Randomized, Double-blind, Placebo-controlled, Multicenter Phase 3 Study to Assess the Efficacy, Safety And Immunogenicity of Vaccination With ExPEC9V in the Prevention of Invasive Extraintestinal Pathogenic Escherichia coli Disease in Adults Aged 60 Years And Older with a History of Urinary Tract Infection in the Past 2 Years

Published: 05-07-2021
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This study has been transitioned to CTIS with ID 2023-506589-30-00 check the CTIS register for the current data. The purpose of this study is to demonstrate the efficacy of 9-valentextraintestinal pathogenic Escherichia coli vaccine (ExPEC9V)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON56258

Source
ToetsingOnline

Brief title
E.mbrace (ICON #2786/0197)

Condition

- Bacterial infectious disorders

Synonym
urinary tract infection

Research involving
Human

Sponsors and support

Primary sponsor: Janssen Vaccines & Prevention B.V
Source(s) of monetary or material Support: Janssen Vaccines & Prevention B.V

Intervention

Keyword: Invasive E. Coli Disease, Urinary Tract Infection, vaccine

Outcome measures

Primary outcome

The primary analysis of the primary endpoints will evaluate:

• the number of participants with at least 1 IED event, with

microbiological confirmation in blood, other sterile sites, or urine,

caused by ExPEC serotypes O1, O2, O4, O6, O15, O16, O18, O25,

and O75 with onset at least 29 days after vaccination (from Day 30) in

the active vaccine (ExPEC9V) group compared to the placebo group in

the PPE population and

• the number of participants with at least 1 IED event with

microbiological confirmation in blood or other sterile sites, excluding IED

cases with microbiological confirmation from urine only, caused by

ExPEC serotypes O1, O2, O4, O6, O15, O16, O18, O25, and O75 with

onset at least 29 days after vaccination (from Day 30) in the active

vaccine (ExPEC9V) group compared to the placebo group in the PPE population.

Secondary outcome

Timepoint(s) of evaluation of this end point:

• First IED event , with microbiological confirmation from blood, other sterile sites, or urine, caused by ExPEC9V O serotypes O1, O2, O4, O6, O15, O16, O18, O25, and O75

•First IED event, with microbiological confirmation from blood or other sterile sites, excluding IED cases with microbiological confirmation from urine only, caused by ExPEC9V O serotypes

Secondary endpoints:

•All IEDs (including multiple IEDs per participant) caused by ExPEC9V O serotypes

• First hospitalized IED event caused by ExPEC9V O serotypes

• First IED event meeting criteria for sepsis caused by ExPEC9V O serotypes

• First bacteremic IED event caused by ExPEC9V O serotypes

• First pyelonephritis event caused by ExPEC9V O serotypes

• First UTI event caused by ExPEC9V O serotypes

• All UTIs (including multiple UTIs per participant) caused by ExPEC9V O serotypes

• First IED event caused by E. coli

• First pyelonephritis event caused by E. coli

• First UTI event caused by E. coli

• Antibody titers to vaccine O-serotype antigens in the Immunogenicity Subset, as determined by multiplex ECL-based immunoassay and multiplex opsonophagocytic killing assay (MOPA) on Day 30, Day 181, Year 1, Year 2, and Year 3

• Solicited local and systemic AEs (collected until 14 days postvaccination [from Day 1 to Day 15] in the Safety Subset)

• Unsolicited AEs (collected until 29 days post-vaccination [from Day 1 to Day 30] in all participants)

• Serious adverse events (SAEs) in all participants

• SF-36 and EQ-5D-5L responses at scheduled timepoints

• Frailty index as a measure of frailty at baseline, Year 1, Year 2, Year 3, and at the time of an IED

• Medical resource utilization for IED events

• Medical resource utilization for UTI events (Immunogenicity Subset only)

• Hospitalization and length of stay in the hospital, including ICU hospitalization and ICU length of stay, for IED, UTI or ABP events

• IED-related and all-cause mortality

Study description

Background summary

ExPEC9V is being developed based on the sponsor*s preceding clinical experience with ExPEC10V and ExPEC4V, an earlier vaccine candidate which comprised a subset of 4 of the O-antigen conjugates (O1A, O2, O6A, and O25B) also found in ExPEC9V.

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). Based on theresults from these studies, ExPEC4V was well-tolerated by the study participants and no vaccine-related safety signals were observed at doses up to 16 µg PS per serotype (O1A, O2, O6A, and O25B).

Study objective

This study has been transitioned to CTIS with ID 2023-506589-30-00 check the CTIS register for the current data.

