# Safety, Reactogenicity, and Immunogenicity of 3 Different Doses of VAC52416 (ExPEC10V) in Adults Aged 60–85 Years in a Randomized, Multicenter, Interventional, First-in-Human Phase 1/2a Study


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## OBJECTIVE

- Results reported for cohort 1 of the phase 1/2a study (NCT03819049) of ExPEC10V, a prophylactic vaccine candidate to prevent invasive *Escherichia coli* disease (IED)
  - Cohort 1 was used to assess safety, reactogenicity, and immunogenicity of ExPEC10V, and to select the optimal dose for further clinical development

## CONCLUSIONS

- ExPEC10V exhibited a strong safety profile and robust immunogenic response
- A vaccine-induced functional immune response was not observed for serotype O8 in the multiplex opsonophagocytic assay (MOPA) due to the used strain, necessitating additional assay optimization
- A reformulated, 9-valent serotype vaccine, ExPEC9V, is currently in a phase 3 trial (NCT04899336) to address the important unmet need for a prophylactic vaccine against IED


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## INTRODUCTION

- Extraintestinal pathogenic *Escherichia coli* (ExPEC) is a leading cause of systemic infections of the bloodstream or other normally sterile body sites[1,2]
- Invasive *E. coli* disease (IED), also known as invasive EXPEC disease, 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 patients with urosepsis with no other identifiable source of infection[3]
- Increasing microbial resistance of ExPEC strains is contributing to a rising incidence and burden of IED,[4,5] with an estimated case fatality rate between 12.4% and 18.4%[6,7]
- ExPEC10V is a 10-valent *E. coli* bioconjugate vaccine containing the O-antigen polysaccharides of ExPEC serotypes O1A, O2, O4, O6A, O8, O15, O16, O18A, O25B, and O75
- ExPEC4V, a 4-valent precursor vaccine targeting ExPEC O-antigens O1A, O2, O6A, and O25B, was well tolerated and immunogenic in healthy adults[8-10]
- This report describes data from cohort 1 through year 1 of the phase 1/2a study (NCT03819049) of ExPEC10V as a potential prophylactic vaccine to prevent IED

## METHODS

### Overall study design

- This was a randomized, multicenter, interventional study conducted across 6 sites in the United States
  - Cohort 1 was used to assess safety, reactogenicity, and immunogenicity of 3 doses of ExPEC10V and to select the optimal dose for further clinical development
  - Cohort 2 was used to characterize safety and immunogenicity of the optimal dose of ExPEC10V, selected based on the analysis of cohort 1, in participants with a history of urinary tract infection (within the past 5 years) utilizing a double-blind, placebo-controlled design

### Cohort 1: Study design and participants

- Cohort 1 utilized an observer-blind, active-controlled design and consisted of a maximum 28-day screening period and an observer-blind 181-day follow-up with vaccination on day 1
  - Those who received ExPEC10V at the dose selected for further study in cohort 2 and those who received the pneumococcal-13 vaccine (PCV13) were also invited to an open-label, long-term follow-up from day 182 through 5 years post vaccination
- The data cut-off date was October 27, 2021
- Healthy adults ≥60 and ≤85 years of age were enrolled
- Participants were randomly assigned to receive a single 0.5-mL intramuscular injection to the deltoid muscle of 1 of 5 vaccinations: low-dose ExPEC10V; medium-dose ExPEC10V; high-dose ExPEC10V; ExPEC4V; PCV13 (**Table 1**)

**TABLE 1: ExPEC study vaccination**

| Study vaccination group | O1A (µg) | O2 (µg) | O4 (µg) | O6A (µg) | O8 (µg) | O15 (µg) | O16 (µg) | O18A (µg) | O25B (µg) | O75 (µg) | EPA (µg) | PS (Tot) (µg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Low-dose ExPEC10V** | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 8 | 4 | 159 | 44 |
| **Medium-dose ExPEC10V** | 8 | 4 | 4 | 8 | 4 | 4 | 4 | 4 | 16 | 4 | 217 | 60 |
| **High-dose ExPEC10V** | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 16 | 8 | 319 | 88 |
| **ExPEC4V** | 4 | 4 | - | 4 | - | - | - | - | 8 | - | 72 | 20 |

