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Evaluation of a drinkable vaccine against enterotoxigenic E. coli diarrhoea

Submission date
29/11/2012

Recruitment status
No longer recruiting

Registration date
12/12/2012

Overall study status
Completed

Last Edited
05/03/2019

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims:
Infection with enterotoxigenic E. coli bacteria (ETEC) is a common cause of diarrhoea among children in developing countries and of travellers to such countries. However there is no vaccine available against ETEC disease. Our research team has developed a drinkable vaccine against ETEC infection which consists of killed bacteria and a protein from the bacteria. A first generation of our ETEC vaccine has been tested in several thousand people around the world. This ETEC vaccine was shown to provide some protection against ETEC diarrhoea among adult travellers but did not protect young children in developing countries. Our team has now developed a new vaccine against ETEC diarrhoea, similar to the earlier vaccine. This study assesses how effective the new vaccine is. We will monitor the health of all participants regularly throughout the study period to ensure that the new vaccine does not give rise to any side effects.

Who can participate?
Adults aged between 18 and 45 years in good health, who have not previously have been vaccinated against cholera or ETEC diarrhoea.

What does the study involve?
The vaccine will be given as a drink. Participants will be randomly divided into four different groups which will be given different combinations of vaccine or only the buffer (dummy vaccine). Participants in good health and suitable for participating in the study, will drink vaccine or buffer on two different occasions two weeks apart. Participants will visit the vaccination unit 7-8 times over a period of 7-10 weeks for physical examination (2 times), to provide blood samples (7-8 times) and faecal specimens (5-6 times). Participants will be asked to keep a diary in which they should report how they are feeling and whether they are taking any medicines throughout the study.

What are the possible benefits and risks of participating?
Participants will receive a free medical check-up, and immunized participants may develop some protection against ETEC and cholera infection. Participation will promote the development of a new vaccine, which will hopefully diminish the risk for both children and adults of developing ETEC diarrhoea in the future. Side effects are rare in adults, but if there are any they would

consist of mild diarrhoea, nausea, occasional vomiting, bloating, and abdominal pain. Any side effects are expected to be rare, and then only mild and short-lived.

Where is the study run from?
Sahlgrenska University Hospital, Gothenburg, Sweden

When is the study starting and how long is it expected to run for?
The study started in March 2012 and is due to end in March 2013.

Who is funding the study?
PATH Enteric Vaccine Initiative, USA
Sahlgrenska University Hospital, Sweden
Swedish Research Council

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2011-003228-11

Protocol serial number
OEV-121

Study information

Scientific Title

A double-blind, randomized, placebo-controlled phase I study to evaluate the safety and immunogenicity of an oral inactivated tetravalent ETEC vaccine alone and in combination with dmLT adjuvant in healthy adult volunteers

Study objectives
Enterotoxigenic E. coli (ETEC) bacteria are known to be a primary cause of diarrhoea in children in developing countries and of travellers´diarrhoea. ETEC bacteria produce heat-labile toxin (LT), heat stable toxin (ST) or both toxins and colonize the intestine by means of different colonization factors (CFs).

The aim of this study is to determine if a new ETEC vaccine, consisting of inactivated bacteria overexpressing the most prevalent colonization factors; i.e. CFA/I, CS3, CS5 and CS6, plus a hybrid of the binding subunits of LT and cholera toxin (LCTBA) administered with and without the double mutant LT adjuvant (LT(R192G/L211A)) is safe and immunogenic.

Primary study hypothesis:
1. Orally administered tetravalent ETEC vaccine (containing LCTBA), both the adjuvanted and un-adjuvanted vaccine formulations, will be safe and well-tolerated.
2. One, two or all three vaccine regimens under test will elicit immune responses in a majority of fully immunized subjects; the responses observed would be significantly higher than the responses in the placebo group to most of the five vaccine antigens tested (LTB, CFA/I, CS3, CS5, and CS6) by fecal IgA and/or ALS IgA and/or IgA ELISPOT assays.

Secondary study hypothesis:
The dmLT adjuvanted vaccine will induce stronger intestinal and/or intestine-derived and serum anti-LTB and anti-CF/CS antibody responses than the tetravalent vaccine alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Independent Ethics Committee in the Gothenburg region in Sweden, 21/11/2011, ref: 946-11
2. Western Institutional Review Board, Olympia, Washington, USA, 16/01/2012, ref: 20112026

Primary study design
Interventional

Study design
Four-armed double-blind randomized placebo-controlled phase I study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Enterotoxigenic E. coli (ETEC) diarrhoea

Interventions
Healthy adult volunteers will be given two consecutive doses of tetravalent ETEC vaccine, with or without dmLT adjuvant, or placebo (vaccine buffer alone) with 12-16 days interval. The tetravalent ETEC vaccine consists of approximately 8x10e10 formalin inactivated E. coli bacteria

that over-express the colonization factors CFA/I, CS3, CS5 and CS6 and are combined with 1 mg LCTBA hybrid protein. The vaccine will be administered with and without dmLT adjuvant (LT (R192G/L211A) in two different dosages (10 µg and 25 µg). The vaccines will be mixed with a bicarbonate buffer and administered orally. The total duration of follow up will be 42 days (40-56 days) from administration of the first vaccine dose.

