INFORMATION FOR THE PUBLIC

Vaccitech Ltd.

A Phase 1b/2, Randomised, Placebo-controlled, Dose-ranging Study to Evaluate Safety, Tolerability and Immunogenicity of a Chimpanzee Adenovirus (ChAdOx1)-vectored Multigenotype High Risk Human Papillomavirus (hrHPV) Vaccine and Modified Vaccinia Ankara (MVA)-vectored Multigenotype hrHPV Vaccine in Women with Low-grade HPV-related Cervical Lesions

European notification number
B/BE/20/BVW2

The release of genetically modified organisms (GMOs) in the environment is strictly regulated at European level by directive 2001/18/EC of 12 March 2001 repealing directive 90/220/EEC and at Belgian level by a new Royal Decree "regulating the deliberate release and/or marketing of GMOs or products that contain GMOs into the environment" repealing the Royal Decree of 18 December 1998. The transposition procedure is still ongoing for the moment.

To ensure the safe use of GMOs, the provisions of the Royal Decree above stipulate that the release of GMOs for experimental aims is prohibited without prior consent from the competent Minister. The decision is based on a thorough evaluation of the biosafety of the planned release, which is conducted by the Biosafety Advisory Council, composed of different Scientific Committees grouping independent experts from Belgian universities and governmental institutes.

To acquire the necessary authorization from the competent Minister, Vaccitech Limited submitted an application dossier to the competent authority. On the basis of the advice of the Biosafety Council, the competent minister could grant a permission to Vaccitech Limited to conduct experiments with a candidate vaccine treatment as stipulated in the application B/BE/20/BVW2

The release will take place at four hospitals in Flanders and Brussels:

Department of Gynaecology & Gynaecological Oncology
Universitair Ziekenhuis Brussel
Laarbeeklaan 101, 1090 Jette, Belgium

Center for Vaccinology (CEVAC)
Universitair Ziekenhuis Gent
Corneel Heymanslaan 10, 9000 Gent, Belgium

Department of Gynaecology & Obstetrics
Hôpital Erasme
Lenniksebaan 808, 1070 Brussel, Belgium

Department of Gynaecology & Gynaecological Oncology
Universitair Ziekenhuis Antwerpen
Wilrijkstraat 10, 2650 Edegem, Belgium

The study is expected to start on 08-Jun-2020 and to be completed on 31-Nov-2021.

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GENERAL INFORMATION

DESCRIPTION OF THE GENETICALLY MODIFIED MICRO-ORGANISM (GMM)

Introduction

In this clinical trial, two new vaccines called ChAdOx1-HPV and MVA-HPV are being tested as a possible new treatment of **H**uman **P**apilloma **V**irus (**HPV**) infection.

One injection of each vaccine is given 28 days apart.

Description of GMM

A vaccine works in a similar way to a virus – it enters a cell and stimulates the body to produce an "immune response" in the same way that the body produces an immune response to a virus.

Vaccines are often developed from viruses which are "**genetically modified"** using different engineering techniques, so that they do not cause or spread disease and instead stimulate the body (host) to produce an immune response against the disease. Genetic modification can include having pieces of genetic material removed, changed and replaced.

The vaccines ChAdOx1-HPV and MVA-HPV are, therefore, considered to be **G**enetically-**M**odified **M**icro-organsims (**GMMs**)

ChAdOx1-HPV

ChAdOx1-HPV has been designed to stimulate the body to produce an immune response to the HPV virus. It has been developed from a **Ch**impanzee **Ad**enovirus* and undergone "genetic engineering" to ensure that it cannot divide any more – it has been made "replication-incompetent". This work was carried out at the Jenner Institute at **Ox**ford University, hence the name **ChAdOx1**.

*Adenoviruses are a group of viruses that cause infections such as the common cold, flu, eye infections, tonsillits

ChAdOx1 is a "vector" or "carrier"; it then had a specifically constructed part of the HPV virus inserted into it to create the ChAdOx1-HPV vaccine. The inserted part of the HPV virus is called a "transgene" and consists of sections of HPV genetic material which ChAdOx1 effectively carries into the cell. The HPV transgene is man-made (synthetic), and has been designed so that it will trigger the body to develop an immune response against HPV, but will not cause the HPV infection.

MVA-HPV

MVA-HPV has also been designed to stimulate the body to produce an immune response to the HPV virus.

It has been developed from a **V**accinia **A**nkara virus ("pox" virus), which has been **M**odified by genetic engineering so that it cannot divide in mammals (including humans), any more – it has been made "replication-deficient". Thus, the name "**M**odified **V**accinia **A**nkara, or **MVA**. It was used as a vaccine to eradicate the smallpox virus in the 1980s.

MVA has undergone further genetic engineering at Oxford University and has also had the HPV transgene inserted into it to construct the MVA-HPV vaccine. Thus, the MVA vector carries the HPV transgene into the cell.

TYPE AND PURPOSE OF THE ENVISAGED TRIAL

This is a First-in-Human (FIH) study of treatment with ChAdOx1-HPV and MVA-HPV vaccines for HPV infection. It will be conducted in a total of 105 female participants (32 in Belgium) and the UK, aged 25-55, who have persistent HPV infection and low grade changes in the cells of their cervix – these are referred to as "cervical lesions".

The two trial vaccines have been developed to produce a strong and long-lasting immune response, notably to stimulate the body to increase the number of defence cells called 'T cells' in the blood. T-cells are known to be very important in the clearance of HPV-infection.

The main aim of the trial is to determine the safety of these two vaccines.

The study will also provide information on:

(i) The effectiveness and safety of three different doses of ChAdOx1-HPV and two different doses of MVA-HPV
(ii) How effective the vaccine treatment is at clearing the HPV infection, including the level of immune response that is stimulated, notably the production of T-cells
(iii) The effect of the vaccine treatment on the cervical lesions

The ChAdOx1 vaccine is given first (it is the "prime" vaccine), followed by the MVA-HPV ("boost" vaccine) after 28 days. Occasionally, the body can prevent some of the prime vaccine

working by producing "neutralising antibodies" against it; if this occurs with ChAdOx-HPV, the boost MVA-HPV will ensure that a sufficiently strong immune response is stimulated against the HPV infection.

Some participants in the clinical trial will receive dummy injections (placebo); this is necessary to compare the effects of the two trial vaccines against the body's own natural response to infection; about 11 participants in Belgium will receive placebo injections.

The clinical trial is being conducted at four hospital sites in Belgium. Participants will visit the hospital to receive the vaccinations and to have assessments done. As the infection does not actually cause any symptoms and the participants do not feel "ill", they do not have to stay in the hospital, but can carry on with their normal home and work lives.

RESEARCH/DEVELOPMENT ACTIVITIES

PREVIOUS DEVELOPMENT ACTIVITIES

This is the first clinical trial of these two vaccines in humans. Prior to this, studies have been conducted in animals to:

(i) Demonstrate that the effectiveness of the vaccines – studies in mice were conducted which demonstrated that ChAdOx1-HPV vaccination followed by MVA-HPV vaccination do stimulate an immune response to HIV infection

(ii) Demonstrate the safety of the vaccines – a study in mice was conducted using doses of ChAdOx1-HPV and MVA-HPV that related to the maximum doses that will be given in this FIH clinical trial; there were no significant adverse effects reported

KNOWLEDGE AND EXPERIENCE OBTAINED IN PREVIOUS DEVELOPMENT ACTIVITIES

Although no clinical trials have been conducted on ChAdOx1-HPV and MVA-HPV before, studies have been conducted using the ChAdOx1 and MVA vectors, with transgenes inserted against other diseases.

ChAdOx1 has been administered to over 200 subjects in clinical trials for malaria (EudraCT: 2017-001049-28), influenza (flu) Middle East Respiratory Syndrome (MERS), prostate cancer (EudraCT: 2017-001992-22)[1] and chikungunya (NCT03203421, NCT01818362, NCT01623518, NCT01829490, NCT03815942 and NCT02390063)[2]

MVA has been administered to in numerous clinical trials for human immunodeficiency virus (HIV), hepatitis C virus, tuberculosis, malaria, influenza and prostate cancer (Draper, 2010).

Results of these clinical trials have shown that these vaccines both induce immune responses. No serious adverse effects have been reported to the vaccines in clinical trials conducted to date.

[1]For trial registered on EudraCT visit https://www.clinicaltrialsregister.eu/ctr-search/search
[2]For trials registered on ClinicalTrials.gov (NCT) visit https://clinicaltrials.gov/

FUTURE ACTIVITIES

If the results of this clinical trial demonstrate that the vaccine treatment has suitable safety and indicate that it is effective against HPV infection, further larger clinical trials will be conducted. These are necessary to confirm the safety and effectiveness of this vaccine treatment.

These larger clinical trials will be conducted using the dose (or doses) that provides the best results in this FIH clinical trial. Participants will be included from more countries in Europe and around the world and may include both female participants and male participants (who have HPV-related lesions in other areas such as the anus). A wider age-range may also be studied.

When sufficient data has been generated, the results will be submitted to regulatory authorities in different countries; these authorities conduct a thorough assessment of the data and, if satisfied that it does demonstrate suitable safety and effectiveness, will then grant a licence for the vaccine treatment to be available for patients in their countries.

BENEFITS

It is envisaged that this FIH clinical trial will be part of a clinical development programme for a new vaccine treatment for HPV infection. Currently, this infection causes nearly all cases of cervical cancers, as well as other HPV-related cancers in the vagina, penis and anus.

Although there is now a preventative vaccine for HPV infection, not everyone receives this and it is not effective in people who have the infection. Screening programmes for cervical cancers are carried out in a number of countries and low-grade pre-cancerous lesions are removed by resection (cutting out) or cryotherapy (freezing); if cancer develops, surgery is required to remove the tumour and chemotherapy if often required following this. The World Health Organisation (WHO) stated that 311,000 women died of cervical cancer in 2018.

RISKS

As the vaccines are both GMMs, a thorough environmental risk assessment complements the standard risk assessment for clinical trials. The most important concern is:

(i) The risk that the vaccine could change so that it causes the actual disease after it is injected.

The vaccines have been genetically engineered so that they either cannot divide at all, or cannot divide in mammals, which includes humans.

The parts of the HPV virus that have been inserted into the vaccine are not those that actually cause infection.

(ii) The risk that the vaccine could be passed onto other people.

The vaccine could leak out of the injection site; however, both vaccines are given into a muscle; this is deeper than the skin, so it is unlikely that there will be any leakage afterwards.

After the vaccines are injected, there is no evidence to suggest that they will travel from the injection site to other parts of the body. Both vaccines cannot divide in humans, so will not be

able to persist long-term. However, even if the vaccines were passed out of the body in a person's breath, sweat, urine or faeces, and in the highly unlikely event that they did infect another person, that person would only be receiving a negligible amount of a potential treatment for HPV infection.

CONTAINMENT, CONTROL AND MONITORING MEASURES

CONTROL OF GMM AND GENE SPREADING

If vaccines leak outside of the injected animal or person, this is called "shedding". Neither ChAdOx1-HPV or MVA-HPV can divide in humans, so will not be able to survive for any length of time following injection. There is no evidence to suggest that either ChAdOx1-HPV or MVA-HPV travel from the site of injection, therefore, it is highly unlikely that they will be shed by any route from the injected person. Shedding from the injection site is also improbable, as the vaccines are injected into the muscle, which is deeper than the skin, so it is unlikely that any will leak out when the needle is removed. The site will be cleaned with an alcohol wipe afterwards, which will kill any vaccine that is present on the skin. It is, therefore, considered most unlikely that the vaccines will spread to other people from the participants in this clinical trial; even if they were to do so, neither vaccine virus will then be able to divide, so their ongoing survival will be extremely limited.

ChAdOx1-HPV and MVA-HPV vaccines are designed so that after they have entered cells, they do not transfer any of their genetic material to that cell.

GENETIC STABILITY OF THE GMM

ChAdOx1-HPV has been genetically engineered so that it cannot divide – it is replication-incompetent. For it to be able to change back into a virus that could divide again (revert), it would need to come into contact with the original Chimpanzee adenovirus from which it was developed. This virus only occurs in Chimpanzees which do not live in the wild in Belgium. It is, therefore, extremely unlikely that this could occur.

Even if ChAdOx1-HPV did come into contact with the original Chimpanzee adenovirus, it would be very difficult for it to become a virus that can divide (replication-competent). This is because the section of genetic material that would need to be transferred back to ChAdOx1-HPV is very large, making it highly unlikely that this would happen; furthermore, the space needed for this genetic material is now being occupied by the HPV transgene.

MVA-HPV has been genetically engineered so that it cannot divide in human or other mammalian cells. The original Vaccinia virus from which MVA was developed does not exisit anymore since small pox was eradicated and there is no other known pox virus with which MVA would be able to revert if it came into contact with it.

Both ChAdOx1-HPV and MVA-HPV vaccines do not transfer any of their genetic material to the cells that they enter. Therefore, the risk of a replication-competent cell developing which contains parts of the HPV virus is removed; furthermore, the HPV transgene is synthetic and has been constructed so that it will not cause infection i.e. it is "non-pathogenic".

When the ChAdOx1-HPV and MVA-HPV vaccines are manufactured, they are tested at different stages to ensure that none of the vaccine has become replication-competent. The tests that are carried out are widely-used and very reliable. Every batch of vaccine is tested in this way.

Destruction of GMM Containing Material

This notification is for the deliberate release of ChAdOx1-HPV and MVA-HPV in a clinical trial. The vaccines will be used for this clinical trial only. It is prohibited for them to be used for any other purpose and unused vials will be returned to the manufacturer.

All waste materials from use of the vaccines in this clinical trial will be destroyed by companys who have been specially certified for the destruction of GMM waste. This waste includes empty vials, syringes, and needles, as well as plastic gowns and disposable gloves worn by those handling the vaccines in any way.