ExPEC4V consisted of the O-antigen PSs of the ExPEC serotypes O1A, O2, O6A, and O25B separately bioconjugated to the EPA carrier protein. ExPEC10V consisted of the O-antigen PSs of the ExPEC serotypes O1A, O2, O4, O6A, O8, O15, O16, O18A, O25B, and O75 separately bioconjugated to the EPA carrier protein. The EPA (µg) was calculated using a ratio of 0.276 for PS/EPA. However, the final EPA dose was confirmed at the release. EPA, a genetically detoxified form of exotoxin A derived from *Pseudomonas aeruginosa*; PS, polysaccharide; Tot, total.

### Cohort 1: Assessments

- Solicited local and systemic adverse events (AEs) until day 15, unsolicited AEs until day 30, and serious AEs (SAEs) until day 181 were assessed
- Immunogenicity via multiplex electrochemiluminescent-based immunoassay (ECL) and MOPA was assessed at baseline (prevaccination) and on day 15
- Safety and immunogenicity outcomes were used to select the optimal ExPEC10V dose to be studied in cohort 2

### Cohort 1: Statistics

- The full analysis set (FAS) included all randomized participants with a vaccine administration documented and was the primary safety population
- The per protocol immunogenicity (PPI) analysis set included all randomized and vaccinated participants for whom immunogenicity data were available, excluding those samples with major protocol deviations expected to impact immunogenicity outcomes. The PPI population was the primary immunogenicity population
- Descriptive statistics were used to assess safety and immunogenicity data. For immunogenicity endpoints, mean fold change was used to evaluate differences observed between groups
- An immunogenicity dose algorithm was used to select the optimal dose for further characterization in cohort 2

## RESULTS

### Participants

- A total of 416 participants were included in the FAS (median age, 64.0 years; 54.8% female); baseline participant characteristics were balanced across vaccination groups (**Table 2**)

