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# Adaptive study of IL-2 dose frequency on regulatory T cells in type 1 diabetes

**Submission date**
29/10/2014

**Recruitment status**
No longer recruiting

**Registration date**
29/10/2014

**Overall study status**
Completed

**Last Edited**
23/04/2019

**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
Type 1 diabetes is the most common severe chronic autoimmune disease in the world and the number of people developing the disease is rising rapidly. It causes the immune system to mistake cells in the pancreas as harmful and attack them. When these cells are damaged the pancreas is unable to produce insulin, which plays an essential role in transferring glucose out of the bloodstream and into cells to be converted into energy. The management of the condition usually involves measuring the amount of glucose in the blood and injecting artificial insulin to make up for the insulin the pancreas is not producing. This research study is investigating a new medication for use in type 1 diabetes, using a drug called aldesleukin (interleukin-2). The research team are investigating whether this medication can halt the damage to the pancreas of people with newly diagnosed type 1 diabetes and if so, how often is the drug required for the best results.

Who can participate?
Participants should be aged 18-70 years and have been diagnosed with type 1 diabetes within the last five years.

What does the study involve?
The study includes 12 visits spread over approximately 2-5 months depending on the frequency of administration of aldesleukin. The study consists of a screening visit (Visit 1) followed by a medication period that will vary according to the frequency of drug administration (Visit 2  Visit 11). A follow up assessment (Visit 12) will be carried out approximately 4 weeks after the final dose of drug. Clinical assessments and blood tests will also be taken at each visit to monitor participants health and for research purposes. Prior to their start in the study, participants will have discussed with the study team a schedule that facilitates their participation in the DILfrequency study. The study drug aldesleukin is a synthetic form of interleukin-2 that has been made for use in patients. This study will administer between 5 to 8 doses of ultra-low dose aldesleukin and is given by subcutaneous injection just under the skin.

What are the possible benefits and risks of taking part?
There is no guarantee that participants will benefit from taking part in this study. They will receive intensive management of their diabetes by the study doctors during the study, which

should increase their understanding of their condition, and help improve your own management of it. The study medication may halt the destruction of their pancreas cells for a short while, but the main purpose of the study is to see whether this medication, when given regularly, could benefit future patients. As with all medicines, there is a risk that participants may experience some unwanted side effects. The most common side effects at the ultra-low doses of aldesleukin to be used in this study are; some temporary redness at the point where the drug is injected and flu-like symptoms (tiredness, muscle pain and headaches). If encountered, all of these mild side effects are only likely to last a short time and should completely resolve.

Where is the study run from?
University of Cambridge and Cambridge University Hospitals NHS Foundation Trust (UK).

When is the study starting and how long is it expected to run for?
October 2014 to October 2016

Who is funding the study?
1. Sir Jules Thorn Charitable Trust (UK)
2. Juvenile Diabetes Research Foundation Limited (JDRF)/Wellcome Trust (UK)
3. Biomedical Research Centre (UK)

Who is the main contact?
Dr Frank Waldron-Lynch
DILT1D@cimr.cam.ac.uk

### Study website
http://www.clinical-trials-type1-diabetes.com

# Contact information

### Type(s)
Scientific

### Contact name
Dr Frank Waldron-Lynch

### Contact details
JDRF/Wellcome Trust Diabetes & Inflammation Laboratory
NIHR Cambridge Biomedical Research Centre
Cambridge Institute for Medical Research
University of Cambridge
WT/MRC Bldg, Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0XY
-
DILT1D@cimr.cam.ac.uk

# Additional identifiers

### EudraCT/CTIS number

### IRAS number

### ClinicalTrials.gov number
NCT02265809

### Secondary identifying numbers
17571

# Study information

### Scientific Title
Adaptive study of IL-2 dose frequency on regulatory T cells in type 1 diabetes (DILfrequency)

### Acronym
DILfrequency

### Study objectives
Type 1 diabetes (T1D) is the most common severe autoimmune disease worldwide and is caused by the body's immune destruction of its own insulin producing pancreatic beta cells leading to insulin deficiency and development of elevated blood sugars. Currently, medical management of T1D focuses on intensive insulin replacement therapy to limit complications (retinopathy, nephropathy, neuropathy); nevertheless clinical outcomes remain suboptimal. There are intensive efforts to design novel immunotherapies that can arrest the autoimmune process and thereby preserve residual insulin production leading to fewer complications and better clinical outcomes.

Genetics are in part the cause of T1D and the majority of genes contributing to T1D produce proteins involved in immune regulation (called "tolerance"). A key player in immune tolerance is a molecule called interleukin-2 (IL-2) which enhances the ability of cells called T regulatory (Treg) cells to suppress the destruction the insulin producing beta cells. Aldesleukin is a human recombinant IL-2 product produced by recombinant DNA technology using a genetically engineered E. coli strain expressing an analogue of the human IL-2 gene. There is substantial data to suggest that ultra-low doses (ULD) of IL-2 (aldesleukin) can arrest the autoimmune mediated destruction of pancreatic beta cells by the induction of functional Treg cells.

The former study "Adaptive study of IL-2 dose on regulatory T cells in type 1 diabetes" (DILT1D) (ISRCTN27852285) was a single dose mechanistic study designed to establish the doses of IL-2 (aldesleukin) required to induce a minimal Treg increase (0.1 fold from baseline) or to induce a slightly larger Treg increase (0.2 fold from baseline) (maximal increase). Following on from the DILT1D study, the goal of the DILfrequency study is to use an adaptive design to determine the optimal dose and frequency of ULD IL-2 (aldesleukin) to maximize Treg function by frequently injecting ultra-low doses of IL-2 (aldesleukin). The responsiveness of each T1D participant to a particular frequency of IL-2 (aldesleukin) administration informs the frequency of dosing given to the next patient. This strategy focuses on improving the function of regulatory T cells that are exquisitely sensitive to IL-2 (aldesleukin).

### Ethics approval required
Old ethics approval format

## Ethics approval(s)
Cambridge East REC, 12/08/2014, ref 14/EE/1057

## Study design
Non-randomised; Interventional; Design type: Treatment

## Primary study design
Interventional

## Secondary study design
Non randomised study

## Study setting(s)
Other

## Study type(s)
Treatment

## Participant information sheet
Not available in web format, please email DILT1D@cimr.cam.ac.uk to request a patient information sheet.

## Health condition(s) or problem(s) studied
Topic: Diabetes, Primary Care; Subtopic: Type 1 , Diabetes; Disease: Diabetic Control, All Diseases, Education, Metabolic

## Interventions
Aldesleukin will be administered subcutaneously at varying doses and frequencies for a period of up to 98 days from first administration depending on the treatment assignment. The maximum dose allowed is 0.6 X 10^6 IU/m2.

## Intervention Type
Drug

## Phase
Phase I/II

## Drug/device/biological/vaccine name(s)
Aldesleukin

## Primary outcome measure
Change from baseline of CD4 T regulatory cells, CD4 T effector cells and CD25 expression on T regulatory cells during treatment with ultra low dose IL-2. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment).

## Secondary outcome measures
1. T regulatory cell number, phenotype and proliferation. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
2. T effector cell number, phenotype and proliferation. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)

3. Natural Killer cell number, phenotype and proliferation. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
4. B lymphocyte cell number, phenotype and proliferation. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
5. T cell and Natural killer cell intracellular signalling. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
6. Full blood count. Timepoint(s): Visits 1-12 (between day -30 and day -1 up to a maximum of approximately day 98 depending on treatment assignment)
7. Blood levels of IL-2, IL-6, IL-10, TNF-alpha, soluble CD25, IP-10, soluble rIL-6, and CRP. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
8. Change in metabolic control. Timepoint(s): Visits 1-12 (between day -30 and day -1 up to a maximum of approximately day 98 depending on treatment assignment)
9. Safety and tolerability. Timepoint(s): Visits 1-12 (between day -30 and day -1 up to a maximum of approximately day 98 depending on treatment assignment)
10. Genotype of T1D associated loci. Timepoint(s): Visit 1 (between day -30 and day -1)
11. Gene expression analysis of purified lymphocyte subsets and peripheral blood mononucleated cells. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
12. IL-2 sensitivity of T regulatory, T effector and NK subsets. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
13. Treg suppression and T effector proliferation assays. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
14. Antigen specific T cell assays. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
15. Sysmex® analysis of whole blood. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
16. Epigenetic analysis of analysis of purified lymphocyte subsets and peripheral blood. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
17. Serum/plasma level of cytokines, soluble receptors and inflammatory markers. Timepoint(s): Visits 2-12 (day 0 up to a maximum of approximately day 98 depending on treatment assignment)
18. Serum/plasma and cellular metabolites. Timepoint(s): Visits 1-12 (between day -30 and day -1 up to a maximum of approximately day 98 depending on treatment assignment)
19. Recruitment analysis. Timepoint(s): Visit 1 (between day -30 and day -1)

