A Phase 1 Clinical Trial to Evaluate the Safety and Immunogenicity of Recombinant HIV-1 Envelope Protein ConM SOSIP.v7 gp140 Vaccine, Adjuvanted with MPLA Liposomes, in Healthy, HIV-Uninfected Adults

Published: 04-03-2019
Last updated: 10-01-2025

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Ethical review	Approved WMO
Status	Completed
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON48531

Source
ToetsingOnline

Brief title
ACTHIVE-001

Condition

- Viral infectious disorders

Synonym
HIV infection, HIV/AIDS

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: HIV, Immune response, SOSIP, Vaccine

Outcome measures

Primary outcome

1. Proportion of volunteers with a >= grade 3 adverse event, from the day of each vaccination up to 7 days post each vaccination.

2. Proportion of volunteers with >= grade 3 and/or vaccine related adverse events, including safety laboratory (biochemical, haematological) parameters, from the day of each vaccination up to 28 days post each vaccination.

3. Proportion of volunteers with vaccine-related serious adverse events throughout the study period.

Secondary outcome

1. Autologous neutralising antibodies induced by ConM SOSIP.v7 gp140 vaccine, adjuvanted in MPLA liposomes:

a. Serum titres of autologous neutralising antibodies;

b. Proportion of volunteers with autologous neutralising antibodies.

2. Trimer binding antibody responses induced by ConM SOSIP.v7 gp140 vaccine, adjuvanted in MPLA liposomes:

a. Magnitude of the trimer binding antibody response;

b. Proportion of volunteers with a trimer binding antibody response.

3. Heterologous neutralising antibodies induced by ConM SOSIP.v7 gp140 vaccine, adjuvanted in MPLA liposomes:

a. Serum titres of heterologous neutralising antibodies (i.e. against additional (Tier 1a/b, Tier 2) virus strains);

b. Proportion of volunteers with heterologous neutralising antibodies.

4. Induction of Env-specific B cell responses will be analysed and comparisons made between individuals with low, high and durable NAb titres (i.e. persistent at 12 and 18 months follow-up):

- Env-specific plasmablast repertoire sequence analysis in peripheral blood;
- Env-specific germline and memory B cell repertoire sequence analysis in peripheral blood;
- Env-specific germinal centre B cell repertoire sequence analysis in the draining lymph node(s).

Study description

Background summary

Human immunodeficiency virus (HIV) causes a global pandemic that affects nearly 37 million people and continues to spread at a rate of 1.8 million new infections annually. With currently only 21.7 million people on antiretroviral therapy (ART), a protective vaccine is crucial to reduce HIV spread and eliminate the pandemic. Given their protective capacity, a vaccine that induces neutralising antibodies (NAbs) against the HIV envelope protein (Env) would be a major step forwards. Nevertheless, the design of an effective NAb inducing vaccine has proven to be extremely challenging due to the instability and

conformational flexibility of the trimeric Env protein. However, the development of stabilised, native-like trimeric Env proteins, termed SOSIP trimers, has revolutionised the HIV vaccine field by overcoming this obstacle. The SOSIP prototype, BG505 SOSIP.664, was the first ever Env-based immunogen that consistently induced NAbs against neutralisation-resistant viruses in animals and BG505 trimer immunisation of non-human primates protected against BG505 virus acquisition. Yet, HIV-1 diversity is a major hurdle for generating broad protection by broadly neutralising antibodies (bNAbs). It is thought that consensus-based vaccines might be more amendable for driving neutralisation breadth, because consensus sequences contain less strain-specific antigenic determinants and are closer to individual viral strains than strains are to one another. Therefore, the native-like Env trimer ConM SOSIP.v7 gp140, to be used in the proposed study, was modelled after the BG505 SOSIP.664 prototype, but based on a consensus sequence of all HIV-1 isolates in group M, responsible for the global HIV epidemic. Previous nonclinical studies in rabbits and non-human primates found the ConM SOSIP.v7 gp140 vaccine to be safe. Moreover, it induced remarkably strong autologous NAb responses and elicited modest levels of cross-neutralisation. Bearing these promising results in mind, we wish to evaluate the safety and tolerability of the ConM SOSIP.v7 gp140 vaccine, adjuvanted with monophosphoryl lipid A (MPLA) liposomes, in healthy HIV-uninfected individuals, as well as to explore its immunogenic properties.

Study objective

The primary objective of this study is to evaluate the safety and tolerability of intramuscular administration of the HIV-1 envelope protein ConM SOSIP.v7 gp140 vaccine, adjuvanted with MPLA liposomes, in HIV-uninfected adults. The secondary objective is to determine the ability of the HIV-1 envelope protein ConM SOSIP.v7 gp140 vaccine, adjuvanted with MPLA liposomes, to induce humoral immune responses in HIV-uninfected adults and to characterise these responses in the systemic and lymphoid compartments.

Study design

The present study is a single centre, randomised, open-label, uncontrolled, phase 1 clinical trial, which will be conducted at the Amsterdam UMC, location AMC. Twenty volunteers will be randomised in a 1:1 ratio between two treatment groups with a different dosing regimen (See Intervention). The randomisation will be stratified for gender in order to pick up on potential differences in immunological outcomes between men and women. To account for up to 20% dropout, an over-enrolment of two volunteers per treatment arm will be permitted. Volunteers will be screened up to 70 days before the first vaccination and will be actively followed for six months after the last vaccine administration. An additional volunteer contact will occur 12 months after the last vaccination to monitor persistent immunogenicity.
Participants will undergo three intramuscular vaccinations, 18 blood samplings

by venipuncture, two leukapheresis procedures (baseline and week 10) and two axillary lymph node fine needle aspirations (FNA) (weeks 3 and 11), during 22 visits over a study period of 21 months. This includes screening and four check-ups conducted by telephone.