**TABLE 2: Baseline participant demographics**

| | ExPEC10V, low | ExPEC10V, medium | ExPEC10V, high | ExPEC10V, all | ExPEC4V | PCV13 | Total |
|---|---|---|---|---|---|---|---|
| **N** | 104 | 102 | 104 | 310 | 52 | 54 | 416 |
| **Age, mean (SD), y** | 66.2 (5.8) | 66.4 (5.2) | 65.1 (5.2) | 65.9 (5.4) | 64.8 (4.6) | 65.9 (5.4) | 65.8 (5.3) |
| Range | 60–85 | 60–82 | 60–83 | 60–85 | 60–80 | 60–83 | 60–85 |
| 60–64 years | 57 (54.8) | 48 (47.1) | 63 (60.6) | 168 (54.2) | 32 (61.5) | 29 (53.7) | 229 (55.0) |
| 65–69 years | 26 (25.0) | 27 (26.5) | 24 (23.1) | 77 (24.8) | 12 (23.1) | 12 (22.2) | 101 (24.3) |
| 70–74 years | 9 (8.7) | 20 (19.6) | 8 (7.7) | 37 (11.9) | 6 (11.5) | 9 (16.7) | 52 (12.5) |
| ≥75 years | 12 (11.5) | 7 (6.9) | 9 (8.7) | 28 (9.0) | 2 (3.8) | 4 (7.4) | 34 (8.2) |
| **Sex** | | | | | | | |
| Female | 59 (56.7) | 45 (44.1) | 65 (62.5) | 169 (54.5) | 31 (59.6) | 28 (51.9) | 228 (54.8) |
| Male | 45 (43.3) | 57 (55.9) | 39 (37.5) | 141 (45.5) | 21 (40.4) | 26 (48.1) | 188 (45.2) |
| **Race** | | | | | | | |
| White | 93 (89.4) | 91 (89.2) | 90 (86.5) | 274 (88.4) | 48 (92.3) | 50 (92.6) | 372 (89.4) |
| Black/African American | 10 (9.6) | 10 (9.8) | 13 (12.5) | 33 (10.6) | 3 (5.8) | 4 (7.4) | 40 (9.6) |
| Asian | 0 (0.0) | 0 (0.0) | 1 (1.0) | 1 (0.3) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| Native Hawaiian/Pacific Islander | 1 (1.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| American Indian/Alaska Native | 0 (0.0) | 1 (1.0) | 0 (0.0) | 1 (0.3) | 1 (1.9) | 0 (0.0) | 2 (0.5) |
| **Ethnicity** | | | | | | | |
| Not Hispanic or Latino | 85 (81.7) | 85 (83.3) | 86 (82.7) | 256 (82.6) | 46 (88.5) | 47 (87.0) | 349 (83.9) |
| Hispanic or Latino | 17 (16.3) | 15 (14.7) | 15 (14.4) | 47 (15.2) | 4 (7.7) | 7 (13.0) | 58 (13.9) |
| Not reported | 2 (1.9) | 2 (2.0) | 3 (2.9) | 7 (2.3) | 2 (3.8) | 0 (0.0) | 9 (2.2) |
| **Body mass index, kg/m², mean (SD)** | 27.8 (3.9) | 28.2 (3.6) | 27.8 (3.9) | 27.9 (3.8) | 28.0 (3.9) | 28.1 (3.9) | 28.0 (3.8) |
| Range | 19–35 | 19–35 | 19–35 | 19–35 | 21–35 | 19–35 | 19–35 |

Data presented are n (%) unless otherwise specified. Total number of participants with nonmissing data used as denominator.