The purpose of this study is to demonstrate the efficacy of 9-valent extraintestinal pathogenic Escherichia coli vaccine (ExPEC9V) compared to placebo in the prevention of the first invasive extraintestinal pathogenic Escherichia coli disease (IED) event caused by ExPEC9V O-serotypes.

Primary objectives:
To demonstrate in a hierarchical manner:
- the efficacy of ExPEC9V compared to placebo in the prevention of the first IED event with
microbiological confirmation from blood, other sterile sites, or urine caused by ExPEC serotypes O1, O2, O4, O6, O15, O16, O18, O25, and O75 and
- the efficacy of ExPEC9V compared to placebo in the prevention of the first IED event with microbiological confirmation from blood or other sterile sites caused by ExPEC serotypes O1, O2, O4, O6, O15, O16, O18, O25, and O75

Secondary objectives:
To demonstrate the efficacy of ExPEC9V compared to placebo in the prevention of
•all IEDs caused by ExPEC9V O-serotypes
•the first hospitalized IED event caused by ExPEC9V O-serotypes
•the first IED event meeting criteria for sepsis caused by ExPEC9V Oserotypes
•the first bacteremic IED event caused by ExPEC9V O-serotypes
•the first pyelonephritis event caused by ExPEC9V O-serotypes
•the first UTI event caused by ExPEC9V O-serotypes
•all UTIs caused by ExPEC9V O-serotypes

•the first IED event caused by E. coli
•the first pyelonephritis event caused by E. coli
•the first UTI event caused by E. coli
To evaluate:
•the immunogenicity of ExPEC9V in the Immunogenicity Subset
•the safety and reactogenicity of ExPEC9V
•the preservation of health status and health-related quality of life (HRQoL) of ExPEC9V compared to placebo
the impact of IED and UTI, caused by ExPEC9V O-serotypes, on physical and mental health, and overall HRQoL

Study design

As the mechanism of action of conjugate vaccines in the prevention of invasive disease is not expected to be affected by antibiotic resistance mechanisms, that is, resistance mechanisms are not linked to O-polysaccharide structures, the sponsor believes that IED caused by antimicrobial-resistant and susceptible O-serotypes will be prevented by the ExPEC9V vaccine. This study incorporates an inferentially seamless group sequential design. This study consists of a Screening Phase (Day 1), Vaccination Phase (Day 1) and Follow-up Phase (up to 3 years postvaccination).
The total study duration is up to 5 years and 11 months. Key safety assessments include serious adverse events (SAEs), physical examination, and vital signs.

The design of the trial is controlled, randomised and double blind, with 2 treatment arms where a placebo will be used.

Intervention

Participants will receive either a single intramuscular (IM) injection of 9-valent extraintestinal pathogenic Escherichia coli vaccine (ExPEC9V) or single IM injection of matching placebo on Day 1.

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Study burden and risks

Risks and possible side effects of vaccines in general
All types of injections can cause:
• Stinging, itching, arm discomfort, pain, soreness, redness, hardness, bruising and swelling at the site of injection
• Fever and chills
• Rash
• Itching in other areas of your body
• Aches and pains

• Muscle and joint pain
• Throwing up and nausea
• Headache
• Dizziness
• Feeling very tired

The side effects usually last 48 to 72 hours.

Feeling afraid of an injection might lead to:
• Fainting (can cause someone to fall, but study staff will make sure procedures are in place to avoid falling injuries)
• Fast breathing
• In children, throwing up, breath-holding, and rarely seizures

Rarely, people may have more severe side effects that limit their normal activities or make them go to the doctor. The subject may take medicines to help with pain and inflammation after the injection, but the subject will be asked to please report this to the study staff when taking this.

The medicinal product we are investigating can also have side effects that we do not know about at the moment.

The subject will return to the study site 1 time after the vaccination (Visit 3). Visit 3 will be about one month after Visit 1. If needed, the investigator may ask the subject to come to the study site for additional visits.
The remaining 6 visits will be via telephone calls with the study staff (Visits: 2 and 4-8). If needed, the investigator may ask the subject to come to the study site to complete these visits.

The ExPEC9V vaccine is based on the experience collected on the two earlier candidate vaccines of the same nature (ExPEC4V and ExPEC10V) that were given to people in clinical studies. So far the ExPEC9V vaccine has only been studied in test tubes and in animals. This is the first time that this vaccine is used in people. As ExPEC9V vaccine is very closely related to its earlier versions, namely to the ExPEC4V and ExPEC10V vaccines, the potential discomforts, side effects, and risks are expected to be very similar. Both ExPEC4V and ExPEC10V vaccines were well tolerated, and the observed side effects were within the expected range for vaccines in general. Most of the observed side effects started within 2 days following the vaccination. The most frequently reported side effects were: arm discomfort, pain or soreness at the site of injection, general muscle pain, headache, and fatigue (feeling tired). In some of the study participants, the side effects occurred 6 days or more after vaccination (this is called late onset). The late onset side effects mostly concerned redness, swelling or pain/tenderness at the injection site. Most of the reported side effects were mild or moderate in intensity.