### Overall study start date
03/10/2014

### Completion date
03/10/2016

# Eligibility

### Key inclusion criteria
1. Type 1 diabetes
2. 18-70 years of age
3. Duration of diabetes less than 60 months from diagnosis
4. Written informed consent to participate
5. Male & Female

## Participant type(s)
Patient

## Age group
Adult

## Lower age limit
18 Years

## Upper age limit
70 Years

## Sex
Both

## Target number of participants
Planned Sample Size: 36; UK Sample Size: 36

## Total final enrolment
38

## Key exclusion criteria
1. Hypersensitivity to aldesleukin or any of the excipients
2. History of severe cardiac disease
3. History of malignancy within the past 5 years (with the exception of localized carcinoma of the skin that had been resected for cure or cervical carcinoma in situ)
4. History or concurrent use of immunosuppressive agents or steroids
5. History of unstable diabetes with recurrent hypoglycaemia
6. History of live vaccination two weeks prior to first treatment
7. Active autoimmune hyper or hypothyroidism
8. Active clinical infection
9. Major pre-existing organ dysfunction or previous organ allograft
10. Females who are pregnant, lactating or intend to get pregnant during the study
11. Males who intend to father a pregnancy during the study
12. Donation of more than 500 ml of blood within 2 months prior to aldesleukin administration
13. Participation in a previous therapeutic clinical trial within 2 months prior to aldesleukin administration
14. Abnormal ECG
15. Abnormal full blood count, chronic renal failure (Stage 3,4,5) and/or evidence of severely impaired liver function
16. Positive HBsAg or HepC serology or HIV test
17. Any medical history or clinically relevant abnormality that is deemed by the principal investigator/delegate and/or medical monitor to make the patient ineligible for inclusion because of a safety concern

## Date of first enrolment
03/10/2014

## Date of final enrolment
26/05/2016

# Locations

**Countries of recruitment**
England

United Kingdom

**Study participating centre**
**NIHR Cambridge Biomedical Research Centre**
Cambridge
United Kingdom
CB2 0XY

# Sponsor information

**Organisation**
Cambridge University Hospitals NHS Foundation trust & University of Cambridge (UK)

**Sponsor details**
Research Services Department, Box 277 , Addenbrookes Hospital Hills Road
Cambridge
United Kingdom
CB2 2QQ

**Sponsor type**
Other

**ROR**
https://ror.org/04v54gj93

# Funder(s)

**Funder type**
Other

**Funder Name**
Sir Jules Thorn Charitable Trust; Grant Codes: RG72272

**Alternative Name(s)**
The Sir Jules Thorn Charitable Trust

### Funding Body Type
Private sector organisation

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

### Location
United Kingdom

### Funder Name
Juvenile Diabetes Research Foundation Limited (JDRF)/Wellcome Trust; Grant Codes: RG58018

### Funder Name
Biomedical Research Centre; Grant Codes: RG64229

## Results and Publications

### Publication and dissemination plan
Not provided at time of registration

### Intention to publish date

### Individual participant data (IPD) sharing plan

### IPD sharing plan summary
Not provided at time of registration

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol article | protocol | 08/12/2015 | | Yes | No |
| Results article | results | 04/10/2018 | | Yes | No |
| HRA research summary | | | 26/07/2023 | No | No |