**TABLE 3: Adverse events**

| Study vaccination group | ExPEC10, low | ExPEC10V, medium | ExPEC10V, high | ExPEC10V, all | ExPEC4V | PCV13 |
|---|---|---|---|---|---|---|
| **N** | 104 | 102 | 104 | 310 | 52 | 54 |
| **Solicited AEs** | 59 (56.7) | 61 (59.8) | 69 (66.3) | 189 (61.0) | 23 (44.2) | 40 (74.1) |
| **Solicited AEs of Grade 3** | 3 (2.9) | 2 (2.0) | 6 (5.8) | 11 (3.5) | 0 | 0 |
| **Solicited local AEs** | 46 (44.2) | 54 (52.9) | 60 (57.7) | 160 (51.6) | 15 (28.8) | 40 (74.1) |
| Pain/tenderness | 46 (44.2) | 52 (51.0) | 60 (57.7) | 158 (51.0) | 15 (28.8) | 39 (72.2) |
| Erythema | 11 (10.6) | 19 (18.6) | 19 (18.3) | 49 (15.8) | 1 (1.9) | 5 (9.3) |
| Swelling | 9 (8.7) | 15 (14.7) | 14 (13.5) | 38 (12.3) | 2 (3.8) | 2 (3.7) |
| **Solicited local AEs of Grade 3** | 3 (2.9) | 2 (2.0) | 4 (3.8) | 9 (2.9) | 0 | 0 |
| **Solicited systemic AEs** | 41 (39.4) | 47 (46.1) | 47 (45.2) | 135 (43.5) | 17 (32.7) | 26 (48.1) |
| Fatigue | 21 (20.2) | 29 (28.4) | 24 (23.1) | 74 (23.9) | 8 (15.4) | 13 (24.1) |
| Headache | 19 (18.3) | 25 (24.5) | 25 (24.0) | 69 (22.3) | 11 (21.2) | 10 (18.5) |
| Myalgia | 26 (25.0) | 36 (35.3) | 37 (35.6) | 99 (31.9) | 10 (19.2) | 21 (38.9) |
| Fever | 2 (1.9) | 0 (0.0) | 3 (2.9) | 5 (1.6) | 1 (1.9) | 0 (0.0) |
| Nausea | 5 (4.8) | 9 (8.8) | 11 (10.6) | 25 (8.1) | 1 (1.9) | 2 (3.7) |
| **Solicited systemic AEs of Grade 3** | 0 (0.0) | 0 (0.0) | 3 (2.9) | 3 (1.0) | 0 (0.0) | 0 (0.0) |
| **Solicited systemic AEs thought to be related to study vaccine** | 39 (37.5) | 44 (43.1) | 44 (42.3) | 127 (41.0) | 16 (30.8) | 24 (44.4) |
| **Solicited systemic AEs of at least Grade 3 thought to be related to study vaccine** | 0 (0.0) | 0 (0.0) | 3 (2.9) | 3 (1.0) | 0 (0.0) | 0 (0.0) |
| **Any unsolicited AEs[a]** | 25 (24.0) | 21 (20.6) | 23 (22.1) | 69 (22.3) | 9 (17.3) | 15 (27.8) |
| Upper respiratory tract infection | 3 (2.9) | 4 (3.9) | 1 (1.0) | 8 (2.6) | 3 (5.8) | 3 (5.6) |
| Injection site pruritis | 1 (1.0) | 5 (4.9) | 3 (2.9) | 9 (2.9) | 2 (3.8) | 1 (1.9) |
| Vaccination site erythema | 2 (1.9) | 0 (0.0) | 2 (1.9) | 4 (1.3) | 0 (0.0) | 1 (1.9) |
| Fatigue | 1 (1.0) | 1 (1.0) | 1 (1.0) | 3 (1.0) | 0 (0.0) | 0 (0.0) |
| Myalgia | 1 (1.0) | 3 (2.9) | 2 (1.9) | 6 (1.9) | 0 (0.0) | 0 (0.0) |
| Back pain | 1 (1.0) | 1 (1.0) | 0 (0.0) | 2 (0.6) | 1 (1.9) | 0 (0.0) |
| Systolic blood pressure increase | 1 (1.0) | 1 (1.0) | 1 (1.0) | 3 (1.0) | 0 (0) | 0 (0.0) |
| Diarrhea | 1 (1.0) | 0 (0.0) | 4 (3.8) | 5 (1.6) | 1 (1.9) | 0 (0.0) |
| Headache | 1 (1.0) | 1 (1.0) | 2 (1.9) | 4 (1.3) | 0 (0.0) | 0 (0.0) |
| **Any unsolicited AEs of Grade 3** | 2 (1.9) | 3 (2.9) | 2 (1.9) | 7 (2.3) | 0 (0.0) | 3 (5.6) |
| **Any unsolicited AEs of Grade 4** | 1 (1.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| **Unsolicited AEs thought to be related to study vaccine** | 5 (4.8) | 10 (9.8) | 11 (10.6) | 26 (8.4) | 3 (5.8) | 5 (9.3) |
| **SAE[b]** | 2 (1.9) | 2 (2.0) | 0 (0.0) | 4 (1.3) | 0 (0.0) | 1 (1.9) |

[a]AEs by preferred term are those occurring in at least 3 participants overall. [b]One low-dose ExPEC10V participant reported osteoarthritis (grade 2) on day 128, which resolved after 6 days. One low-dose ExPEC10V participant and 1 medium-dose ExPEC10V participant reported intervertebral disc protrusion (grade 2) on days 138 and 16, respectively, which resolved after 134 and 2 days. One medium-dose ExPEC10V participant experienced grade 3 nephrolithiasis on day 163, which resolved after 1 day. One PCV13 participant experienced grade 3 osteoarthritis on day 112, which resolved after 1 day. None of the SAEs were considered related to the study vaccine.
Data presented are n (%) unless otherwise specified. Participants are counted only once for any given event, regardless of the number of times they experienced the event. There were no solicited AEs of grade 4.

### Safety and reactogenicity

- Incidence of solicited AEs was higher in the pooled ExPEC10V groups (local, 160 [51.6%]; systemic, 135 [43.5%]) than in the ExPEC4V group (local, 15 [28.8%]; systemic, 17 [32.7%]; **Table 3**)
  - The high-dose ExPEC10V group (local, 60 [57.7%]; systemic, 47 [45.2%]) experienced a lower or similar incidence of most solicited AEs relative to the PCV13 group (local, 40 [74.1%]; systemic, 26 [48.1%])
  - Incidence of solicited local AEs was 57.7% for high-dose ExPEC10V, 52.9% for medium-dose, and 44.2% for low-dose
  - Incidence of unsolicited AEs was similar across vaccination groups (pooled ExPEC10V, 22.3%; ExPEC4V, 17.3%; PCV13, 27.8%)
- 5 SAEs, not vaccine related, were reported (**Table 3**)
- No deaths were reported

### Immunogenicity

- The ECL revealed a robust total immunoglobulin G antibody response to ExPEC10V against all vaccine serotypes on day 15 (geometric mean fold increase: low [range, 2.33–9.54]; medium [range, 2.38–10.05]; high [range, 3.06–12.31]; **Table 4**)
- Opsonophagocytic killing activity was demonstrated against all but serotype O8 (**Table 4**)
- Excluding O8, the geometric mean fold increase from baseline to day 15 on the MOPA ranged from 1.92–14.39 in low-dose ExPEC10V participants, 1.69–17.78 in medium-dose ExPEC10V participants, and 2.51–30.19 in high-dose ExPEC10V participants
- High-dose ExPEC10V was the most immunogenic and was consistently selected for further clinical development by the immunogenicity dose selection algorithm, irrespective of population (FAS vs PPI analysis set) or assay
- The MOPA immunogenicity analysis of cohort 1 showed that the O8 strain used in the assay for clinical testing was not able to discriminate a vaccine-induced immune response at baseline and day 15, necessitating additional assay optimization
- In order to expedite clinical development, serotype O8 was excluded from the MOPA assay and removed from the vaccine composition
- A reformulated 9-valent serotype vaccine, ExPEC9V, was advanced for further clinical development in a phase 3 study. The removal of O8 allowed for an increase in the O75 polysaccharide content in the ExPEC9V vaccine since O75 had the lowest ECL response

**TABLE 4: Immunogenic response to high-dose ExPEC10V on day 15**

| Serotype | Geometric mean fold increase from baseline to day 15 (95% CI) | |
|---|---|---|
| | ECL | MOPA |
| **O1A** | 5.26 (4.38–6.32) | 6.14 (4.55–8.29) |
| **O2** | 12.31 (10.56–14.33) | 30.19 (22.50–40.49) |
| **O4** | 9.17 (7.61–11.05) | 5.47 (4.17–7.18) |
| **O6A** | 5.11 (4.41–5.92) | 3.54 (2.78–4.51) |
| **O8** | 3.90 (3.36–4.53) | 1.15 (1.00–1.32) |
| **O15** | 6.20 (5.25–7.33) | 6.87 (4.73–9.98) |
| **O16** | 7.02 (5.90–8.34) | 10.18 (7.53–13.76) |
| **O18A** | 4.84 (4.13–5.68) | 6.20 (4.65–8.28) |
| **O25B** | 8.24 (6.53–10.39) | 2.51 (2.03–3.10) |
| **O75** | 3.06 (2.62–3.56) | 2.58 (1.98–3.36) |

Data presented are from the PPI analysis set. The 95% CI for the geometric mean fold increase is based on the t-distribution.


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