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A phase I clinical trial to investigate the safety, tolerability and efficacy of two candidate Mycobacterium avium subspecies paratuberculosis (MAP) vaccines in patients with active Crohn's disease

Submission date
24/05/2019

Recruitment status
No longer recruiting

Registration date
03/03/2020

Overall study status
Completed

Last Edited
07/02/2025

Condition category
Digestive System

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

Plain English summary of protocol

Background and study aims
Crohn's disease is a long-term condition that causes inflammation of the lining of the digestive system. There are currently at least 115,000 people living with the condition in the UK. Inflammation can affect any part of the digestive system, from the mouth to the back passage, but most commonly occurs in the last section of the small intestine (ileum) or the large intestine (colon). Common symptoms can include: diarrhoea, abdominal pain, fatigue (extreme tiredness), unintended weight loss, blood and mucus in your faeces (stools). Over time, inflammation can damage sections of the digestive system, resulting in complications such as narrowing of the intestine (stricture), or a channel developing between the end of the bowel and the skin near the anus or vagina (fistula). These problems usually require surgical treatment and health care costs are substantial. There's currently no cure for Crohn's disease, so the aim of treatment is to stop the inflammatory process and relieve symptoms (induce and maintain remission). Once symptoms are under control, further medication may be needed to help maintain this. The exact cause of Crohn's disease is unknown. However, research suggests a combination of factors may be responsible. These include: genetics, the immune system, smoking, environmental factors and previous infection.

Mycobacterium avium subspecies paratuberculosis (MAP) belongs to a class of microbes called mycobacteria which cause diseases such as tuberculosis and leprosy. The microbe can be found in the environment and is known to cause a very similar chronic bowel disease in cattle. The scientific evidence suggests it can also play an important role in the development of Crohn’s disease in humans. A vaccine against MAP could potentially lead to significant clinical improvement of Crohn’s disease.

The purpose of this study is to assess two parts of the new MAP vaccine, the initial “prime” ChAdOx2 HAV vaccine and the “boost” MVA HAV vaccine, at different doses in patients with

active Crohn’s disease. If the results from this first part of the trial show that the vaccines are safe, we will then give some patients both the “prime” ChAdOx2 HAV vaccine and the “boost” MVA HAV vaccine The study will enable us to assess the safety of the vaccines and the extent of the immune response in patients with active Crohn’s disease. We will do this by giving participants the vaccine/s in addition to doing blood tests and collecting information about any symptoms that occur after vaccination.

Who can participate?
Patients aged 18 - 50 years with Crohn's disease.

What does the study involve?
Patients will visit the Guy's Clinical Research Facility where they'll undergo a screening visit, to check they're suitable for the study. They'll consent to take part and then undergo a number of tests. If the doctor leading the study confirms the patient is eligible, meaning they're able to take part, they will return for a vaccination visit, where they'll receive one or both of the drugs under investigation. They will be carefully follow-up over several weeks, and further tests; such as blood tests, ECGs and blood pressure measurements.

What are the possible benefits and risks of participating?
Participants will not necessarily gain any direct benefit from the trial, but the information gained from the study might help to develop an effective vaccine against Crohn’s disease.
Risks:
1. Blood sample
Drawing blood may cause slight pain and occasionally bruising at the site where the needle enters. Rarely, people feel light-headed or even faint. During the course of the trial we will need to take up to 72 mL of blood (approximately 5 tablespoons) at a single visit. The total amount we will take over the period of the trial is approximately 230mL for those in groups 1 to 4 and 480mL for those in group 5, which is less than the amount taken if participants donate blood.
2. Vaccination Side Effects
It is likely that participants will experience some symptoms at the vaccination site as well as general symptoms due to vaccination. It is important to remember these are vaccines in the early stage of development and the amount of safety data available is limited. For this reason, there is a chance participants could experience a side effect that is more severe than what is described below, or that has not been seen before.
The vaccine has been previously tested in healthy human volunteers (in a phase 1 trial). The vaccine was well tolerated, with the majority of adverse events being mild or moderate in nature. The study demonstrated that the higher dose (5 x 1010 vp) is safe in healthy volunteers. We can predict from past experience what the symptoms should be like with this new vaccine. We expect that symptoms will be mild in strength most of the time, although symptoms may also be moderate or severe. All symptoms should resolve completely within a few days.
a) Local Reactions
Participants may experience some discomfort at the injection site as the vaccination is given. This usually gets better in 5 minutes. Later, participants might experience pain resulting in some difficulty moving your arm, but this should resolve within a few days. In addition to pain, participants may experience redness, swelling, or warmth at the injection site.
b) General reactions
During the first 24 - 48 hours after vaccination participants may experience flu-like symptoms such as muscle aches, joint aches, feverishness, chills, headache, nausea, tiredness and/or feeling generally unwell. Some participants might experience moderate abdominal pain. These symptoms should usually resolve within a few days.
c) Serious Reactions
With any vaccination there is a risk of rare serious adverse events, such as an allergic reaction.

These may be related to the immune system or to the nervous system. Severe allergic reactions to vaccines (anaphylaxis) are rare, but can be fatal. In case of this unlikely event, medication for treating allergic reactions is kept in the clinic room and the investigators are appropriately trained. Reactions in the nervous system are also extremely rare, but can cause an illness called Guillain-Barré syndrome. This is a condition in which people can develop severe weakness and can be fatal. These adverse events have not previously been seen following administration of the ChAdOx1 or ChadOx2 based vaccines.
With any new medicine or vaccine there is always a possibility of an unexpected side effect. Participants will be provided with the 24h study mobile number. If participants experience unexpected events or become in any way concerned participants can use this to contact one of the study doctors at any time. We will ask participants to record these symptoms too.
3. Endoscopy with biopsy samples
Biopsy samples will be taken at the time of colonoscopy. The biopsies are very small (each less than 2mm): participants will not feel the biopsies being taken, and such sampling is not associated with significant risk.

Where is the study run from?
Guy's and St Thomas' NHS Foundation Trust, UK

When is the study starting and how long is it expected to run for?
September 2019 to November 2022

Who is funding the study?
HAV Vaccines Limited, UK.

Who is the main contact?
Professor Jeremy Sanderson, jeremy.sanderson@gstt.nhs.uk

Study website
http://hav-vaccines.com/

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2018-003462-14

IRAS number
262209

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
HAV002, IRAS 262209

Study information

Scientific Title
A clinical trial to determine the safety, tolerability and immunogenicity of the candidate Mycobacterium avium subspecies paratuberculosis (MAP) vaccines ChAdOx2 HAV and MVA HAV in patients with active Crohn's disease

Acronym
HAV002

Study objectives
To assess the safety of ChAdOx2 HAV and MVA HAV in patients with active Crohn's disease administered alone and in a prime-boost regimen.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/12/2019, London - Westminster Research Ethics Committee (St Thomas' Hospital, London, SE1 7EH, UK; +44 (0)207 104 8310; nrescommittee.london-westminster@nhs.net), ref: 19/LO/1738

Study design

Open-label dose escalation heterologous prime-boost study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Crohn's disease

Interventions
This is a phase I open-label dose escalation study to assess the safety and immunogenicity of the candidate Mycobacterium avium subspecies paratuberculosis (MAP) vaccine, ChAdOx2 HAV in patients with active Crohn’s disease aged 18-50.

Participants will be enrolled and doses will be escalated according to a study plan. The duration of participation will be 20 weeks.

Further information on the study plan has been omitted to preserve blinding.

Intervention Type
Biological/Vaccine

Phase
Phase I

Drug/device/biological/vaccine name(s)
1. ChAdOx2 HAV 2. MVA HAV

Primary outcome measure
1. Occurrence of solicited local reactogenicity signs and symptoms for 7 days following the vaccination
2. Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following the vaccination
3. Occurrence of unsolicited adverse events for 28 days following the vaccination
4. Change from baseline for safety laboratory measures
5. Occurrence of serious adverse events during the whole study duration

Secondary outcome measures

1. ELISPOT to enumerate IFN-γ producing T cells. (Other exploratory immunology may be carried out in collaboration with other specialist laboratories. This would involve the transfer of serum /plasma and/or peripheral blood mononuclear cells (PBMC), but samples would be anonymised. Participants will be consented for this.)
2. Sampling of exploratory immunology responses: 50-60ml of whole blood will be taken at baseline and days 28 and 56 (groups 1 – 4) and additionally on days 14, 70, 84 and 112 (group 5 only) of the study for use in assays to measure immune responses of various types to the vaccine.
3. Assessment of clinical response
All participants will undergo an evaluation of Crohn's disease activity at screening and at day 56 for groups 1 – 4. Group 5 will undergo an evaluation of Crohn's disease activity at screening, on day 56 and again on day 112. Endoscopic scoring by flexible sigmoidoscopy or colonoscopy will be undertaken by the CD-SES (simple endoscopic score) at the baseline and follow up at day 112.

Overall study start date
01/08/2019

Completion date
19/11/2022

Eligibility

Key inclusion criteria
1. Age 18 to 50 years.
2. Confirmed diagnosis of Crohn's disease diagnosed according to standard clinical, endoscopic, radiological or histological criteria.
3. Mild to moderately active Crohn's inflammation as defined by one or more of a raised CRP >10mg/L, faecal calprotectin >150 and a CDAI >150 but <320.
4. Active Crohn's inflammation in at least one segment of ileum or colon on colonoscopy or flexible sigmoidoscopy.
5. No immunomodulatory treatment (thiopurines, methotrexate, tacrolimus, anti-TNFalpha antibody therapy, anti-alpha4beta7 antibody therapy, anti-p40 antibody therapy) currently or within the last 3 months.
6. Able to comply with all study requirements.
7. For females only, willingness to practice continuous effective contraception (see below) during the study and a negative pregnancy test on the day(s) of screening and vaccination.
8. Agreement to refrain from blood donation during the course of the study.
9. Provide written informed consent.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
50 Years

Sex
Both

Target number of participants
28

Total final enrolment
28

Key exclusion criteria
Current exclusion criteria as of 18/11/2021:

1. Participation in another research study involving receipt of an investigational product in the 30 days preceding enrolment, or planned use during the study period.
2. Prior receipt of an investigational vaccine likely to impact on interpretation of the trial data.
3. Prior receipt of an adenoviral vectored vaccine in the last 28 days.
4. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate.
5. Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; recurrent, severe infections.
6. Any immunosuppressive medication currently or within the preceding 3 months including corticosteroids (except inhaled steroid or topical steroid), thiopurines, methotrexate, tacrolimus and any biological therapy.
7. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine (e.g. Egg allergy)
8. Any history of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
9. Any history of anaphylaxis in relation to vaccination.
10. Unable to provide written informed consent.
11. Pregnancy, lactation or willingness/intention to become pregnant during the study.
12. History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
13. History of serious psychiatric condition likely to affect participation in the study.
14. Bleeding disorder (e.g. Factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.
15. Any other serious chronic illness requiring hospital specialist supervision.
16. Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units every week.
17. Suspected or known injecting drug abuse in the 5 years preceding enrolment.
18. Seropositive for hepatitis C (antibodies to HCV).
19. Seropositive for hepatitis B surface antigen (HBsAg).
20. Any clinically significant abnormal finding on screening biochemistry or hematology blood tests or urinalysis.
21. Any other significant disease, disorder or finding which may significantly increase the risk to the participant

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Previous exclusion criteria:

1. Participation in another research study involving receipt of an investigational product in the 30 days preceding enrolment, or planned use during the study period.
2. Prior receipt of an investigational vaccine likely to impact on interpretation of the trial data.

3. Prior receipt of an adenoviral vectored vaccine in the last 12 months.
4. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate.
5. Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; recurrent, severe infections.
6. Any immunosuppressive medication currently or within the preceding 3 months including corticosteroids (except inhaled steroid or topical steroid), thiopurines, methotrexate, tacrolimus and any biological therapy.
7. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine (e.g. Egg allergy)
8. Any history of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
9. Any history of anaphylaxis in relation to vaccination.
10. Unable to provide written informed consent.
11. Pregnancy, lactation or willingness/intention to become pregnant during the study.
12. History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
13. History of serious psychiatric condition likely to affect participation in the study.
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Date of first enrolment
04/05/2021

Date of final enrolment
30/04/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
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Sponsor information

Organisation
HAV Vaccines Limited

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Sponsor type
Industry

Website
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Funder(s)

Funder type
Industry

Funder Name
HAV Vaccines Limited

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
31/12/2024

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 6.1	25/05/2022	27/12/2023	No	No
Statistical Analysis Plan	version 2.0	20/11/2020	27/12/2023	No	No
Results article		07/02/2025	07/02/2025	Yes	No