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Randomised, open-label international trial with Verapamil alone compared with Verapamil plus another immunotherapy for people with newly diagnosed type 1 diabetes

Submission date
23/12/2023

Recruitment status
Recruiting

Registration date
23/02/2024

Overall study status
Ongoing

Last Edited
08/05/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
This trial is set up within the framework of the INNODIA network - a global partnership between 27 academic institutions, 4 industry partners, a small-sized enterprise and 2 patient organisations, bringing their knowledge and experience together in a common goal to fight type 1 diabetes (https://www.innodia.eu). INNODIA's overall aim is to advise in a decisive way how to predict, stage, evaluate and prevent the onset and progression of type 1 diabetes (T1D). INNODIA has established a comprehensive and interdisciplinary network of T1D leading clinical and basic scientist experts in Europe and the United Kingdom (UK), with complementary expertise from the areas of immunology, beta-cell biology, biomarker research and T1D therapy, joining forces with industry partners and two foundations and all major stakeholders in the process. Including regulatory bodies, patients with T1D and their families. The trial will also include sites in the Australasian Type 1 Diabetes Immunotherapy Collaborative in Australia.
T1D occurs when a person's own immune system attacks their insulin-producing cells. Many T1D patients still have 10-20% of their functioning insulin-producing cells when newly diagnosed.

Who can participate?
Adults (18-44 years) with newly diagnosed T1D.

What does the study involve?
T1D-Plus is a randomised, adaptive, open-label, parallel group, multi-centre platform trial in adults (18-44 years) with newly diagnosed T1D. Participants will be randomised to either:
Verapamil alone (once daily dose, which will be escalated in increments of 120mg every month until 360mg is reached) versus
Verapamil + ATG (Infusion. 2.5 mg/kg given over 2 days)
OR
Verapamil alone (dose as above) + Golimumab (Simponi) (Subcutaneous injection 50 mg over 12 months).
All patients will receive Verapamil at the same dose.

Participants will attend at 3 monthly intervals for 12 months to monitor their beta cell function via a Mixed Meal Tolerance Test. This involves drinking a liquid meal and measuring the levels of C-Peptide released over a 2-hour period after the meal.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
The research team will be available at all times during the study to watch closely for possible health problems that may occur and to answer any questions. As with all medicines, side effects may occur and they will be treated if this is what is required. Participants may be asked to give an extra blood sample or clinical test if they have any side effects that the research team need to look at. Participants are advised to inform study staff about any side effects or health problems whilst taking part in the study and advised to report them, even if they do not think that the side effects are caused by the study medicine.
Participants will be asked not to receive any live vaccines whilst on treatment in study, specific details are in the protocol.
Blood sampling: small amounts of blood will be taken, allowing the research team to see how the participants are doing and if or how the study medicine works. They will be advised that they may feel a little discomfort, bruising, bleeding or swelling where the needle enters the skin. There is also a very small risk of infection where the needle enters the skin. Staff are trained in this procedure and will attempt to minimise discomfort or distress that may be experienced to perform the procedure quickly and as painlessly as possible.
ECG: The skin may react to the sticky electrode patches. Any skin irritation usually disappears when the patches are removed. Participants can be asked if they have known reactions to the electrodes and an alternate electrode may be sought.
Low blood sugar: physical warnings may be mild, with only a few symptoms, e.g. cold sweats, hunger, headache, nausea, light-headedness, palpitations. Hypoglycaemia can potentially, in very rare cases, be more severe and in very rare cases, develop into a serious condition caused diabetic ketoacidosis. The research team will explain to the participant how to check and adjust their blood sugar, which could help decrease the risk of high blood sugar. Participants will continue to see their clinical care teams whilst on the trial for their diabetes care.
Pregnancy information for women and men: Women who are pregnant, breast-feeding or planning a pregnancy over the trial period cannot take part in the trial. All participants should use highly effective birth control. Full information is in the participant information sheet. If pregnancy does occur, we will collect information about the pregnancy.
Verapamil SR side effects are explicitly detailed in the protocol and in the Summary of Product Characteristics. Participants to be treated and followed up under strict medical monitoring and 24-hour cover is provided by each site by the PI or a medically qualified delegate. The dose can be reduced to the lowest acceptable dose if side effects limit dose escalation. Participants will be provided with a treatment-specific patient leaflet.
ATG side effects are explicitly detailed in the protocol and Summary of Product Characteristics. All participants are under strict medical supervision for the duration of each infusion, as well as before and after infusions and will not be discharged according to the investigator's clinical judgement. Premedication is given on both infusion days and careful monitoring is undertaken by the clinical team. Treatment can be discontinued without gradual tapering of the dose as per protocol. Dose interruptions and reductions are permitted and reasons for this are recorded in the case report forms. There is detailed guidance in the protocol on how to manage toxicity reactions.
Golimumab: side effects are explicitly detailed in the protocol and Summary of Product Characteristics. The first two doses will be given in clinic, thereafter all doses are self-administered and full instructions will be given. Participants will be provided with a treatment-