The hospitals are equipped with biohazard containers to place these materials in before they are collected for destruction:

Soft waste bins: cartons, dressings, gowns, gloves

Sharps bins: vials, syringes, needles, dilution kits

All these biohazard containers are clearly labelled and will be transported to specified areas in the hospital for collection.

Training Requirements

All staff at the hospitals who are involved in the handling of the vaccines in any way will receive full training on the correct handling of GMM materials and will follow hospital written procedures; this will include the use of Personal Protective Equipment (PPE) which includes, gowns, gloves and eye protection. In addition, staff who will receive and store the vaccine and will be involved in preparing the doses and giving the injections to trial participants will be trained according to a Pharmacy Manual that has been prepared specifically for this clinical trial.

Emergency Situations

Any accidental exposure to the vaccines will be reported according to the hospital policy and dealt with as specified in the Pharmacy Manual and hospital procedures. Both vaccines can be killed with suitable disinfectants which will be available at the hospitals and can be used to clean up any spillages.

- Needle-stick injury: the area will be thoroughly cleaned with disinfectant
- Ingestion (mouth): the mouth will be washed thoroughly with clean water and the incident reported to the relevant doctor at the hospital; the Poisons Centre will also be contacted
- Inhalation: the person will be moved outside into the fresh air and their breathing monitored; a doctor at the study site will be contacted if any symptoms occur
- Skin/eye exposure: the area will be cleaned with the hospital eye washes; they will be flushed for at least 15 minutes; a doctor at the study site will be contacted if any symptoms occur

- Spills: the affected area will be cleared of all people and cleaned by trained staff wearing PPE and using a disinfectant; all waste will be disposed of in relevant GMM biohazard containers

OTHER CONTAINMENT, CONTROL AND MONITORING MEASURES

RESPONSIBILITIES OF THE NOTIFIER

The consent that could be given to the notifier by the competent Minister stipulates that the notifier takes complete civilian liability regarding the damage that could be caused by the deliberate release to the health of humans, animals or environment.

INSPECTION BY THE PUBLIC AUTHORITIES

Inspectors are in charge of inspecting the trials for compliance with the conditions specified in the consent and to investigate potential breaches of the consent. If mismanagement or fraud is identified, specific sanctions will be imposed.

ACTIVITY REPORT

At the end of the trial an activity report prepared by the notifier needs to be delivered to the competent authority. This activity report includes at least the following data:

- The site and period of release,
- The precise nature of the actually released GMMs,
- The aim(s) of the trial,
- The measures that were taken to prevent unwanted release of transgenic material,
- If applicable, the measure that were taken to protect the subject during administration of the GMM-containing study drug,
- If applicable, the measures that were taken to protect the relatives of the treated subjects,
- The measures that were taken to protect the workers who had to manipulate the GMM-containing material,
- The results obtained during the trial,
- An overview of the monitoring of the subjects for GMM shedding,
- An overview of the monitoring of GMM or recombinant DNA in the environment.

REFERENCES

Simon J. Draper, Sumi Biswas, Alexandra J. Spencer, Edmond J. Remarque, Stefania Capone, Mariarosaria Naddeo, Matthew D. J. Dicks, Bart W. Faber, Simone C. de Cassan, Antonella Folgori, Alfredo Nicosia, Sarah C. Gilbert and Adrian V. S. Hill. Enhancing Blood-Stage Malaria Subunit Vaccine Immunogenicity in Rhesus Macaques by Combining Adenovirus, Poxvirus, and Protein-in-Adjuvant Vaccines. J Immunol December 15, 2010, 185 (12) 7583-7595; DOI: https://doi.org/10.4049/jimmunol.1001760

GLOSSARY

Cervix	The lower part of the womb (uterus) in the female reproductive system
Gene	Material included within the central part of a cell, that provides the code for what the cell should make or do
GMM – Genetically Modified Micro-Organisms	Any organism whose genetic material has been altered using genetic engineering techniques.
Immune response	The body's response to a "foreign" entity, such as an infectious virus
Replication-deficient	Unable to divide in most cell types
Replication-incompetent	Unable to divide and therefore unable to multiply
T-cells	A type of white blood cell that take part in the body's immune response and help kill infected cells
Transgene	A gene that has been transferred by genetic engineering from an organism to a vaccine
Vaccine	A medicine that stimulates the body to produce an immune response to a disease (usually an infection)
Vector	The "carrier" part of a vaccine that transports the transgene
Virus	A small infectious organism that enters the body's cells

CONTACT

If you have any comment on the public dossier or our activities, or wish to obtain additional information on the deliberate release, please contact us at the following address:

You can also have access to a summary of the notification (SNIF) on the website of the Joint Research Centre of the European Commission (http://gmoinfo.jrc.ec.europa.eu/). Comments can be addressed to the Commission via this website.

Notifier

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