogenicity (PPII) Set will include all randomized participants who received the first study vaccination (ExPEC9V in combination with seasonal influenza vaccine for the CoAd group and seasonal influenza vaccine alone for the Control group), and for whom immunogenicity data are available for at least one of the influenza strains in the vaccine. Samples taken after a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPII analysis.

The Per-protocol ExPEC9V Immunogenicity (PPEI) Set will include all randomized participants who received ExPEC9V in combination with seasonal influenza vaccine for the CoAd group and ExPEC9V alone for the Control group and for whom O-antigen immunogenicity data are available. Samples taken after a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPEI analysis.

The list of major protocol deviations that would lead to elimination from the immunogenicity analysis will be specified in the SAP or major protocol violation criteria document, which will be finalized before database lock and unblinding.

The primary analysis set for analyses related to influenza immunogenicity is the PPII Set, the primary analysis set for analyses related to O-antigen immunogenicity is the PPEI Set. As a sensitivity analysis, key tables may also be based on the FA Set.

9.4. Statistical Analyses

The SAP will be finalized prior to database lock of the primary analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The primary analysis will be performed when all participants have completed the visit 29 days after the second study vaccination or discontinued earlier.

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

9.4.2. Participant Information

For all participants, demographic characteristics (eg, age, height, body weight, BMI, race, and gender) and other baseline characteristics will be tabulated and summarized descriptively by group.

9.4.3. Immunogenicity Analyses

The primary immunogenicity objectives will be assessed by calculating:

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

For HI antibody titers against each of the 4 influenza vaccine strains and for O-serotype antibody titers against each of the 9 O-serotypes, an ANOVA model will be fitted with the respective titers as dependent variable and group (Control or CoAd), age category, and history of UTI (as stratified) as independent variables. Based on these ANOVA models, the CIs around the difference will be calculated and will be back-transformed (by exponentiation) to CIs around a GMT ratio ($GMT_{Control\ group}/GMT_{CoAd\ group}$) and compared to the non-inferiority limit of 1.5.

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

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

Seroconversion is defined for each of the 4 influenza vaccine strains at 29 days after the administration of a seasonal influenza vaccine as:

- HI titer ≥1:40 in participants with a prevaccination HI titer of <1:10, or
- a ≥4-fold HI titer increase in participants with a prevaccination HI titer of ≥1:10

Seroprotection is defined for each of the 4 influenza vaccine strains as HI titer ≥1:40 at 29 days after the administration of a seasonal influenza vaccine.

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

For ExPEC9V serotype antibodies as measured by multiplex ECL-based immunoassay and MOPA, and EPA as measured by multiplex ECL-based immunoassay only, the following measures of immunogenicity will be evaluated and tabulated by the study vaccination groups, for all immunogenicity timepoints:

- proportion of participants with a ≥2-fold and ≥4-fold increase in serum antibody titers from prevaccination to 29 days after the administration of ExPEC9V
- geometric mean titer
- geometric mean of fold change from prevaccination, calculated from the 29-days post-vaccination/prevaccination value.

Graphical representations of immunological parameters will be made as applicable.

9.4.4. Safety Analyses

No formal statistical testing of safety data is planned. All safety data will be analyzed descriptively by group. All safety analyses will be made on the FA Set.

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). Any AE occurring at or after the initial administration of study vaccination through the day of last dose plus 29 days is considered to be treatment emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by vaccination group.

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

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

Solicited local (at injection site) and systemic AEs will be summarized descriptively. The number and percentages of participants with at least one solicited local (at injection site) or systemic AE will be presented. The frequencies by vaccine group as well as frequencies according to severity

and duration will be described for solicited AEs. Frequencies of unsolicited AEs, separately for all and vaccination-related only, will be presented by System Organ Class and preferred term, while those of solicited AEs will be presented only by preferred term.

Vital Signs

Vital signs (systolic and diastolic blood pressure [sitting], heart rate, respiratory rate, and body temperature) will be measured both before vaccination and after the end of the 30-minute observation period.

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

Baseline and emerging vital signs abnormalities will be listed.

Physical Examinations

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

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

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

9.5. Interim Analysis

No formal interim analysis is planned for this study.