specific patient leaflet. There is a risk with TB and this will be well managed by pre-treatment assessment (TB test) and on-treatment monitoring.
All Participants are informed in advance about the risks and treatment options during a detailed conversation and receive an emergency card with the relevant contact details of the site trial team.

Where is the study run from?
Cardiff University (UK)

When is the study starting and how long is it expected to run for?
December 2023 to December 2027

Who is funding the study?
1. Juvenile Diabetes Research Foundation International (USA)
2. Helmsley Trust (USA)
3. Juvenile Diabetes Research Foundation (Australia)

Who is the main contact?
Professor Colin Dayan, DayanCM@cardiff.ac.uk

Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
2023-505328-78-00

IRAS number
1006723

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
1921-22

Study information

Scientific Title
T1D-PLUS: An adaptive platform trial by INNODIA - a randomised, adaptive, open label, parallel group, multi-centre platform trial in adults with newly diagnosed type 1 diabetes

Acronym
T1D-Plus

Study objectives
Primary objective:
To determine the difference in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) after 12 months adjusted for baseline for 360mg Verapamil SR administered orally once daily versus each immunotherapy combination arm.

Secondary objectives:
1. To provide evidence on safety of the combination of Verapamil SR with each additional immunotherapy.
2. Changes in insulin dose, HbA1c, CGM parameters, hypoglycaemic events, estimated C-peptide area under the curve (AUC).
3. Changes in patient reported outcome measures (PROMs) between the groups.
4. Collection and analysis of samples for markers of mechanism of action and response.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 15/02/2024, North East - Newcastle & North Tyneside 2 Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8016; newcastlenorthtyneside2.rec@hra.nhs.uk), ref: 24/NE/0020

Study design
Phase II Interventional randomized parallel group controlled adaptive platform trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
New onset Type 1 diabetes in adults

Interventions
Verapamil. Oral. Once daily. V0 (Day 0) 120 mg daily. V1 (week 4) 240 mg daily. V2 (Week 8) 360 mg daily – continues until V6 (month 12)

ATG (Thymoglobuline). Infusion. Given at V0 (Day 0 or within 7 days of randomisation day). On one occasion at a total dose of 2.5 mg/kg divided over 2 consecutive days

Golimumab (Simponi). Sub-cutaneous injection. V0 (Day 0) 100 mg. Week 2 100 mg. Thereafter 50 mgs self-administered every two weeks until V6 (month 12).

Follow up for all arms is at V1 (week 2), V2 (week 8), V3 (month 3), V4 (month 6), V5 (month 9), V6 (month 12), optional V7 (24 months). Plus, three telephone calls at Week 1, Week 5 and week 9.

Randomisation – online tool.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacodynamic, Bioequivalence, Dose response

Phase
Phase II

Drug/device/biological/vaccine name(s)
Verapamil, Simponi [golimumab], Thymoglobuline [rabbit anti-human thymocyte immunoglobulin]

Primary outcome measure
The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) after 12 months therapy between the Verapamil SR only arm and the Verapamil SR plus immunotherapy arm.

Secondary outcome measures
1. The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) at baseline, 3, 6, 9 and 24 months
2. Estimated C-peptide AUC at baseline, 3, 6, 9, 12 and 24 months.
3. Fasting C-peptide after 12 months therapy compared between intervention and control arms.
4. Change in HbA1c baseline to 12 months.
5. Number of treatment emergent severe hypoglycaemic episodes (Level 3). Severe hypoglycaemia denotes severe cognitive impairment requiring external assistance for recovery according to the American Diabetes Association (ADA)
6. Number of treatment emergent significant hypoglycaemic episodes (Level 2). Significant hypoglycaemia denotes events with capillary blood glucose < 3.0mmol/L (54mg/dl) according to the American Diabetes Association (ADA)
7. Number of treatment emergent episodes of diabetic ketoacidosis (DKA)
8. Change in insulin requirements, baseline to 12 months as the daily total dose (three days average) in units per kg body weight (BW)
9. Change in T1D associated autoantibodies (GADA, IA-2A and ZnT8A) from baseline to 12 months.

10. The area under the stimulated C-peptide response curve over the first two hours of a mixed meal tolerance test (MMTT) at 24 months
11. CGM metrics (Time in range, time below range, variability, other derived parameters) at baseline, 3, 6, 9, 12 and 24 months.

Overall study start date
21/12/2023

Completion date
01/12/2027

Eligibility

Key inclusion criteria
1. Have given written informed consent
2. Age ≥18 and <45 years at consent
3. Must have had a clinical diagnosis of stage 3 T1D within 6 weeks of screening (from date of the first insulin injection) – defined as hyperglycaemia satisfying ADA criteria for diabetes and a clinical decision to commence insulin treatment
4. Must have at least one or more of the following diabetes-related autoantibodies present at screening: GADA, IA-2A and/or ZnT8A
5. Must have fasting serum C-peptide levels ≥100 pmol/L measured at screening
6. Be willing to comply with intensive diabetes management.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex
Both

Target number of participants
71

Key exclusion criteria
1. Be immunodeficient or have clinically significant chronic lymphopenia
2. Have active signs or symptoms of acute infection at the time of randomisation
3. Be currently pregnant or lactating, or anticipate getting pregnant during the 12-month trial period
4. Require use of immunosuppressive agents, including chronic use of systemic steroids
5. Evidence of current or past human immunodeficiency virus (HIV), Hepatitis B or C infection and be serologically tested for these

6. Any complicating medical issues or abnormal clinical laboratory results that interfere with trial conduct, or cause increased risk to include pre-existing cardiac disease, chronic obstructive pulmonary disease (COPD), sickle cell disease, neurological, or blood count abnormalities
7. Have a persistent history of malignancies (including lymphoma) other than skin
8. History of liver insufficiency or laboratory evidence of liver dysfunction with aspartate aminotransferase (AST) or alanine transaminase (ALT) greater than 3 times the upper limits of normal
9. History of renal insufficiency or evidence of renal dysfunction with creatinine greater than 1.5 times the upper limit of normal
10. Current or ongoing use of non-insulin pharmaceuticals that affect glycaemic control within 7 days prior to screening
11. Use of other investigational drug in the previous 30 days and/or intent to use any investigational drug that does not form part of T1D Plus trial for the duration of the trial
12. Current use of Verapamil SR or other calcium channel blockers
13. Known hypersensitivity to Verapamil SR or any of its excipients
14. Current use of Ivabradine
15. Known allergies, severe reaction, intolerance, hypersensitivity, or anaphylaxis to human, humanized, or murine monoclonal antibodies, or any of its components or excipients
16. Any autoimmune disease other than T1D (eg, rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, multiple sclerosis, systemic lupus erythematosus), with the exception of stable thyroid or celiac disease
17. Active infection and/or fever ≥38.5°C (101.3°F) within the 48 hours prior to randomisation, prone to infections, or chronic, recurrent or opportunistic infectious disease, including but not limited to renal, respiratory or skin infections, Pneumocystis carinii, aspergillosis, latent or active granulomatous infection, histoplasmosis, or coccidioidomycosis
18. History of or serologic evidence at screening of current or past infection with HIV, hepatitis B or C virus
19. Symptoms of Epstein-Barr virus, Cytomegalovirus or TB (Tuberculosis) – test for Interferon-gamma release assay (IGRA)
20. A history of significant cardiovascular disease, including heart failure
21. Current or prior (within 30 days before screening) treatment known to cause a significant, ongoing change in the course of T1D or immunologic status, including high-dose inhaled, extensive topical, or systemic glucocorticoids
22. Current or prior (within 30 days before screening) use of drugs other than insulin to treat hyperglycemia (eg, metformin, sulfonylureas, glinides, thiazolidinediones, exenatide, liraglutide, dipeptidyl peptidase-4 [DPP-IV], sodium-glucose cotransporter 2 [SGLT2] inhibitors or amylin
23. Current or prior (within 30 days before screening) use of medication known to significantly influence glucose tolerance (eg, atypical antipsychotics, diphenylhydantoin, niacin)
24. Recent or planned vaccinations as follows:
24.1. Live virus vaccines (eg, varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, and smallpox): Within the 8 weeks before randomization and initiation of trial drug or planned/required administration to 52 weeks after last dose of trial drug
24.2. Non-infectious (eg, recombinant, inactivated or otherwise 'non-live') vaccines: Within 2 weeks before and 6 weeks after each trial drug.
25. Concomitant medication known for inducing or inhibiting CYP3A4 and/or glycoprotein-P metabolism
26. Regular daily intake of grapefruit juice, liquorice, St. John's Wort, cannabidiol or ginkgo biloba
27. Substantial daily intake of CYP3A4 and/or glycoprotein-P metabolism inhibiting substances
28. Hypotension, sick sinus syndrome, uncompensated heart failure or severe left ventricular dysfunction; marked bradycardia, atrial flutter or atrial fibrillation in the presence of an accessory bypass tract, hypertrophic cardiomyopathy, acute myocardial infarction, attenuated

neuromuscular transmission
29. ECG 2nd or 3rd degree atrioventricular block, incomplete branch block or PR interval
30. Current use of beta blockers
31. Any condition may adversely affect trial participation, as per PI opinion
32. Participating in INNODIA Ver-A-T1D or other T1D-Plus trial arm already randomised to
33. Hypersensitivity to ATG (Thymoglobuline) or related drugs.
34. Previous use of ATG or rabbit-derived polyclonal serum preparations.

Date of first enrolment
01/06/2024

Date of final enrolment
30/06/2026

Locations

Countries of recruitment
Australia

Austria

Belgium

France

Germany

Italy

United Kingdom

Study participating centre
University of Wales and Llandough Hospital NHS Trust
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
The Royal Melbourne Hospital
300 Grattan St, Parkville
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Sponsor information

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Sponsor type
University/education

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ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Charity

Funder Name
Juvenile Diabetes Research Foundation International

Alternative Name(s)
Juvenile Diabetes Research Foundation, International, JDRF

Funding Body Type
Private sector organisation

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

Location
United States of America

Funder Name
Helmsley Trust

Funder Name
Juvenile Diabetes Research Foundation Australia

Alternative Name(s)
JDRF Australia, Juvenile Diabetes Foundation Australia, JDRF

Funding Body Type
Government organisation

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

Location
Australia

Results and Publications

Publication and dissemination plan
Peer-reviewed scientific journals
Conference presentation
Publication on website
Submission to regulatory authorities
Data sharing will only take place via contractual arrangements with Cardiff University. All data will be anonymised.

Intention to publish date
31/08/2028

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date