Please refer to the risk sections in the IB, Protocol and ICF for more detailed

information.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Participant must be >=60 years of age on the day of signing the ICF and is expected to be available for the duration of the study, with no current intention of moving away from a study site area or travelling for periods longer than 30 consecutive days during the course of the study. -Participant must have a history of UTI in the past 2 years for which evidence of diagnosis was verified by the investigator. In case of a recent history of UTI or ABP (acute bacterial prostatitis), the condition must have resolved >14 days prior to randomization. -Participant 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. -Before randomization, participants who were born female must be either (as defined in Section 10.5, Appendix 5, Contraceptive Guidance and Collection of Pregnancy Information): a. postmenopausal or permanently sterile, and b. not intending to conceive by any methods. -Participant must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study. -Participant and his/her designated caregiver (if applicable) must be able to read, understand, and complete questionnaires in the electronic clinical outcome assessment system (eCOA, ie, the electronic patient-reported outcomes [ePROs] and the eDiary). If the participant and caregiver are unable/unwilling to work with the eCOA system to complete the ePROs, participant or caregiver must agree to be available to be contacted by the site to complete all eCOA activities (ePROs) via site-assisted interview at the timepoints specified in the protocol. Participants in the Safety Subset must be willing and able to work with the eCOA system to complete the eDiary.

-Participant must have at least one additional risk factor for invasive extraintestinal pathogenic Escherichia coli disease (IED), beyond a history of urinary tract infection (UTI) in the past 2 years. Additional risk factors for IED are defined as one or more of the following:
a. a history of urosepsis and/or E. coli bacteremia at any time prior to randomization, and/or
b. a history of inpatient hospitalization (for a medical/surgical cause) in the two years prior to randomization, and/or
c. presence at baseline of at least one risk factor for complicated UTI of any toxicity grade.

Exclusion criteria

-Participant has a serious chronic disorder or significant cognitive impairment for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise well-being) or that could prevent, limit, or confound the protocolspecified assessments. - Participant has end-stage renal disease for which dialysis is required.

- Participant has a history of malignancy within 5 years before screening that does not include the following categories: (a) Participants with curatively treated 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 diagnosis of localized prostate cancer may be enrolled at the discretion of the investigator if they completed treatment, 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 (c) Participants with a history of other malignancy within 5 years, which is considered adequately treated with minimal risk of recurrence per the investigator's judgment, may be enrolled. - Participant has a known history of severe allergic reaction, anaphylaxis or other serious adverse reactions to vaccines or vaccine excipients (including specifically the excipients of the study vaccine; refer to IB).

- 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. 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 or more of prednisone or equivalent. c. Administration of antineoplastic and immunomodulating 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. - Participant has a history of acute polyneuropathy (eg, Guillain-Barre* syndrome) or chronic inflammatory demyelinating polyneuropathy - Participant has received any E. coli or ExPEC vaccine. - Participant has received a hematopoietic stem cell transplant based on medical history, treatment with immunoglobulins within 2 months, apheresis therapies within 4 months, or blood products within 3 months prior to the planned administration of the study vaccine or has any plans to receive such treatment during the study. - Participant has received or plans to receive: (a) licensed live attenuated vaccines - within 28 days before or after planned administration of the study vaccination; (b) other licensed (not live) vaccines - within 14 days before or after planned administration of the study vaccination; (c) vaccination with a vaccine authorized for Emergency Use Authorization, conditional Marketing Authorisation or a similar program is permitted when given at least 28 days before or after planned administration of the study vaccination. - Participant has had major surgery (per the investigator's judgment) within 4 weeks before dosing or will not have recovered from surgery per the investigator's judgment at time of vaccination. - Participant has chronic active hepatitis B or hepatitis C infection based on medical history. Note: participant may have stable HBV or HCV infection. - Participant has evidence of HIV type 1 or type 2 infection by medical history. Note: participant may have stable/well-controlled HIV.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-05-2022
Enrollment:	1600
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ExPEC9V

Ethics review

Approved WMO Date:	05-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	17-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-12-2022
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	27-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-01-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-04-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-506589-30-00
EudraCT	EUCTR2020-005273-27-NL
ClinicalTrials.gov	NCT04899336
CCMO	NL77665.000.21