Intervention

Vaccination will take place at month 0, 2 and 6. Ten participants will receive 100 µg of ConM SOSIP.v7 gp140 at each time point (group A). Ten participants will receive a one-fifth fractional boosting dose of 20 µg at the third and final time point (group B). All vaccinations will be adjuvanted with 500 µg MPLA liposomes. It is thought that fractional dose boosting leads to competitive antigen binding in lymph node germinal centres, which results in selection and expansion of B cells with surface immunoglobulins showing the highest antigen affinity. To investigate this effect, the second treatment group (group B) is implemented in the vaccination schedule.

Study burden and risks

Participants will undergo three intramuscular vaccinations, 18 blood samplings by venipuncture, two leukapheresis procedures (baseline and week 10) and two axillary lymph node fine needle aspirations (FNA) (weeks 3 and 11), during 22 visits over a study period of 21 months. This includes screening and four check-ups conducted by telephone. Burden and risks can be subdivided into those potentially related to the intervention and to the sampling procedures. The combination of ConM SOSIP.v7 gp140 trimer vaccine and MPLA liposome adjuvant has been proven safe and well tolerated in nonclinical (toxicology) studies. In these studies, no serious adverse events were observed. Furthermore, thousands of individuals have been safely vaccinated with other recombinant HIV-1 envelope proteins in previous clinical studies. Finally, the MPLA adjuvant is commonly used in human vaccinations, in clinical trials as well as licensed vaccines, without safety concerns being raised. Therefore, we expect a minimum risk associated with vaccination. The burden and risks of sampling are associated with the venipunctures, lymph node FNAs and leukapheresis procedures at different time points throughout the course of the study. The procedures are considered minimally invasive and low-risk. There is no group relatedness or benefit to the participants.

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

1. Men and women, aged between 18 and 50 years on the day of screening.
2. Willing to comply with the requirements of the protocol and available for follow-up for the planned duration of the study.
3. Willing and able to give written informed consent.
4. Willing to undergo HIV testing, risk reduction counselling and receive HIV test results, including the possibility of vaccine-induced seropositivity (VISP).
5. All individuals engaging in sexual activity that could lead to pregnancy must commit to use of an effective method of contraception for four months following Investigational Medicinal Product administration.
6. All female volunteers must be willing to undergo urine pregnancy tests.
7. Willing to abstain from donating blood, eggs or sperm from the day of first vaccination until at least 3 months after the end of their participation in the trial.
8. All volunteers must be registered with a general practitioner.

Exclusion criteria

1. Confirmed HIV-1 or HIV-2 infection
2. Self-reported risk for HIV exposure or STIs prior to screening.
3. If female, pregnant or planning a pregnancy during the period of enrolment until four months after the last study vaccination; or lactating.
4. Any clinically relevant medical condition that is considered in the opinion of the investigator to make the volunteer unsuitable for participation in the study (under which underlying haematological disorders, specified infectious diseases, hyposplenia, auto-immune diseases, bleeding disorders, seizure disorders, immunodeficiency, gastrointestinal, hepatic and cardiopulmonary disorders). This also includes a history of malignancy in the past five years (prior to screening) or ongoing malignancy. (Note: A history of a completely excised malignancy that is considered cured is not an exclusion).
5. Receipt of any vaccine within 60 days of vaccination with the Investigational Medicinal Product.
6. Receipt of blood products or blood-derived products within four months of screening.
7. Participation in another clinical trial of an Investigational Medicinal Product currently, within the previous three months or expected participation during this study. Concurrent participation in an observational study, not involving medicinal products and not requiring any blood or tissue sample collection is not an exclusion criterion.
8. Prior receipt of another investigational HIV vaccine or HIV monoclonal antibody (product). (Note: receipt of placebo in a previous HIV vaccine trial will not exclude a volunteer from participation if documentation is available.)
9. Known hypersensitivity to any component of the vaccine formulation used in this trial, or severe or multiple allergies to drugs or pharmaceutical agents.
10. Positive reaction in antinuclear antibody (ANA) screen and/or subsequent anti-dsDNA assessment; or clinically significant immunoglobulin (IgA, IgG or IgM) values.
11. Use of any medications, including over-the-counter products, which, in the opinion of the investigators, would either interfere with the study or potentially cause harm to the volunteer. Use of corticosteroids, immunosuppressants, chemotherapeutics, anti-tuberculosis or other medications considered significant by the investigator within the previous six months. Specified exceptions apply.
12. Unable to read and speak Dutch or English to a fluency level adequate for the full comprehension of procedures required in participation and consent.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-11-2019
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Recombinant HIV-1 envelope protein ConM SOSIP.v7 gp140

Ethics review

Approved WMO Date:	04-03-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-10-2019

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-01-2021
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
EudraCT	EUCTR2018-003769-32-NL
ClinicalTrials.gov	NCT03961438
CCMO	NL69161.000.19

Study results

Date completed:	17-04-2023
Results posted:	14-04-2022
Actual enrolment:	24

First publication
01-01-1900