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

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

The SAP will describe the planned analyses in greater detail.

9.6. Independent Data Monitoring Committee

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

The IDMC responsibilities, authorities, and procedures will be provided in its charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

AE	adverse event
ANOVA	analysis of variance
CI	confidence interval
CMA	Conditional Marketing Authorization
CoAd	Co-administration
COVID-19	Coronavirus Disease 2019
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRO	contract research organization
CTM	clinical trial manager
E. coli	*Escherichia coli*
ECL	Electrochemiluminescent
eCRF	electronic case report form
eDC	electronic data capture
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
ExPEC	extraintestinal pathogenic *Escherichia coli*
ExPEC10V	10-valent extraintestinal pathogenic *Escherichia coli* vaccine
ExPEC4V	4-valent extraintestinal pathogenic *Escherichia coli* vaccine
ExPEC9V	9-valent extraintestinal pathogenic *Escherichia coli* vaccine
FA	full analysis
FDA	(United States) Food and Drug Administration
FOIA	Freedom of Information Act
GLP	Good Laboratory Practice
GMT	geometric mean titer
HA	Hemagglutinin
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	high-dose
HI	hemagglutination inhibition
HI assay	hemagglutination inhibition assay
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IED	invasive extraintestinal pathogenic *Escherichia coli* disease
IgG	immunoglobulin G
IM	intramuscular(ly)
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IWRS	interactive web response system
LTM	local trial manager
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MOPA	multiplex opsonophagocytic killing assay
NI	non-inferiority
NZW	New Zealand White
OHRP	Office for Human Research Protections

OPA	opsonophagocytic killing assay
P. aeruginosa	*Pseudomonas aeruginosa*
PCC	protocol clarification communication
PCR	Polymerase chain reaction
PPEI	Per-protocol ExPEC9V Immunogenicity
PPII	Per-protocol Influenza Immunogenicity
PQC	Product Quality Complaint
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SARS-COV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
US	United States
UTI	urinary tract infection
WHO	World Health Organization

Definitions of Terms

eDiary	The electronic technology used to record solicited signs and symptoms by the participants.
Home health visit	A home visit by a healthcare professional in the event that the participant is unable to come to the site.
Remote visit	A visit for which collection of samples is not required and which will be conducted via telephone call.

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1. Regulatory and Ethical Considerations

The term "sponsor" refers to the sponsor or its designee, as applicable.

Investigator Responsibilities

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

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

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

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 participants, 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.

In situations where a departure from the protocol is unavoidable during the study, 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 must 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 CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

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

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study vaccination 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, participant 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 participant:

- 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

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 participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants 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 participants
- 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 participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant 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 participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB 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 vaccination
- New information that may adversely affect the safety of the participants or the conduct of the study

- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants 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 participants, 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.

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1., Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1., Study-Specific Ethical Design Considerations.

10.2.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.2.3. Informed Consent Process

Each participant must give 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 participant can read and understand. The informed consent must 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 participants the aims, methods, reasonably anticipated benefits,

and potential hazards of the study, and any discomfort participation in the study may entail. Participants 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 participant will receive. Finally, they will be told that the investigator will maintain a participant 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 participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

The participant 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 must be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

10.2.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants 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 participants confidential.

The informed consent obtained from the participant includes information about, and where required per applicable regulations, 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. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant 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, or make requests concerning his or her personal data in accordance with applicable data protection law. 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.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as

necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory research is not conducted under standards appropriate for the return of data to participants. 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 participants 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.

10.2.5. Long-term Retention of Samples for Additional Future Research

No additional research on study participants, study samples, or data derived from the study will be conducted by the institution(s) or by a third party, without the prior written consent of the Sponsor.

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 VAC52416 (JNJ-78901563), to understand IED, to understand differential vaccination responders, and to develop tests/assays related to VAC52416 (JNJ-78901563) and IED. The research may begin at any time during the study or during 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. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1., Withdrawal from the Use of Research Samples).

10.2.6. Committees Structure

The IDMC membership, responsibilities, authorities, and procedures will be provided in its charter.

10.2.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding VAC52416 (JNJ-78901563) 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 the goals of 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 VAC52416 (JNJ-78901563) 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 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 participant identifiers will not be used in the 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 (ICMJE) 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 the 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 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 interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.2.8. Data Quality Assurance

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 CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor may review the CRF 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.

10.2.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the eCRF. 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 the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms must be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to an 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.

10.2.10. Source Documents

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: participant 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/MAAEs and follow-up of AEs/MAAEs; concomitant medication; vaccination receipt/dispensing/return records; study vaccination administration information; and date of study completion and reason for early discontinuation of study vaccination or withdrawal from the study, if applicable.

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

The participant's eDiary used to collect information regarding solicited signs and symptoms after vaccination will be considered source data.

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 other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data.

- Race
- Blood pressure and pulse/heart rate
- Respiratory rate
- Height and weight
- Details of physical examination

An eSource 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 eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

10.2.11. Monitoring

The sponsor will use a combination of monitoring techniques (central, 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 may 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.

Central monitoring will take place for data identified by the sponsor as requiring central review.

There will be independent monitoring of the pharmacy and preparation of study vaccines by an unblinded monitor (independent study vaccine monitor); regular monitors will be blinded.

10.2.12. 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. Participant 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 must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.2.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, 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.

10.2.14. Study and Site Start and Closure

First Act of Recruitment

The first participant screened is considered the first act of recruitment and it becomes the study start date.

Study/Site 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 intervention.

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 participants by the investigator
- Discontinuation of further study vaccination development

10.3. Appendix 3: Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the study vaccination. 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 Council 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: For the time period of the sponsor's AE collection, see All Adverse Events under Section 8.3.1., Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

Medically-attended Adverse Event

MAAEs are defined as AEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Adverse events (eg, abnormal vitals) identified at a routine study visit will not be considered MAAEs. Routine medical visits for chronic comorbidities (or study visits) will not be considered medically-attended visits.

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 participant 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 was 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 must 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 participant 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 vaccination and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For VAC52416 (JNJ-78901563), the expectedness of an AE will be determined by whether or not it is listed in the IB. For HD Quadrivalent Seasonal Influenza Vaccine with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the applicable product information sheet.

10.3.2. Attribution Definitions

Assessment of Causality

The causal relationship to study vaccination is assessed by the investigator. The following selection must be used to assess all AEs.

Related

There is a reasonable causal relationship between study vaccine administration and the AE.

Not Related

There is not a reasonable causal relationship between study vaccine administration and the AE.

The term “reasonable causal relationship” means there is evidence to support a causal relationship.

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

10.3.3. Severity Criteria

All AEs and laboratory data will be coded for severity using a modified version of the FDA grading table, based on version of September 2007 (US Dept Health 2007a), included in Appendix 5: Toxicity Grading Scale.

For AEs/MAAEs not identified in the grading table, the following guidelines will be applied:

Grade 1	Mild	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2	Moderate	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3	Severe	Symptoms causing inability to perform usual social and functional activities and requires medical intervention
Grade 4	Potentially life-threatening	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability OR ER visit or hospitalization

The severity of solicited signs and symptoms will be graded in the eDiary by the participant based on the severity assessment provided in the eDiary and then verified by the investigator using the toxicity grading scale in Appendix 5: Toxicity Grading Scale. (Note: severity of the measured events will be derived from the diameter [for erythema and swelling] and the temperature measurements [for fever]).

10.3.4. Special Reporting Situations

Safety events of interest on a sponsor study vaccine in an interventional study 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, intercepted medication error or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study vaccine from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

Participant-specific special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the CRF.

10.3.5. Procedures

All Adverse Events

All AEs and MAAEs, 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 or MAAE to study therapy. All measures required for AE and MAAE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant 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 participant 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 personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from 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 (participant 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 participation in the 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 CRF). 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 participant in a study, whether or not the event is expected or associated with the study vaccine, is considered an SAE.

10.3.6. Product Quality Complaint Handling

Definition

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, reliability or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

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.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.3.7. Contacting Sponsor Regarding Product Quality

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

10.4. Appendix 4: Contraceptive Guidance

Participants must follow contraceptive measures as outlined in Section 5.1., Inclusion Criteria.

Pregnancy information will be collected and reported as noted in Section 8.3.5., Pregnancy and Appendix 3: Adverse Events, Serious Adverse Events, Medically-attended Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Female Participants Not of Childbearing Potential

- **postmenopausal**
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- **permanently sterile (for the purpose of this study)**
  - Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.
  - Has congenital abnormalities resulting in sterility.

10.5. Appendix 5: Toxicity Grading Scale

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/Tenderness[#]	Aware of symptoms but easily tolerated; Does not interfere with activity; Discomfort only to touch	Notable symptoms; Requires modification in activity or use of medications; Discomfort with movement	Incapacitating symptoms; Inability to do work, school, or usual activities; Use of narcotic pain reliever	Hospitalization; Pain/tenderness causing inability to perform basic self-care function
Erythema[#]	25 – 50 mm	51 – 100 mm	> 100 mm	Hospitalization; Necrosis or exfoliative dermatitis
Swelling[#]	25 – 50 mm	51 – 100 mm	> 100 mm	Hospitalization; Necrosis

[#] Revised by the sponsor.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F)**	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 - 40.0 102.1 - 104.0	> 40 > 104.0
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	Hospitalization for arrhythmia[#]
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	Hospitalization for arrhythmia[#]
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	Hospitalization for malignant hypertension[#]
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension[#]
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock[#]
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

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

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
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	Hospitalization; Hypotensive shock
Nausea[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities	Hospitalization; Inability to perform basic self-care functions
Diarrhea[#]	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or >800 gms/24 hours or oral rehydration necessary	Hospitalization; Hypotensive shock OR IV fluid replacement indicated
Headache[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Fatigue[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Myalgia[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions

[#] Revised by the sponsor.

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	Hospitalization[#]

[#] Revised by the sponsor.

B: Tables for Laboratory Abnormalities

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

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

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

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

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

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

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

10.6. Appendix 6: Specific Criteria for the Inclusion of Potential Participants with Chronic Stable HIV, HCV, or HBV Infection

The following guidelines should be used to consider for inclusion potential participants with chronic stable HIV, HCV, or HBV infection. If a potential participant does not have relevant laboratory results pertaining to HIV infection in his/her medical records from the last 6 months before screening, they will be instructed to go to their local health care provider and obtain the necessary data for potential entry into the trial. Potential participants will not be screened for laboratory evidence of HIV, HCV, or HBV infection. For a potential participant with a medical history of HCV or HBV infection, the below guidelines regarding stable infection are intended to inform the investigator's judgment of eligibility, but the availability of all the listed laboratory data in the medical records is not mandatory.

1. Stable/well-controlled HIV infection includes:
    a. CD4 cell count ≥300 cells/µL.
    b. HIV viral load <50 copies/mL.
    c. Participant must be on stable anti-retroviral treatment (ART) for 6 months (unless the change is due to tolerability, in which case the regimen can be for only the previous 3 months; changes in formulation are allowed; nationwide guidelines that require transition from one ART regimen to another are allowed) and the participant must be willing to continue his/her ART throughout the study as directed by his/her local physician.

Note: Participants with ongoing and progressive comorbidities associated with HIV infection will be excluded but comorbidities associated with HIV infection that have been clinically stable for the past 6 months are not an exclusion criterion.

Laboratory methods for confirming a diagnosis of HIV infection are: Any evidence (historic or current) from medical records, such as ELISA with confirmation with Western Blot or PCR, or of a detectable viral load (country-specific regulatory approved tests).

2. Stable known HCV infection:

    History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

3. Stable known HBV infection:

    May be defined as presence of hepatitis B surface antigen for ≥6 months and:
    a. HBeAg negative, anti-HBe positive, and/or
    b. Serum HBV DNA <2,000 IU/mL; and
    c. No other findings indicating active inflammatory process in liver.

10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

11. REFERENCES

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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): PPD

Institution: Janssen Vaccines & Prevention B.V.

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.

Signature

User	Date	Reason
PPD	22-Sep-2023 08:40:24 (GMT)	Document Approval