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A trial investigating the safety of thymus-derived regulatory T cell treatment for the prevention of cardiac allograft vasculopathy in children receiving heart transplant

Submission date 20/09/2024	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 20/12/2024	**Overall study status** Ongoing	
Last Edited 10/06/2025	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Heart transplantation is a lifesaving procedure for some children. The long-term success of heart transplants is often limited by inflammatory processes leading to progressive narrowing of blood vessels that supply oxygen to the heart, known as Cardiac Allograft Vasculopathy (CAV). CAV is a leading cause of death and allograft loss in paediatric cardiac transplantation. Once established, CAV is refractory to conventional medical or surgical approaches and constitutes the most important predictor for all-cause mortality in this patient population. No effective treatments are available for established CAV. Furthermore, the incidence of CAV in children has not declined over time. Therefore, prevention of CAV (the main cause of graft damage) remains an unmet goal. Regulatory T cells (Tregs), a subset of CD4+ T cells, are essential for immune homeostasis and are critical mediators of immunological tolerance. Cell therapy with regulatory T cells shows promise as a treatment to generate immune tolerance and improve outcomes for patients in different therapeutic areas. We believe that adoptive Treg therapy can prevent CAV in paediatric heart transplant recipients.

Who can participate?
children receiving heart transplants for CAV

What does the study involve?
Participants will be recruited at Great Ormond Street Hospital and be seen for three years during the study. The process involves removing the thymus during heart transplantation or during the time of having a pump assist device fitted in (which occurs before the transplant), transferring it to a facility for Treg isolation, expansion and cryopreservation for therapeutic administration at 3-6 months post-transplantation. Three patients will be treated with the first low dose of 1-3 x 10^6Tregs/kg and if well tolerated a further three with the second higher dose of 5-10 x 10^6Tregs/kg. An additional three patients will be enrolled at the highest tolerated dose.

What are the possible benefits and risks of participating?
The medicine (TR006) that is given may protect a transplanted heart from CAV, however we do not know this for certain. Patients may not benefit from taking part in this study but the information gained may improve the treatment options available to other children receiving a new heart in the future to help prevent CAV.

If patients decide to take part in this study, most of the check-ups will happen at the same time as their usual medical appointments with the Transplant Team at GOSH. There will be a few extra times where study participants have to come to the hospital for research-related visits.

This is the first time that TR006 will be tested in children in the UK. So, there may be risks we do not know about yet and they could be serious.

We think the risks of TR006 are similar to those seen if someone has an allergic reaction to a blood transfusion. An allergic reaction can occur when somebody's immune system overreacts to a certain substance.

Because TR006 is made from the child's own cells, the risk of such a reaction is less likely compared to a reaction from blood transfusion (when blood is collected from other people or blood 'donors'). Reactions to blood transfusions are uncommon but they can look like: itchy skin, swelling of hands, arms, feet, ankles and legs, dizziness and headaches, high temperature, chills or shivering.

Blood tests will mainly be used as part of the participant's normal medical care and are important to check that everything is OK with the patients who take part in the study. They can be a bit uncomfortable and can cause some bruising or itching, but this is mild. Inserting the plastic straw (or cannula) in the patient's arm before giving TR006 can feel similar to a blood test and can hurt a little. Numbing cream or spray can be given to help with this.

The study team will ask participants to give some extra blood samples which will be taken at the same time as their usual medical blood tests. These extra blood samples are for the study team to look at and they will give us information of how a patient's body is built, and how it reacts to treatment with TR006.

As part of the patient's normal medical care after transplant, the medical team will collect small samples of the new heart to make sure things are going OK after the heart transplant. This is called a cardiac biopsy and this is usually done whilst the patient is asleep (under general anaesthetic). The process used to collect these heart tissues samples is considered low-risk but some of the risks may include: bruising, bleeding, damage to blood vessels or the heart.

The study team may use some of these heart samples to look at the participant's heart and to also see how it reacts to treatment with TR006.

Coronary angiograms and X-ray-guided cardiac biopsies are part of normal care. If a patient takes part in this study, they will not undergo any additional angiograms or biopsies. These procedures use ionising radiation to form images of the body and provide the doctor with other medical information. Ionising radiation may cause cancer many years or decades after the exposure. The chances of this happening to study participants are the same whether they take part in this study or not.

Where is the study run from?
Great Ormond Street Hospital

When is the study starting and how long is it expected to run for?
September 2024 to June 2030

Who is funding the study?
British Heart Foundation

Who is the main contact?
Prof Michael Burch, michael.burch@gosh.nhs.uk

Contact information

Type(s)
Public, Principal Investigator

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1008875

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
23HL27

Study information

Scientific Title
A single ascending dose trial investigating the safety and feasibility of autologous thymus derived regulatory T cell (Tregs) treatment for the prevention of cardiac allograft vasculopathy in children receiving heart transplant

Acronym
ATT-Heart

Study objectives
- To determine the safety and optimal tolerated dose of expanded autologous thymus-derived Tregs to prevent CAV in paediatric heart transplant patients in a Phase I study.

- To assess the feasibility of generating expanded autologous thymus-derived Tregs in the Good Manufacturing Practice facility.
- To investigate the clinical and immunological responses to autologous thymic Tregs in paediatric heart transplant patients.
- To assess the feasibility of retaining participants for the duration of the study and completion of study visits and assessments.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 17/12/2024, South Central - Oxford A Research Ethics Committee (Ground Floor, Temple Quay, House 2, The Square , Bristol, BS1 6PN, United Kingdom; +44 (0)207 104 8118; oxforda.rec@hra.nhs.uk), ref: 24/SC/0333

Study design
Single-ascending-dose trial

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital, Medical and other records

Study type(s)
Safety, Efficacy

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Cardiac allograft vasculopathy (CAV)

Interventions
Autologous thymus-derived Tregs (TR006) infused at one of two doses (in a 3+3 design):
1. Low dose: 1 - 3 x 106 Tregs/Kg

or
2. High (and highest) dose: 5 - 10 x 106 Tregs/Kg

Intervention Type
Biological/Vaccine

Pharmaceutical study type(s)
Pharmacokinetic, Pharmacodynamic, Dose response, Prophylaxis

Phase
Phase I

Drug/device/biological/vaccine name(s)
TR006 thymic regulatory T cell (Treg) product derived from autologous T cells defined as CD4+CD25+ T cells which are FOXP3 positive

Primary outcome measure
The safety and optimal tolerated dose of TR006 to prevent CAV in paediatric heart transplant patients measured using the occurrence and nature of Dose-Limiting Toxicities (DLTs) occurring within 4 weeks post-infusion of the expanded autologous thymus-derived Treg product (ATIMP)

Secondary outcome measures
Secondary outcome measures:
1. To assess the feasibility of generating TR006 in the Good Manufacturing Practice facility is measured using the amount of TR006 manufactured per patient
2. To investigate the clinical and immunological responses to TR006 in paediatric heart transplant patients is measured using the amount of TR006 manufactured per patient

Assessment of Immunological Response:
1. Frequency of circulating leukocyte subsets
2. Quantity of alloantigen-specific conventional T cells, Tregs and CD8+
3. The presence of anti-HLA is used to evaluate tissue infiltrating cells

Assessment of clinical response:
1. Diagnosis of CAV as measured by coronary angiography within 24 months post-infusion of TR006
2. Graft loss as measured by inclusion of patient on the re-transplant waiting list through rejection (acute or chronic) within 24 months post-infusion of TR006
3. Recipient mortality within 24 months post-infusion of TR006
4. Acute graft rejection as measured by endomyocardial biopsy (EMB) within 24 months post-infusion of TR006
5. Antibody-mediated rejection as measured by the development of donor-specific antibodies within 24 months post-infusion of TR006
6. Infection-related rehospitalisation events within 24 months post-infusion of TR006

7. (Cardiac function) Left ventricular ejection fraction measured by echocardiography monthly for 12 months and 24 months post-infusion of TR006
8. (Renal function) Mean calculated GFR at 24 months post-infusion of TR006
9. Description of non-DLT adverse events and those occurring beyond week 4 and up to 24 months post-infusion of TR006
10. Immunosuppressive doses at 12 and 24 months post-infusion of TR006