The volunteers will be randomized into four different study arms:
First arm: Subjects given placebo (buffer only)
Second arm: Subjects immunized with 2 doses of Tetravalent ETEC vaccine
Third arm: Subjects immunized with 2 doses of Tetravalent vaccine + 10 µg dmLT
Fourth arm: Subjects immunized with 2 doses of Tetravalent vaccine + 25 µg dmLT

Intervention Type
Biological/Vaccine

Phase
Phase I

Primary outcome(s)
1. To evaluate the safety, reactogenicity, and tolerability of the oral tetravalent ETEC vaccine containing 4 different inactivated E. coli strains over-expressing respectively CFA/I, CS3, CS5 and CS6 and a hybrid LCTBA protein given alone and together with two different dosages of dmLT adjuvant
2. To evaluate intestinal, i.e. fecal secretory IgA (SIgA) antibody responses against CFA/I, CS3, CS5, CS6 and LTB
3. To determine intestine-derived antibody secreting cell (ALS or ELISPOT) IgA responses against CFA/I, CS3, CS5, CS6 and LTB
4. To determine adjuvant effect of dmLT at two different dose levels on vaccine immune responses compared to responses when giving vaccine alone

Key secondary outcome(s)
1. To evaluate serum antibody responses against the vaccine antigens
2. To evaluate intestinal and intestine derived immune responses against O78 LPS

The safety of the vaccines will be determined by evaluation of study diaries throughout the study period (day 0-42), by clinical chemistry and hematology tests (at screening and 7 days after each immunization) and by physical examination (at screening and on day 42). Serum and intestinal antibody responses are based on ELISA measurements of specific antibodies in sera (day 0-42) and stool (day 0-28), respectively. Intestine-derived antibody responses are based on ELISA measurements of specific antibodies secreted from cultured peripheral blood cells (using the ALS method) or on ELISPOT assay determinations of the numbers of specific antibody secreting cells (ASC) among peripheral blood mononuclear cells (day 0-21).

Completion date
31/03/2013

Eligibility

Key inclusion criteria
1. Male or female aged 18-45 years
2. Healthy constitution as established by medical history, medical examination and clinical

chemistry and haematology testing.
3. Willing and able to communicate with the investigators/physician and understand the requirements of the study
4. Give written informed consent to participate
5. Sexually active females should unless being menopausal agree to use reliable contraception as assessed by the investigator/physician, during 1 month prior to inclusion and one month after the last intake of study vaccine and should have a negative urine pregnancy test at screening and also negative urine pregnancy tests before each vaccination.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex
All

Key exclusion criteria
1. An acute or chronic medical condition that, in the opinion of the investigator/physician, would render ingestion of the investigational products unsafe or would interfere with the evaluation of responses. This includes, but is not limited to gastrointestinal diseases and autoimmune diseases.
2. Gastroenteritis within two weeks prior to vaccination
3. Antibiotic therapy within two weeks prior to the vaccination
4. Known Hepatitis A, B, C, and/or HIV infection
5. Concomitant intake of immunomodulating drugs during the study period or less than four weeks prior to the first immunization
6. Psychiatric symptoms and treatments during the last year deemed by the investigator /physician to be relevant for participation in the OEV-121 study.
7. Intends to receive any other vaccine during the study period, or within two weeks prior to trial vaccination
8. Any known hypersensitivity to any ingredient in the vaccines
9. Has received Dukoral or other ETEC or cholera vaccines
10. Brought up in ETEC-endemic areas (e.g., urban and rural areas of Central and South America, Caribbean, most countries in Asia, Africa, etc.).
11. Has travelled to ETEC-endemic areas within the last 3 years or spent > two months in ETEC endemic areas during the last 10 years
12. Intends to travel to ETEC endemic countries during the study period
13. Known or suspected history of drug, chemical or alcohol abuse, as deemed by the investigator/physician
14. Receipt of any other investigational product in the month before study entry or during the study deemed by the investigator/physician to be relevant for the OEV-121 study

15. Concomitant participation in any other clinical study deemed by the investigator/physician to be relevant for the OEV-121 study
16. Intends to donate blood at any time during the study
17. Females who are pregnant
18. Females who are nursing
19. Unable to participate in all study visits
20. Any condition or circumstance which would make the subject unsuitable for participation in the study in the opinion of the investigator/physician

Date of first enrolment
08/03/2012

Date of final enrolment
31/03/2013

Locations

Countries of recruitment
Sweden

Study participating centre
Gothenburg University Vaccine Research Institute (GUVAX)
Gothenburg
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40530

Sponsor information

Organisation
University of Gothenburg (Sweden)

ROR
https://ror.org/01tm6cn81

Funder(s)

Funder type
Research organisation

Funder Name
PATH Enteric Vaccine Initiative (USA)

Funder Name
LUA/ALF, Sahlgrenska University Hospital, Gothenburg (Sweden)

Funder Name
Swedish Research Council (Sweden)

Alternative Name(s)
Swedish Research Council, VR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Sweden

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	12/12/2014		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes