ISRCTN15367345 https://doi.org/10.1186/ISRCTN15367345

A trial to look for the lowest effective dose of antithymocyte globulin that could preserve insulin production in young people newly diagnosed with type 1 diabetes

Submission date
05/01/2022

Recruitment status
No longer recruiting

Registration date
11/05/2022

Overall study status
Completed

Last Edited
16/12/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
People develop type 1 diabetes (T1D) because their immune system, the part of the body which helps fight infections, mistakenly attacks and destroys the insulin-producing cells in the pancreas (beta cells). When the immune system destroys these cells, the body's ability to produce insulin decreases, blood glucose levels run high, and T1D develops.
At the time of diagnosis of T1D, there are usually a small number of beta cells (10-20%) left in the pancreas, which still produce small amounts of insulin. We call this level of activity beta-cell function. Most people with T1D will eventually stop producing insulin themselves. This may occur rapidly in a few months, or more slowly over several years. However, the longer people with T1D can produce their own insulin, the better it is for the control of blood glucose levels and to avoid long-term complications.
Previous research has shown that a drug called anti-thymocyte globulin (ATG) may help prevent the immune system from attacking and destroying the insulin-producing beta cells. The aim of this study is to find the minimum effective low dose of ATG in young people newly diagnosed with T1D that can slow the decline of beta-cell function and preserve the body's own insulin production, and has manageable side effects.

Who can participate?
Patients aged 5 to 25 years diagnosed with T1D in the previous 3 weeks

What does the study involve?
Participation will involve 8-10 hospital/clinic visits over about 13 months, and some at-home collections. Most visits take 1-4 hours. Treatment is given over two consecutive days and includes one overnight stay for most participants.
After signing the Consent Form, participants will be invited for a screening visit to see if they are eligible for the study. They will be asked about their diabetes diagnosis, medical history, and recent medications and vaccinations. They will have blood samples taken which include tests to check they are fit and well, and to screen for T1D related auto-antibodies and c-peptide levels.

Eligible participants will have a baseline visit no more than 3 weeks after the screening visit and undergo a number of assessments including height/weight, a physical exam, blood pressure, heart rate, temperature/breathing rate, review of any recent changes in health and medications and a mixed meal tolerance test (MMTT).
If they are fit and well, participants will have a treatment visit no more than 9 weeks from the T1D diagnosis. Most participants will need an overnight stay for this visit, as there is no gap between treatment days 1 and 2. They will be able to eat and drink and take insulin as normal. Treatment will be assigned in a random way (by chance), much like flipping a coin, by a central computer programme. This treatment will be either an active drug (a low dose of ATG) or a placebo (dummy drug). Neither participants nor the research team will know which treatment they are given but overall 3 out of 4 people will get the active treatment.
On treatment day 1 a nurse or doctor will talk to participants about their health. A cannula (tube) will be inserted into a vein, through which the study treatment will be given. Pre-treatment medications (an antihistamine, an anti-inflammatory and paracetamol) will be given. Some are given orally and others through the cannula. These medications are a precaution because some people can react to the study treatment. Treatment infusion will take at least 12 hours, blood samples will be collected and vital signs (blood pressure, heart rate, oxygen saturation, breathing rate and temperature) will be checked throughout.
On treatment day 2 participants will start their second trial treatment infusion at least 12 hours after completing the first. With the exception of the study drug infusion which will only last 8 hours, day 2 is the same as day 1, including pre-treatment medications, collecting blood samples, and measuring vital signs. Where possible, the cannula will be kept in place and used again on day 2. Participants will be able to go home after the infusion, once the research team agrees they are fit and well enough to do so.
Participants will have six follow-up visits at the hospital/clinic during the 12 months after finishing the study treatment. Visits will include medical review, height/weight, vital signs, blood samples and for visits 3, 6 and 12 an MMTT.
Participants will also be asked to collect the following samples at home: collection of dried blood spot samples (via a small finger prick) and blood glucose measurements before and after a liquid meal (like the milkshake drink for the mixed-meal tolerance test); collection of urine and stool samples at home within 1 week before or after the baseline, 3, 6- and 12-month follow up visits; a short trial diary to complete at home following trial treatment, covering things like taking any medications and describing any possible side effects; a continuous glucose monitoring (CGM) device (provided by the study) for 14 days after each of the 3-, 6- and 12-month follow up visits, to measure blood glucose levels 24 hours a day.

What are the possible benefits and risks of participating?
Where possible, study visits will be booked to coincide with normal hospital visits to minimise the number of trips. Participants may experience some brief and/or minor discomfort when blood is taken or the cannula is inserted, and mild bruising or swelling can occur at the site. Occasionally, some people may become lightheaded during the procedure. Participants will need to have fasted for 8 hours (drinking water is allowed) before four of the hospital/clinic visits and before the monthly at-home dried blood spot sample collection. Participants may experience side effects from the study treatment (details in the participant information sheet). Participants should discuss their participation in this study with any insurance providers they have (e.g. travel insurance, protection insurance, life insurance, income protection, critical illness cover and private medical insurance) and seek advice if necessary, as failure to notify them may affect or invalidate their cover.

Where is the study run from?
University of Cambridge (UK) on behalf of the sponsor University Hospital Leuven (UZ Leuven, Belgium).

When is the study starting and how long is it expected to run for?
August 2018 to November 2024

Who is funding the study?
European Commission

Who is the main contact?
Dr Emile Hendriks
MELD-ATG@medschl.cam.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr A.E.J. Hendriks

ORCID ID
https://orcid.org/0000-0002-0795-1832

Contact details
Department of Paediatrics, Box 116, Level 8
University of Cambridge
Cambridge Biomedical Campus
Cambridge
United Kingdom
CB2 0QQ
+44 (0)1223 217360
aejh6@medschl.cam.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2019-003265-17

Integrated Research Application System (IRAS)
273083

ClinicalTrials.gov (NCT)
NCT04509791

Central Portfolio Management System (CPMS)
43669

Study information

Scientific Title

MELD-ATG: Phase II, dose ranging, efficacy study of anti-thymocyte globulin (ATG) within 6 weeks of diagnosis of type 1 diabetes (T1D)

Acronym
MELD-ATG

Study objectives
The treatment of new-onset type 1 diabetes patients with the minimally effective dose of anti-thymocyte globulin, to preserve β cell function, as assessed by a mixed meal tolerance test (MMTT), is associated with improved glycaemic control.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/06/2021, East of England - Cambridge Central Research Ethics Committee (Royal Standard Place, Nottingham, The Old Chapel, NG1 6FS, UK; +44 (0)207 1048384; cambridgecentral.rec@hra.nhs.uk), REC ref: 21/EE/0002

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Type 1 diabetes mellitus

Interventions
MELD-ATG is a double-blind, randomised controlled trial:
Double-blind: neither the treating doctor/nurse nor the participant will know whether they are being treated with active drug (ATG) or placebo (sometimes called the "dummy drug").
Randomised, controlled: Participants will be randomly allocated to receive a dose of ATG (up to 2.5 mg/kg) or placebo (the control) within their cohort. A computer programme will be used to ensure this is done fairly. The researchers randomise in order to be sure than any effects of the drug are due to the ATG and not due to differences in participants.

Participants in this trial will be recruited sequentially in different cohorts:
Cohort 1:
The first cohort of 30 participants will be randomised into:
- Placebo
- 2.5 mg/kg ATG total dose
- 1.5 mg/kg ATG total dose
- 0.5 mg/kg ATG total dose
- 0.1 mg/kg ATG total dose

Randomisation will be in a 1:1:1:1:1 ratio; this means there is an equal chance of being allocated any of the five options. In cohort 1, there will be an initial age step down selection of this cohort

with recruitment starting with those aged 12-25 years and, providing no safety concerns are raised in the first 10 participants aged 12-17 years to receive a non-placebo dose of ATG, progressing to all ages (5-25 years).

Cohorts 2 and 3:
The next two cohorts of 12 participants will be randomised in a 1:1:1:1 ratio to:
- Placebo ATG total dose
- 2.5 mg/kg ATG total dose
- Two selected middle ATG total doses

Cohorts 4, 5, 6 and 7:
The next four cohorts of 15 participants will be randomised in a 1:1:1 ratio to:
- Placebo ATG total dose
- 2.5 mg/kg ATG total dose
- One single selected middle ATG total dose

The trial design allows sequential adjustment of the middle doses to be explored following a review of all safety and early efficacy data by the Independent Data Monitoring Committee (IDMC) to seek the minimum effective dose of ATG. In order to form an accurate assessment of any differences between the cohorts, the researchers will need to recruit a total of 114 patients into the trial. They plan to recruit from approximately 12 centres across approximately 10 UK and European countries.

Key stages for participants:
Approach & Consent:
Potentially eligible individuals or parents/legal guardians (in the case of children) will be approached by healthcare professionals and/or local research teams during routine clinical appointments. Approach by phone would also be possible if the person has previously agreed that their personal details can be used for research studies purposes, as per local site processes. Interested people may also contact the site research team directly in response to any advertisement of the trial e.g. on social media or websites. People approached for the trial will have been diagnosed with T1D in the previous 3 weeks (+ or - 3 weeks), therefore approaches will need to be made sensitively and made in the knowledge that these recently diagnosed individuals will be receiving a lot of information about T1D and what it means for them.

After being told about the trial and given the appropriate Participant Information Sheet, potential participants will have time to think and will have the opportunity to ask a member of the research team questions. If they decide to take part, they will be asked to sign an Informed Consent Form and will be given a copy to keep. Children and young persons not classed as "adults" according to local laws will be asked to provide written evidence of their assent prior to any study procedures being undertaken, while their parents/responsible legal guardians sign the Informed Consent Form. Following informed consent, the participant will be registered using de-identifiable information only and a participant trial ID number generated.

Screening Visit:
A member of the research team will ask some basic medical information to confirm eligibility for the trial. This will include medical details about their diabetes diagnosis, medical history, and recent medications and vaccinations. They will have blood samples taken (up to a maximum of about 4 teaspoons [about 24 ml]), which include tests to check they are fit and well (including HIV, hepatitis, Epstein-Barr Virus), and to screen for T1D-related auto-antibodies and c-peptide levels.

Baseline Visit:
For eligible participants who pass through the screening stage, the research team member will ask the participants to come into the hospital/clinic having fasted (from midnight). They will have their height/weight measured, a physical exam, blood pressure, heart rate, temperature and respiratory rate measured, and a review of any recent changes in health and medications to ensure they are fit and well. For applicable participants, puberty staging will be performed, using a self-assessment questionnaire if preferred. A urine pregnancy test will be carried out (if applicable).

As the researchers do not want to give the drug to anyone who has COVID-19, they will be screening for the virus at the baseline visit. Similarly, if anyone comes in contact with the virus or develops symptoms, the researchers will re-test and delay or cancel the administration of ATG.

Participants will have blood samples taken (up to a maximum of about 8 teaspoons or 2.5 tablespoons [about 80 ml]). All participants will have a 120 minutes mixed meal tolerance test (MMTT) with EnsurePlus for measuring c-peptide as a measurement of beta-cell response. The first dried blood spot (DBS) sample collection will also occur in clinic (future DBS samples will be collected at home - see below).

Treatment Visit:
Treatment - Day 1:
Participants will be treated in the clinical research facility (or hospital). Participants will receive a pre-treatment of infusion of corticosteroid over about 30 min before the treatment (ATG or placebo). Additionally, medicines to control possible allergic reactions will be given orally. Following pre-treatment, the first ATG dose of 0.5 or 0.1 mg/kg IV or saline placebo according to their randomisation will be infused over a minimum of 12 hours. They will be given heparin and hydrocortisone intravenously at the same time, to minimise side effects of infusion.

Vital signs (pulse, blood pressure, respiratory rate, oxygen saturation, temperature) will be checked every 30 min for the first 2 hours followed by every 60 minutes intervals or as clinically indicated. At the end of the infusion, they will have blood samples taken for safety tests (a maximum of about half a tablespoon, or about 10.5 ml). An overnight stay may be required between treatment day 1 and treatment day 2, according to participant preference and clinical need.

Treatment Visit: Day 2
The next day, if the first dose has been tolerated, the same pre-treatment as described in Day 1 will be given and participants will receive the second dose of ATG or saline placebo according to their randomisation by infusion over a minimum of 8 hours. Vital signs will be checked and blood samples take for safety tests at the end of the infusion, the same as for Day 1. The participants will be discharged no sooner than 2 hours after the completion of the infusion and according to clinical judgement.

After treatment follow-up:
Participants will come for a total of six follow-up visits at 1 week, 2 weeks, 4 weeks, 3 months, 6 months and 12 months after their 2-day hospital treatment visit.

At all of these follow-up visits:
Participants will be asked how they have been feeling, have a physical exam and vital signs measured, medication (including vaccination) will be recorded and pregnancy test (if applicable)

performed - except for at week 1. They will have blood samples taken (the amount per visit will vary depending on the tests being done, but it will be between about 1 - 2.5 tablespoons, or 50-80 ml, on each occasion).

Additionally at the 3, 6 and 12 months visits (fasted):
Participants will have their height, weight and diabetes care reviewed. A 120-minute mixed meal tolerance test (MMTT) will be carried out, like at the baseline visit.
Participants will be asked to use Continuous Glucose Monitoring (CGM) for 14 days post visit. The devices will be provided to the participants free of charge for use in the trial.

Home collections:
Capillary glucose and dried blood spots (DBS) will be collected at home pre and 60 min post consumption of a liquid meal, monthly, for the full 12 months follow-up. A urine sample will be collected for biomarkers and stool samples for microbiome and metabolome studies on four occasions, for the baseline, 3, 6 and 12 month follow up visits. Written instructions are provided for participants for these home collections.

Procedures at the end of the trial:
Participants will receive the appropriate standard of care during MELD-ATG participation, and this care continues after the study. Participants finish their participation in the trial at the end of the last visit (including CGM measurements) at 12 months after their 2 day treatment hospital visit.

Informed consent is sought upon joining the study to confirm that parents/participants are happy to be contacted about the study results and future intervention and studies organised by INNODIA.

Participants will be invited to join the ongoing INNODIA observational study for an additional 12 months post the end of the trial which will involve 1 single visit at 24 months from diagnosis.

Procedure for dose determination:
As the trial progresses, a statistician, unblinded, will analyse all the data available at the time (interim analysis) and a Dose-Determining Committee will recommend to the Independent Data Monitoring Committee (IDMC) which dose(s) should be tested in the subsequent cohort. There will be six of these interim analyses, one just before the initiation of cohorts 2 - 7. The interim analyses will be only used to determine the doses below 2.5mg/kg (middle doses) that should be allocated to the next cohort of participants.

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
Anti-thymocyte globulin

Primary outcome(s)
The area under the stimulated C-peptide response curve measured using immunoassay over the first 2 hours of an MMTT at 12-months post-treatment

Key secondary outcome(s))
1. The area under the stimulated C-peptide response curve over the first 2 hours of an MMTT measured using immunoassay at baseline, 3, 6 and 12 months
2. Dried blood spot (DBS) C-peptide measurements measured using immunoassay at all observation times (requested monthly for 12 months)
3. CD4-positive T cells and CD8-positive T cells measured using flow cytometry at baseline, 1,2 and 4 weeks and 3, 6 and 12 months
4. HbA1c measured using immunoassay at baseline, 3, 6 and 12 months
5. Insulin requirements measured using patient history at baseline, 1,2 and 4 weeks and 3, 6 and 12 months
6. T1D-associated autoantibodies (GADA, IAA, IA-2A and ZnT8A) measured using immunoassay at screening and 12 months
7. CGM measurements (time in range, time above, time below) measured using a Dexcom G6 continuous glucose monitor at 3, 6 and 12 months

Exploratory outcome measure
The effects of treatment on other biomarkers related to immunological changes and β-cell death /survival in this population, measured using multiple specialist lab methods at baseline, 1,2 and 4 weeks and/or at 3, 6 and 12 months

Completion date
30/11/2024

Eligibility

Key inclusion criteria
1. Have given written informed consent to participate or have a parent or legal guardian provide informed consent if the subject is under the age of consent (age may vary in different countries; <16 years of age in the UK)
2. Age ≥5 years ≤25 years at consent
3. Have been diagnosed with T1D within 3-9 weeks of planned treatment day 1
4. Have random C-peptide levels ≥200 pmol/l measured at screening, as tested centrally
5. Have 1 or more diabetes-related autoantibody (GADA, IA-2A or ZnT8A) present at screening, as tested centrally
6. Will be ≥6 weeks from last live immunisation at planned treatment day 1 and be willing to forgo live vaccines during the trial until 6 months post-treatment
7. Be willing to comply with intensive diabetes management

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
5 years

Upper age limit

25 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Type 2 diabetes
2. Evidence of prior or current tuberculosis (TB) infection
3. Clinically significant abnormal full blood count (FBC), renal function or liver function at screening, including:
3.1. Immunodeficient or clinically significant chronic leucopenia, neutropenia, lymphopenia or thrombocytopenia at the screening visit, according to local reference ranges
3.2. Evidence of liver dysfunction with aspartate aminotransferase (AST) or alanine transaminase (ALT) greater than 3 times the upper limit of normal (ULN), at screening
3.3. Evidence of renal dysfunction with creatinine greater than 1.5 times the ULN at screening
4. Requiring use of other immunosuppressive or immunomodulation agents, including chronic use of systemic steroids
5. Any active chronic infections at screening, or any active acute or chronic infections at baseline or on treatment day, which would contraindicate any additional immunosuppression
6. Seropositive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection at screening
7. Positive for SARS-CoV-2 based on local testing regimen
8. Unwilling to use appropriate contraception if sexually active during the trial, from date of written informed consent until completion of the 12-month follow-up visit
9. Any history of malignancies, other than skin
10. Current or ongoing use of non-insulin pharmaceuticals that affect glycaemic control
11. Active participation in another T1D treatment interventional trial in the previous 30 days prior to screening (excluding treatment with insulin)
12. Any prior treatment with ATG, abatacept or anti-CD3
13. Known allergy to ATG or to similar products
14. Any condition, complicating medical issues, or abnormal clinical laboratory results that the investigator judges may adversely affect trial conduct, cause increased risk to the participant, or compromise the trial results

Date of first enrolment
01/02/2021

Date of final enrolment
31/10/2023

Locations

Countries of recruitment
United Kingdom

Study participating centre

Cambridge Biomedical Campus
Hills Road
Cambridge
England
CB2 0QQ

Sponsor information

Organisation
Universitair Ziekenhuis Leuven

ROR
https://ror.org/0424bsv16

Funder(s)

Funder type
Government

Funder Name
European Commission; Grant Codes: 115797

Alternative Name(s)
European Union, Comisión Europea, Europäische Kommission, EU-Kommissionen, Euroopa Komisjoni, EC, EU

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan

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?
Results article		18/09/2025	16/12/2025	Yes	No
Protocol article		07/12/2021	31/01/2022	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	11-15 Years version 2.0	22/01/2021	31/01/2022	No	Yes
Participant information sheet	5-10 Years version 2.0	22/01/2021	31/01/2022	No	Yes
Participant information sheet	Adult version 1.0	01/12/2020	31/01/2022	No	Yes
Participant information sheet	Parent version 1.0	01/12/2020	31/01/2022	No	Yes
Study website		11/11/2025	11/11/2025	No	Yes