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Low dosE GlibENclamide and Dapagliflozin in type 1 Diabetes (LEGEND-D)

Submission date
02/08/2023

Recruitment status
No longer recruiting

Registration date
25/09/2023

Overall study status
Completed

Last Edited
20/03/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Type 1 diabetes (T1D) affects around 400,000 people in the UK, and is caused by a nearly complete loss of insulin-producing cells in the pancreas. Managing blood sugar levels with insulin injections can be challenging in T1D, and very low blood sugar (hypos) are one of the most feared complications. Disruption of other hormones such as glucagon, which raises blood sugar and counter-balances the effects of insulin during hypos, is now also recognised as part of the disorder. How this happens is not clear, and a better understanding of this mechanism could lead to treatments aimed at reducing the risk of hypos.
Glibenclamide (sulfonylurea) is a type of anti-diabetic medication that is commonly used to increase the amount of insulin released by the pancreatic beta-cells. Preclinical studies have shown that sulfonylureas can also improve glucagon levels when used in very small doses by working on pancreatic alpha cells, which release glucagon. In addition, another type of anti-diabetic medication called dapagliflozin has also been shown to work on pancreatic alpha cells. A small pilot study suggested that low doses of glibenclamide (0.3 mg/day) could alter glucagon release in some people with type 2 diabetes without increasing the risk of hypos. The aim of this study is to find out whether similar doses of glibenclamide or a single dose of dapagliflozin could restore glucagon release in people with T1D. It is hoped that add-on therapies such as these may become a new way of helping people with T1D prevent hypo episodes.

Who can participate?
People with T1D and a control group (non-DM group) without diabetes

What does the study involve?
People with T1D will be given a liquid form of glibenclamide for a maximum of 54 days, followed by a single dose of dapagliflozin, and undergo five controlled hypoglycaemia challenges (hypo clamps) over 8-10 weeks. The control group (non-DM group) without diabetes will undergo one hypoglycaemia challenge without extra medication

What are the possible benefits and risks of participating?
As this is a new method of using glibenclamide and dapagliflozin, the researchers are not sure whether it will make a difference to blood sugar levels. For participants with type 1 diabetes, the researchers can provide a print-out of the Libre 2 report at the end of each study step, which will

display the blood sugar levels day and night throughout the trial time frame.
Although this study at present might not change the way diabetes is managed, it will help get a better understanding of the mechanisms underlying hypoglycaemia in type 1 diabetes and whether these commonly used medications might have a new role in helping people with type 1 diabetes prevent hypoglycaemia episodes in the future.
The main serious side-effect of glibenclamide is hypoglycaemia, but the overall risk is low and is dose-dependent. In addition, it is not expected to have any effect on insulin release in participants with type 1 diabetes, as they will have lost most of their insulin-producing cells due to their condition. However, in case of hypoglycaemia, the symptoms can be managed by immediately having a glass of fruit juice (or a sugary drink), then having something to eat such as a banana, a slice of toast or your normal meal.
Other possible side effects of glibenclamide (relating to doses higher than those used in this study) include skin rashes, nausea and abdominal discomfort, particularly after drinking alcohol. Dapagliflozin can be associated with increased frequency in passing urine, dizziness or a mild skin rash, but these side effects are usually related to regular dosing rather than as a single dose.
The trial will be divided into four 2-week blocks (steps) and each will include a set-up visit and an induced hypoglycaemia challenge. It is not required to complete blocks back to back.
The hypoglycaemia challenge (hyperinsulinaemic hypoglycaemic clamp) involves continuous intravenous infusion of insulin and glucose, along with frequent (5 min) blood sampling to maintain blood glucose levels within specific targets. After a period of euglycaemia (target blood glucose 6 mmol/L), glucose levels will be gradually dropped and maintained at the hypoglycaemic range (target 2.5 mmol/L) for a total of 40 min, before glucose levels are then recovered back to euglycaemia. While this is a well-established procedure, the induction of hypoglycaemia can be stressful and the symptoms (sweating, palpitations, agitation, confusion) will likely not have been experienced previously by participants without diabetes. All participants will be screened for high-risk conditions, such as a history of seizures, significant ischaemic heart disease, hypertension or arrhythmias, and they will be monitored closely during the entire procedure.
Although only a small amount of blood is taken during each visit of the study and as such no significant after-effects are predicted, however, some people feel dizzy and faint during and after the blood sample is taken or develop an infection from where the blood is drawn. In addition, they might have a small bruise where the needle went in. To minimise these effects, the researchers will use aseptic techniques and appropriate venepuncture methods, as described within the NHS guidelines. Bruises can be painful, but are usually harmless and fade over the next few days. Some individuals may be sensitive to the adhesive that keeps the FreeStyle Libre Sensor (glucose monitoring sensor) attached to the skin. If significant skin irritation around or under your Sensor is noticed, participants will be advised to remove the Sensor and stop using the FreeStyle Libre system.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
July 2023 to May 2025

Who is funding the study?
University of Oxford (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1004710

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
PID16904, IRAS 1004710

Study information

Scientific Title
Low dose glibenclamide and dapagliflozin in type 1 diabetes mellitus

Acronym
LEGEND-D

Study objectives
Primary objectives:
To determine whether treating people with T1D for 14-18 days with glibenclamide at 0.3 mg, 0.6 mg or 3 mg daily can increase the counter-regulatory glucagon response during a hypoglycaemia (low blood sugar) challenge, compared to baseline (pre-treatment).

Secondary objectives:
1. Compare glucagon response during the hypoglycaemia challenge in participants without diabetes, to that of participants with T1D before and after treatment with glibenclamide (0.3 mg /day, 0.6 mg/day and 3 mg/day).
2. Compare increase in glucagon between normal glucose levels and lower levels at each glibenclamide administration in participants with type 1 diabetes against individuals without diabetes
3. Compare the amount of time spent in hypoglycaemia while taking glibenclamide from the baseline
4. Compare glucagon response during the hypoglycaemia challenge in participants without diabetes, to that of participants with T1D pre and post treatment with a single dose of 10mg dapagliflozin.
5. Compare the plasma somatostatin response during the hypoglycaemia challenge in participants without diabetes, to that of participants with T1D before and after treatment with a single dose of 10 mg dapagliflozin.
6. Characterise the development of hypoglycaemia symptoms during the hypo challenge

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 22/09/2023, South West - Central Bristol Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8197; centralbristol.rec@hra.nhs.uk), ref: 23/SW/0098

2. approved 22/09/2023, Medicines & Healthcare Products Regulatory Agency (10 South Colonnade Canary Wharf, London, E14 4PU, United Kingdom; +44 20 3080 6000; MHRA_CT_Ecomms@mhra.gov.uk), ref: CTA 21584/0473/001-0001

Study design
Open randomized controlled cross over trial

Primary study design
Interventional

Study type(s)
Efficacy

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

Interventions
The LEGEND-D trial is a pilot, randomised cross-over, single-centre, non-blinded, clinical trial which aims to investigate the effect low doses of glibenclamide (0.3 mg, 0.6 mg and 3 mg/day) and dapagliflozin (single dose of 10 mg) on the glucagon response during induced hypoglycaemia in people with type 1 diabetes, compared to non-diabetic individuals.

For participants with type 1 diabetes, the trial is divided into five steps and involves five hyperinsulinaemic hypoglycaemic clamps. Once step 1 (no medication) has been completed, the participants with type 1 diabetes will be randomised to a sequence of glibenclamide doses for the subsequent steps, followed by a single dose of 10 mg dapagliflozin. There will be a washout phase of at least 48 hours between each step (the half-life of the glibenclamide suspension is 8 hours). Participants without diabetes will undergo a single hyperinsulinaemic hypoglycaemic clamp, as they will not receive any study medication.

A computer-based randomisation system (Sealed Envelope Ltd, London, UK) will be used to allocate the participants to the specific treatment. It is of note that the randomisation process is not blinded, as participants will be told the doses of study medication they have to administer during each step.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Glibenclamide, dapagliflozin

Primary outcome(s)
Concentration of plasma glucagon will be measured at 40 min during the hypoglycaemic phase of the hyper-insulinaemic hypo-glycaemic clamp, at baseline (no medication) and at each dose step of glibenclamide. This will be performed only in participants with type 1 diabetes

Key secondary outcome(s))

1. Concentration of plasma glucagon measured during the hypoglycaemic phase of the hyperinsulinaemic hypoglycaemic clamp at 0, 15, 30 and 40 minutes. This will be carried out at baseline (no medication) for participants with and without type 1 diabetes, and at each dose step of glibenclamide for participants with type 1 diabetes.
2. Proportion of increase in plasma glucagon quantified by calculating the ratio between glucagon concentrations during the hypoglycaemic and euglycaemic phase at 0, 15, 30 and 40 min (e.g. glucagon concentration at 0 min during the hypoglycaemic phase divided by the glucagon concentration at 0 min during the euglycaemic phase). This will be carried out for participants with and without type 1 diabetes.
3. Percentage of time spent in hypoglycaemia (<4.0 mmol/L) measured from all Freestyle libre data collected at each dose step until the start of the hyper-insulinaemic hypo-glycaemic clamp from Freestyle Libre 2 data. This will be performed only on participants with type 1 diabetes.
4. Proportion of change in plasma glucagon measured by calculating the ratio between glucagon concentrations during the hypoglycaemic and euglycaemic phase at 0, 15, 30 and 40 min. This will be carried out at baseline (no medication) for participants with and without type 1 diabetes, and after a single dose of dapagliflozin 10 mg in participants with type 1 diabetes.
5. Proportion of change in plasma somatostatin measured by calculating the ratio between somatostatin concentrations during the hypoglycaemic and euglycaemic phase at 0, 15, 30 and 40 min. This will be carried out at baseline (no medication) for participants with and without type 1 diabetes, and after a single dose of dapagliflozin 10 mg in participants with type 1 diabetes.
6. Fasting C-peptide measured prior to the baseline hyperinsulinaemic hypoglycaemic clamp by quantifying plasma C-peptide level at the start of the hyperinsulinaemic hypoglycaemic clamp (participants with type 1 diabetes only).

Completion date
30/05/2025

Eligibility

Key inclusion criteria
Type 1 diabetes group:
1. Type 1 diabetes diagnosed ≥12 months prior to screening
2. Age 18-75 years
3. Either on insulin pump or multiple daily injections
4. HbA1c <10% (86 mmol/mol) at screening
5. Prior training regarding insulin dose-adjustment and management of hypoglycaemia
6. Willing and able to give informed consent for participation in the trial
7. In the Investigator’s opinion is able and willing to comply with all trial requirements

Non-diabetic group:
1. Age 18-75 years
2. HbA1c ≤6.0% (42 mmol/mol) at screening
3. Willing and able to give informed consent for participation in the trial
4. In the Investigator’s opinion is able and willing to comply with all trial requirements

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
19

Key exclusion criteria
Type 1 diabetes group only:
1. An episode of diabetic ketoacidosis in the previous 1 month
2. Severe hypoglycaemia requiring third party intervention on more than one occasion in the preceding 12 months
3. Active diabetic retinopathy (including proliferative diabetic retinopathy or vitreous haemorrhage in the past 6 months)

Type 1 diabetes and non-diabetic group:
1. