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Ustekinumab in adolescents with recent-onset type 1 diabetes

Submission date
20/08/2018

Recruitment status
No longer recruiting

Registration date
24/08/2018

Overall study status
Completed

Last Edited
01/09/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Type 1 diabetes (T1D) occurs when a person's own immune system attacks their insulin producing cells. When newly diagnosed, many T1D patients still have 10-20% of their insulin-producing cells still functioning. Ustekinumab is currently being used for other skin and bowel conditions and works by blocking the body's immune system. The aim of this study is to find out whether ustekinumab can delay or stop those remaining insulin-producing cells from being destroyed. If the drug works, it can potentially improve a patient's ability to control their blood sugar levels.

Who can participate?
Adolescents (aged 12-18) newly diagnosed with T1D

What does the study involve?
Participants are tested to see if they still have insulin-producing cells left, and if they do, they are randomly allocated to take either ustekinumab or a placebo (dummy drug) as seven doses over 44 weeks. Blood and urine samples are collected for testing at study visits, which where possible coincide with their routine appointments. The participant and a nominated parent are also asked to complete three quality of life questionnaires. At week 52 there is a follow up appointment at the hospital, after which the researchers remotely follow up their health status using hospital records for another year. All females are asked to take adequate contraceptive protection and undergo pregnancy tests at the study visits.

What are the possible benefits and risks of participating?
Ustekinumab may help the pancreas make insulin for longer. However, this cannot be said for certain until this study is completed. During the study the participants' diabetes will be very closely monitored. This will include regular check-ups with the local diabetes team including routine blood testing. They will have more time with the research team to discuss their diabetes and ask questions than at a normal clinic appointment. They will be provided with a FREE Abbott Freestyle Libre flash glucose monitoring system. They can use this to check their blood sugar levels while they are in the study, although they will still be asked to do some finger prick tests. During the Milkshake test, participants may experience changes in blood glucose level because they will not have taken insulin immediately beforehand. The study nurses and doctors will be

available to help them make any changes to their usual insulin doses after this test. Because the medicine (ustekinumab) acts on the immune system, there is a possibility that it will increase the risk of infections and cancer, but so far this has not been found to be a problem with people treated with this medicine for other diseases. It is also possible that participants may get an allergic reaction to the treatment injection. They will stay for one hour after their first injection to check for any reactions. Participants will have a chest X-ray to rule out TB which is additional to standard care. Chest x-rays involve using ionising radiation to form images of the body. Ionising radiation can cause cell damage in the longer term which can sometimes lead to cancer developing. However, only one x-ray is needed so taking part in this study will add only a very small chance of this happening. The risk is not much greater than that found with natural background radiation.

Where is the study run from?
Swansea University Medical School (UK)

When is the study starting and how long is it expected to run for?
November 2017 to October 2022

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Kym Carter, k.carter@swansea.ac.uk

Contact information

Type(s)
Public

Contact name
Dr Kym Carter

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-000015-24

Central Portfolio Management System (CPMS)
39676

Study information

Scientific Title
Phase II multi-centre, double-blind, randomised trial of ustekinumab in adolescents with new-onset type 1 diabetes

Acronym
USTEKID, USTEK1D

Study objectives
Observations suggest that IL-17 and IL-12/IFN-γ driven responses together have an enhanced pathogenic role in T1D. The overarching hypothesis is that interrupting the IL-17 and IFN-γ axes in individuals with recent-onset T1D will halt or slow the autoimmune destruction of beta cells sufficient to permit beta cell preservation and maintain residual physiological insulin secretion. Given the therapeutic success of biologics that target immune molecules in other autoimmune and inflammatory diseases, and the evidence that IL-17 and IFN-γ producing cells are pathogenic to beta cells, we propose that drugs already approved for use in humans (e.g. Ustekinumab) may be beneficial for the treatment of T1D.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Wales REC 3, 14/06/2018, REC ref: 18/WA/0092

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
Participants are randomised on a 2:1 basis to receive either Ustekinumab as intervention or saline as placebo. Participants will be given Ustekinumab subcutaneously (SC) in an enhanced dose depending on body weight: 2 mg/kg (<40 kg) and 90 mg (>=40 kg) at weeks 0, 4 and 12 weeks and subsequently every 8 weeks up to week 48. Participants allocated to the placebo will receive it at the same intervals.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Ustekinumab

Primary outcome(s)
Mixed Meal Tolerance Test (MMTT) stimulated 2-hour insulin C-peptide area under the curve (AUC) at week 52

Key secondary outcome(s))
1. Number of responders (defined as participant who has HbA1c ≤ 48mmol/mol and mean daily insulin use <0.5 IU/kg/day) measured over 7 consecutive days during the 2 weeks preceding the visit in treatment and placebo group measured at -2, 0, 4, 12, 20, 28, 36, 44 and 52
2. Mixed Meal tolerance Test C-peptide area under the curve values measured at week 28
3. HbA1c measured at weeks 0, 12, 28 and 52
4. Exogenous insulin requirement as reflected in mean daily insulin usage over 7 consecutive days (IU units/kg body weight/day) as recorded in capillary blood glucose testing meters or diaries prior to study visits at weeks 12, 28 and 52
5. Insulin dose adjusted HbA1c (IDAAC) measured at week 52
6. Glycaemic variability parameters downloaded from glucose monitoring at Weeks 0, 4, 12, 20, 28, 36, 44 and 52
7. Clinical hypoglycaemic events determined by patient diary reports and AE reports at week 52
8. Frequency and severity of all adverse events at week 52
9. Quality of life: fear of having a hypoglycaemic event measured using HYPOFEAR; diabetes treatment satisfaction measured using DTSQ; and paediatric quality of life measured using PedsQL. These will be administered to the participant and their parent/carer (parent versions available for each) and compared across time. The data from participants and their parents are also compared at each timepoint (weeks -2, 28 and 52)

Completion date
31/10/2022

Eligibility

Key inclusion criteria
Current inclusion criteria as of 10/12/2019:
1. Clinical diagnosis of immune-mediated Type 1 diabetes mellitus as defined by American Diabetes Association
2. Commenced on insulin within 1 month of clinical diagnosis (defined as confirmed raised blood sugar (ADA criteria), not symptoms alone).
3. An interval of ≤100 days between the confirmed diagnosis (defined as first insulin dose) and the first dose of the IMP
4. Written and witnessed informed consent/assent to participate
5. Male or female, aged 12-18 years inclusive at the time of randomisation
6. Evidence of residual functioning beta-cells (serum C-peptide level > 0.2nmol/L in the MMTT test)
7. Positive for at least one islet autoantibody (GAD, IA-2, ZnT8)
8. Body weight < 100 kg
9. Willing to record all insulin doses and blood glucose levels required for monitoring during the study, including reporting any hypoglycaemic events.

10. Willing to provide dried blood spot (DBS) samples.
11. Willing to wear the FreeStyle Libre Flash Glucose Monitor (FGM) device at least two weeks prior to a study visit.
12. Willing to complete a diary and quality of life questionnaires.
13. Willing to consent to remote follow up via health records and telephone contact
14. Female participants have a negative urine test for pregnancy; all sexually active participants must agree to use adequate contraception (hormonal based contraception, double barrier contraception, abstinence) until 4 months following the date of their final treatment of IMP

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1. Clinical diagnosis of immune-mediated Type 1 diabetes mellitus as defined by American Diabetes Association
2. An interval of ≤100 days between the diagnosis (defined as first insulin dose) and the first dose of the IMP
3. Commenced on insulin within 1 month of diagnosis
4. Written and witnessed informed consent/assent to participate
5. Male or female, aged 12-18 years inclusive at the time of randomisation
6. Evidence of residual functioning beta-cells (serum C-peptide level > 0.2nmol/L in the MMTT test)
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Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
12 years

Upper age limit
18 years

Sex
All

Total final enrolment
88

Key exclusion criteria

Current exclusion criteria as of 10/12/2019:
1. Breastfeeding, pregnancy or unwillingness to comply with contraceptive advice and regular pregnancy testing throughout the trial
2. Prior exposure to Ustekinumab within 3 months of the first dose of IMP
3. Use of more than 10 mg prednisolone daily (or equivalent) for >5 days within 3 months of the first dose of IMP. Note: intranasal, inhaled and topical corticosteroid medications are permitted at recommended doses. Use of systemic corticosteroids during the trial should be avoided unless such treatment is medically necessary and alternative treatments are not considered safe or effective
4. Prior exposure to any anti-lymphocyte monoclonal antibody, such as anti-CD20, anti-thymocyte globulin (ATG), Rituximab (Rituxan®), or Alemtuzumab (Campath®)
5. Use of immunosuppressive or immunomodulatory therapies, including systemic steroids (e.g., methotrexate, cyclosporine, or anti-TNF agents) within 30 days prior to receiving the first dose and/or intent on using any monoclonal antibody therapy given for any indication for the duration (including follow up) of the trial
6. Use of any hypoglycaemia agents other than insulin, for more than 6 weeks, at any time prior to trial entry, including SGLT2 inhibitors.
7. Use of inhaled insulin
8. Known alcohol abuse, drug abuse
9. Evidence of active Hepatitis B, Hepatitis C, HIV or considered by the investigator to be at high risk for HIV infection
10. Significant systemic infection during the 6 weeks before the first dose of the IMP (e.g. infection requiring hospitalisation, major surgery, requiring IV antibiotic treatment). Other infections e.g. glandular fever, bronchitis, sinusitis, cellulitis, or urinary tract infections must be assessed on a case by case basis by the investigator to assess whether they are serious enough to warrant exclusion or delay to inclusion
11. History of current or past active tuberculosis (TB) infection and no latent tuberculosis according to the British Thoracic Society recommendations [27]. Active TB will be assessed using a mandatory chest x-ray and one of the following:
a) a blood test e.g. T-spot (preferred), interferon gamma release assay (IGRA), quantiferon test
b) the Mantoux skin test.
A positive result from any TB test will exclude the subject from the study and the subject and their medical care team will be informed. An intermediate result from blood sample testing will not exclude the participant from randomisation if the chest x-ray is negative. The blood test for TB only needs to be repeated if there is a change in the perceived clinical risk of TB
12. Participants should not have had live immunisations (flu and others) for 1 month prior to trial entry and should not receive any during their time in the trial. Note that most injected (as opposed to nasal) influenza vaccines are not live vaccines and are permitted
13. Previous use of any other investigational drug within the 3 months prior to the first dose and /or intent on using any investigational drug for the duration (including follow up) of the trial
14. Recent (within 3 months) participant's involvement in other research studies which, in the opinion of investigators, may adversely affect the safety of the participants or the results of the study
15. Significantly abnormal laboratory results during the screening period, other than those due to T1D
16. Prior allergic reaction, including anaphylaxis, to any component of the IMP product
17. Prior allergic reaction, including anaphylaxis, to any human, humanised, chimeric or rodent antibody treatment
18. Any major planned surgery within the 30 day period prior to the first drug dose and not anticipating requiring major surgery during the study period
19. Any other medical condition or treatment which, in the opinion of investigators, could affect the safety of the participant's participation or outcomes of the study, including malignancy,

immunocompromised states and autoimmune conditions
20. Participants or parents/carers who lack the capacity to comply with trial requirements

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Previous exclusion criteria:
1. Breastfeeding, pregnancy or unwillingness to comply with contraceptive advice and regular pregnancy testing throughout the trial
2. Prior exposure to Ustekinumab within 3 months of the first dose of IMP
3. Use of more than 10 mg prednisolone daily (or equivalent) for >5 days within 3 months of the first dose of IMP. Note: intranasal, inhaled and topical corticosteroid medications are permitted at recommended doses. Use of systemic corticosteroids during the trial should be avoided unless such treatment is medically necessary and alternative
treatments are not considered safe or effective
4. Prior exposure to any anti-lymphocyte monoclonal antibody, such as anti-CD20, anti-thymocyte globulin (ATG), Rituximab (Rituxan®), or Alemtuzumab (Campath®)
5. Use of immunosuppressive or immunomodulatory therapies, including systemic steroids (e.g., methotrexate, cyclosporine, or anti-TNF agents) within 30 days prior to receiving the first dose and/or intent on using any monoclonal antibody therapy given for any indication for the duration (including follow up) of the trial
6. Use of any hypoglycaemia agents other than insulin, for more than 6 weeks, at any time prior to trial entry
7. Use of inhaled insulin
8. Known alcohol abuse, drug abuse
9. Evidence of active Hepatitis B, Hepatitis C, HIV or considered by the investigator to be at high risk for HIV infection
10. Significant systemic infection during the 6 weeks before the first dose of the IMP (e.g. infection requiring hospitalisation, major surgery, requiring IV antibiotic treatment). Other infections e.g. glandular fever, bronchitis, sinusitis, cellulitis, or urinary tract infections must be assessed on a case by case basis by the investigator to assess whether they are serious enough to warrant exclusion or delay to inclusion
11. History of current or past active tuberculosis infection and no latent tuberculosis according to the British Thoracic Society recommendations. Active TB will assessed using the T-spot interferon gamma release assay. A positive result will exclude the subject from the study and the subject and their medical carers will be informed
12. Participants should not have had live immunisations (flu and others) for 1 month prior to trial entry and should not receive any during their time in the trial. Note that most injected (as opposed to nasal) influenza vaccines are not live vaccines and are permitted
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17. Prior allergic reaction, including anaphylaxis, to any human, humanised, chimeric or rodent antibody treatment
18. Any major surgery within the 30 day period prior to the first drug dose and not anticipating requiring major surgery during the study period
19. Any other medical condition or treatment which, in the opinion of investigators, could affect

the safety of the participant’s participation or outcomes of the study, including malignancy, immunocompromised states and autoimmune conditions
20. Participants or parents/carers who lack the capacity to comply with trial requirements

Date of first enrolment
01/12/2018

Date of final enrolment
30/09/2021

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Royal Aberdeen Children’s Hospital
Westburn Road
Aberdeen
United Kingdom
AB25 2ZG

Study participating centre
Countess of Chester Hospital
Liverpool Road
Chester
United Kingdom
CH2 1UL

Study participating centre
Tayside Children's Hospital
Ninewells Hospital
Dundee
United Kingdom
DD1 9SY

Study participating centre

Royal Devon and Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Royal London Hospital (Barts)
Whitechapel Road
Whitechapel
London
United Kingdom
E1 1BB

Study participating centre
University College Hospital London
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Noah’s Ark Children’s Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Evelina Children’s Hospital
St Thomas' Hospital
Westminster Bridge Road

London
United Kingdom
SE1 7EH

Study participating centre
St James' Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Norwich
United Kingdom
NR4 7UY

Study participating centre
St George's University NHS Trust
Blackshaw Road
London
United Kingdom
SW17 0QT

Study participating centre
Morriston Hospital
Heol Maes Eglwys
Cwmrhydyceirw
Swansea
United Kingdom
SA6 6NL

Study participating centre
Royal Alexandra Children's Hospital
BSUHT
Eastern Road
East Sussex
Brighton
United Kingdom
BN2 5BE

Sponsor information

Organisation
Cardiff University

ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 16/36/01

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be stored in a non-publicly available repository, shared on request and if the journal allows/requires it, published too. The repository will be at Swansea Trials Unit and available by sending a request to STU@swansea.ac.uk where the CI, sponsor etc will review the request. The data will be cleaned and anonymised (no site or patient info provided, only IDs). The researchers have not determined what the requirements for sharing will be as yet.

IPD sharing plan summary
Stored in non-publicly available repository, Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Results article		30/07/2024	31/07/2024	Yes	No
Results article		01/02/2025	01/09/2025	Yes	No
Protocol article		18/10/2021	15/08/2022	Yes	No
HRA research summary			28/06/2023	No	No
Other unpublished results			27/08/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes