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Gene therapy for a rare disorder caused by an enzyme deficiency

Submission date
14/09/2023

Recruitment status
No longer recruiting

Registration date
13/10/2023

Overall study status
Ongoing

Last Edited
06/12/2023

Condition category
Nutritional, Metabolic, Endocrine

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Ornithine transcarbamylase deficiency (OTCD) is an inherited metabolic liver disease which means that the body cannot maintain normal levels of ammonia. Ammonia levels can rise (called hyperammonaemic decompensations) which can be life-threatening and may result in impaired neurological development in children. OTCD is a rare genetic disorder characterised by complete or partial lack of the enzyme ornithine transcarbamylase (OTC). OTC is a key enzyme of the urea cycle, which is how the liver breaks down and removes extra nitrogen from the body. For people with OTCD, the extra nitrogen builds up in the form of excess ammonia (hyperammonemia) in the blood. The HORACE study is testing a new gene therapy (AAVLK03hOTC) which specifically targets the liver so that it can start making the OTC enzyme. It is hoped that a single infusion of gene therapy for children with OTCD could help the liver work normally and reduce hyperammonaemic decompensations and their associated risks. This gene therapy treatment could serve as a 'bridge-to-transplant' where children could grow up in a metabolically stable condition until a liver transplant is possible. This could minimise long-term neurological damage caused by hyperammonaemic decompensations. The purpose of this study is to find out if the new gene therapy AAVLK03hOTC is safe and effective for children with OTCD.

Who can participate?
Patients aged under 16 years old who have a confirmed diagnosis of severe OTCD

What does the study involve?
The gene therapy will be given to the child at Great Ormond Street Hospital (GOSH). The child may be admitted at GOSH the day before they receive the gene therapy if the child is not already admitted. The child will start a course of steroids which will be tablets that are taken for one month, gradually reducing in dose.
In addition, if the child is a girl who has started her period, she will need to give a urine sample to check she is not pregnant. In the event the child is pregnant she would not be able to take part in this study due to unknown risks posed by the gene therapy to an unborn baby or a breastfeeding child.

The gene therapy will be given to the child by infusion into a vein. The infusion will take approximately 2 hours. The child will be monitored continuously by the study doctors while the

gene therapy is given. The child will continue to be closely monitored for 48 hours after receiving the infusion. The child will need to provide blood, urine, stool and saliva samples 3 times during the 48-hour monitoring period. The maximum blood volume to be taken will be 20mL.

After 48 hours, the GOSH study team will meet with the family/guardian and the child and decide if they are able to return home. The child will then have 23 more study appointments during the first 12 months of the study to assess the safety and efficacy of the gene therapy. At each appointment, the child will need to provide blood samples.

The length of time for study appointments will vary. Visits will be tailored to meet the needs of the child and to include an appropriate number of breaks. The appointments at GOSH will take longer as more tests need to be completed.

After the gene therapy infusion, the 7 study follow-up appointments at GOSH will take place on 6, 12, 18, 26, 34, 42 and 52 weeks. They will be asked to complete a diet diary and patient diary for the child prior to each appointment at GOSH. At some appointments at GOSH, the child will also need to provide urine, stool and saliva samples.

At the 52-week appointment at GOSH (1 year after the gene therapy infusion), the child will need to repeat some of the tests they completed at the baseline visit to help us see if the gene therapy has had an effect. These will include:
• Electrocardiogram (ECG) to check the child's heart
• Questionnaires and tasks
• Blood, urine, stool, and saliva samples taken
• Ureagenesis testing (explained below)
• Liver biopsy (only if the child is well)

The child has lots of appointments during the first 12 months of follow-up. After this, the study appointments become less intensive. The child will need to join a separate trial so they can be followed up for 4 more years. During these 4 years, the child will be seen every 6 months, and all appointments will be at GOSH.

What are the possible benefits and risks of participating?
It is hoped that participation in this clinical study may be beneficial for the child. If the gene therapy is safe and effective, it is possible that the child may be able to increase the protein in their diet and reduce the number of ammonia-scavenging drugs they take. The results generated by this study may help to improve the treatment options for children with OTCD, but the child may not benefit directly from their participation in the study.

However, there is no promise that this study will help the child. This gene therapy has not been given to people before so we do not know if it will work, or which dose is safe and effective. All medical procedures involve the risk of harm, but this is usually a low risk. As this study involves a new gene therapy, there might be risks associated with this study that we do not yet know about. Information on the main risks related to the gene therapy and procedures carried out in this study are listed below.

Blood tests:
This study requires blood samples to be given at each visit. The amount of blood required varies depending on the number of tests being completed but is a relatively small amount. Usually, no

more than 4 teaspoons (20mls) are required, although at some visits a little more is taken. Taking blood can be uncomfortable, but rarely results in any serious problems. Reported side effects include feeling light-headed or faint, bruising and/or discomfort at the site of infusion.

Infusion of gene therapy:
Intravenous infusions can be uncomfortable and side effects may include feeling light-headed or faint, bruising and/or discomfort at the site of infusion.
There may be risks associated with the gene therapy itself. This study is the first time this gene therapy has been given to humans, so we cannot be sure of the risk of the introduced gene being transmitted to the child's potential future children.