Additional measures:
The feasibility of retaining participants for the duration of the study and completion of study visits and assessments was measured using the number of study visits completed per participant and responses to items in questionnaires or surveys exploring the study and treatment experience of the participants and their parents/guardians

Overall study start date
18/09/2024

Completion date
30/06/2030

Eligibility

Key inclusion criteria
1. Male or female children aged between 0.5 and 16 (inclusive) years of age at the date of consent/assent and date of transplant
2. Written informed consent obtained from a parent/legal guardian
3. Registered on the heart transplant list at the date of consent and received a heart transplant on enrolment
4. Receiving a single transplanted organ
5. Willing and able to comply with the study visit schedule

Participant type(s)
Patient

Age group
Child

Lower age limit
6 Months

Upper age limit
16 Years

Sex
Both

Target number of participants
9

Key exclusion criteria

1. Active viral infection (with HIV, hepatitis B, hepatitis C and syphilis) at date of admission for transplant
2. Age under 0.5 year or over 16 years at date of consent and at date of transplant
3. Multi-organ transplant
4. Highly sensitive patients at high risk of rejection assessed by HLA antibody measurement
5. Allergy to any component / excipients used for the manufacture of TR006
6. Previous recipient of any organ transplant
7. History of previous sternotomy surgical procedure for congenital heart defect during which has had previous partial or full thymectomy
8. Confirmed diagnosis of DiGeorge Syndrome with absent thymus
9. Participation in another interventional Clinical Trial of Investigational Medicinal Product during the study or within 28 days prior to date of transplant (at the Chief Investigator's discretion)
10. Pregnant and lactating patients (females of childbearing potential* with a positive urine pregnancy test at date of transplant)
11. Female patients of childbearing potential* who are not willing to use a highly effective method of contraception** for the duration of the trial (defined as from date of transplant to 12 months post Treg infusion) to prevent pregnancy, or abstain from heterosexual activity

*Females of child-bearing potential are females who have experienced menarche and are not surgically sterilised (e.g., hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or post-menopausal. Postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

** Highly effective methods of contraception are those with a failure rate of < 1% per year when employed consistently and correctly. For example:
• Combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral, intravaginal, transdermal.
• Transdermal progestogen-only hormonal contraception associated with inhibition of ovulation – oral, injectable, implantable.
• Intrauterine device (IUD).
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomised partner, provided that partner is the sole sexual partner of the FOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
Sexual abstinence is considered to be a highly effective method only if defined as refraining from heterosexual activity from the date of transplant until 12 months post Treg infusion. The reliability of this method should be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

12. Male patients who are not willing to use an effective method of contraception (condoms), for the duration of the study (date of transplant to 12 months post-Treg infusion), when engaging in sexual activity with a female of childbearing potential
13. The patient is considered by the Chief Investigator, for any reason, to be an unsuitable candidate for the study

Date of first enrolment
23/06/2025

Date of final enrolment
06/01/2027

Locations

Countries of recruitment
England

United Kingdom

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

Organisation
Great Ormond Street Hospital

Sponsor details
30 Guilford Street
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WC1N 1EH
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Hannah.Badham@gosh.nhs.uk

Sponsor type
Hospital/treatment centre

Website
https://www.gosh.nhs.uk/

ROR
https://ror.org/00zn2c847

Funder(s)

Funder type

Charity

Funder Name
British Heart Foundation

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer reviewed scientific journals
2. Conference presentation
3. Publication on website
4. Submission to regulatory authorities
5. Anonymised data may be shared with external collaborators, subject to any commercial IP sensitivities with the ATIMP

Intention to publish date
30/06/2031

Individual participant data (IPD) sharing plan
Anonymised datasets generated during and/or analysed during the study will be available upon request from the study Chief Investigator (Prof Michael Burch, michael.burch@gosh.nhs.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.0	28/11/2024	12/02/2025	No	Yes
Participant information sheet	version 1.0	28/11/2024	12/02/2025	No	Yes
Participant information sheet	version 1.0	28/11/2024	12/02/2025	No	Yes
Participant information sheet	version 1.0	16/09/2024	12/02/2025	No	Yes
Participant information sheet	version 1.0	28/11/2024	12/02/2025	No	Yes

Protocol file	version 1.0	28/11/2024	12/02/2025	No		No