Inflammation caused by the infusion:
The infusion consists of a modified virus called adeno-associated virus (AAV) which has been designed to deliver the LK03 gene to the liver to produce OTC. The virus causes no known disease in humans and has been modified so that it cannot cause an infection. There is a small possibility that the vector may cause liver inflammation or hepatitis, but we consider this unlikely to be severe or long-lasting and expect it to respond to medication. To minimise any risk of inflammation the child will be given steroid tablets 1 day before the infusion. The child will continue to take these for one month. Steroids can cause a range of side effects including diabetes and high blood pressure. The study team will monitor the child for signs of these by measuring blood pressure, blood sugar, kidney function and liver function.

Tumour Formation:
There is a theoretical possibility that the new gene might interfere with the activity of other genes, and the child could develop a tumour. Routine monitoring should identify this remote possibility at an early stage so it can be managed.

Virus spread to other sites in the body:
Tiny amounts of the vector may spread to other parts of the body. Although the vector has been designed to deliver the gene therapy to the liver, the risk of spreading elsewhere is very small. Gene therapies are complex treatments and some of the risks can be difficult to understand. The study doctor at GOSH will discuss these with parents/guardians at the baseline visit to make sure they understand them before they give consent for their child to take part.

Ureagenesis:
Ureagenesis studies will measure the child's body's ability to make urea, which is reduced in OTC deficiency. It is a measure of how effective the gene therapy is.
The child will be asked to fast for 2-4 hours and then swallow a liquid. The liquid is labelled sodium acetate (vinegar) marked with a 13C isotope. If the child is unable to swallow the liquid a nasogastric tube might be inserted A nasogastric tube is a tube that carries food and medicine to the stomach through the nose. An x-ray will be needed to check its positioning. The child will give blood samples as part of this test to help us see how well the child's liver produces urea. The child will be asked to repeat this after 48 hours.

Liver biopsy:
A liver biopsy involves taking a small sample of the child's liver. This will be done under a general anaesthetic and may require the child to stay overnight in the hospital. A liver biopsy will only be taken if the child is well. This would also be done again at the 12-week point of the trial for patients under 18 months of age.
Common side effects of general anaesthetic include feeling sick, vomiting, dizziness, shivering or feeling cold. There are also rare but more serious risks including an allergic reaction to the anaesthetic drugs, waking up during the operation, or death but this is all extremely rare.

Insertion of central line:
If it is difficult for doctors to insert a needle into the veins of a child's arm, the study doctors may advise that a central line be inserted into one of the central veins, which will be discussed by the study doctor. A central line needs to be inserted under general anaesthesia (the risks of this are mentioned previously). The central line may be inserted in the child's arm, neck, or chest depending on which would be most suitable. An X-ray is required for the insertion of the central line. A central line stays in place for a few weeks which means the study doctors can take blood samples from the child without needing to use a needle.

Where is the study run from?
University College London (UCL) (UK)

When is the study starting and how long is it expected to run for?
October 2020 to June 2027

Who is funding the study?
Bloomsbury Genetic Therapies (BGTx) (UK)

Who is the main contact?
cctu.horace@ucl.ac.uk (UK)

Contact information

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Principal investigator

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05092685

Clinical Trials Information System (CTIS)
2020-005342-41

Integrated Research Application System (IRAS)
1003541

Protocol serial number
18/0123

Study information

Scientific Title
HORACE (Halting Ornithine transcarbamylase deficiency with Recombinant AAV in ChildrEn). Phase I/II prospective open-label, multicentre, dose-finding clinical trial to assess the safety and efficacy of AAVLK03hOTC for paediatric patients with ornithine transcarbamylase deficiency

Acronym
HORACE

Study objectives
The primary objective will be to assess safety of increasing dose levels of AAVLK03hOTC in paediatric patients with ornithine transcarbamylase deficiency up to 12 months after infusion.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/05/2023, South Central - Oxford A Research Ethics Committee (Ground Floor, Temple Quay House, 2 The Square, Bristol, BS1 6PN, United Kingdom; +44 (0)207 1048171, (0) 207 104 8141, (0)207 104 8272; oxforda.rec@hra.nhs.uk), ref: 23/SC/0018

Primary study design
Interventional

Study design
Phase I/II prospective open-label multicentre dose-finding clinical trial

Study type(s)
Safety

Health condition(s) or problem(s) studied
Ornithine transcarbamylase deficiency

Interventions
HORACE is a trial with a peripheral intravenous infusion of AAVLK03hOTC in three groups with dose escalation from 6x1011vg/kg (low dose), 2x1012vg/kg (intermediate dose) to 6x1012vg/kg (high dose). There is a dose expansion in a fourth group with the most appropriate safety: efficacy ratio.

Intervention Type
Genetic

Primary outcome(s)
Incidence of adverse events (AEs), treatment-related adverse events and serious adverse events (SAEs) for each dosing group during the 12 months post-infusion measured using the study CRF and assessed by severity and relationship to the study product.

Key secondary outcome(s)
Safety:
1. Change from baseline level of transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) at each visit until 52 weeks.
2. Change from baseline level of humoral and cellular immune responses at day 15, and week 4, 12, 26, and 52 post-infusion against the AAV-LK03 capsid.
3. Change from baseline level of cellular immune responses at day 15, and week 4, 12, 26, and 52 post-infusion against hOTC.
4. Viral shedding: plasma, saliva, urine, stool samples at baseline, 6, 24, 48 hours post-infusion, days 10 and 15, and 3, 4, 12, 26 and 52 weeks post-infusion.

Efficacy:
Clinical parameters:
1. Monitoring of number and frequency of hyperammonaemic episodes (NH3>100µM) and hospitalisations.
2. Monitoring of daily protein allowance and number of ammonia scavenger drugs.

Biological parameters:
1. Change from baseline levels of glutamine, glutamate, arginine and citrulline at 6, 12, 26 and 52

weeks post-infusion.
2. Change from baseline levels of ammonaemia pre and post-prandial at 6, 12, 26 and 52 weeks post-infusion.
3. Change from baseline levels of urine orotic acid at 6, 12, 18, 26, 34, 42 and 52 weeks post-infusion.

Functional parameters:
Change from baseline rate of ureagenesis rate at 12 and 52 weeks post-infusion.

Completion date
01/06/2027

Eligibility

Key inclusion criteria
1. Patient (male or female) aged ≤16 years old at the time of written informed consent. For the dose escalation phase patients must be aged 6-16 years, for the dose expansion phase patients must be aged 0-16 years (at the time of written informed consent).
2. OTC deficiency confirmed via enzymatic or molecular analysis. This may include the identification of pathogenic mutations or liver OTC activity that is <20% of normal activity.
3. Patient has severe disease defined by reduced protein allowance and is prescribed at least one ammonia scavenger drug
4. Patient (if capable of signing) and parent or legal representative have signed a written informed consent form
5. Females of childbearing potential must have a negative pregnancy test in serum or urine at the screening and day 0 infusion visits, and use a highly effective contraception method from the screening visit until 4 weeks after the first negative plasma sample monitoring vector genomes copies or the week 52 visit, whichever comes first
6. Sexually active boys must use an adequate contraception method (abstinence or use of condom with spermicide) from at least 14 days prior to the infusion and until 4 weeks after the first negative plasma sample monitoring vector genomes copies or the week 52 visit, whichever comes first
7. Patient’s ammonia level at the baseline visit (pre-gene therapy infusion) is <100 mol/L and is within the range of historical ammonia levels obtained when the patient was clinically stable
8. Patient has been on a stable dose of ammonia scavenger and stable protein allowance for the last 4 weeks at the baseline visit
9. Patient is willing to commit to an additional 4 years of long-term safety follow-up on a separate trial following the first 52 weeks of the HORACE trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
0 Months

Upper age limit
16 Years

Sex
All

Key exclusion criteria
1. Titres of the neutralising antibodies against AAV-LK03 >1:40 serum dilution
2. Significant hepatic inflammation as evidenced by the following laboratory abnormalities: alanine aminotransferase or aspartate aminotransferase or bilirubin >2 x upper limit of normal (ULN), alkaline phosphatase >3 x ULN
3. Evidence of severe unexplained liver disease (unexplained by OTC deficiency) including but not limited to liver malignancy, liver cirrhosis, or acute liver failure
4. Evidence of active hepatitis B or C virus (HBV and HCV respectively) documented by hepatitis B surface antigen (HBsAg) or HCV RNA positivity
5. Positive PCR for human immunodeficiency virus (HIV)
6. Liver transplant including hepatocytes/cells infusion
7. Current participation in another clinical trial of an investigational medicinal product or medical device, or participation within the previous 12 months
8. Patient has contraindications to sodium (1,2-13C2) acetate or immunosuppression including prednisolone
9. Active infection (bacterial or viral)
10. Pregnant or breastfeeding females
11. Patients with other serious underlying medical conditions including malignancy and severe (≥ grade 3) functional organ impairment (liver, kidney, respiratory) according to CTCAE v5.0. For neurological symptoms considered as sequelae of previous hyperammonaemic decompensation and which are considered stable (i.e. not evolving), a grade 3 will be acceptable. Grades 4 and 5 will preclude inclusion
12. Patients with any other significant condition or disability that, in the investigator's opinion, may interfere with the patient’s optimal participation in the study

Date of first enrolment
01/10/2023

Date of final enrolment
01/04/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Great Ormond Street Hospital
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
University of London

ROR
https://ror.org/04cw6st05

Funder(s)

Funder type
Industry

Funder Name
Bloomsbury Genetic Therapies (BGTx)

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository, www.openclinica.com. After completion of the trial, the database will be retained on the servers of UCL for ongoing analysis of secondary outcomes. All data storage will adhere to the UK Data Protection Act 2018 and the General Data Protection Regulation (GDPR).

Pseudonymised patient data will be stored with full data encryption at rest and in transit. Requests for access should be made via email to: CCTU.HORACE@ucl.ac.uk. Data will be available for as long as the trial is open. Consent from participants was required and obtained.

IPD sharing plan summary

Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes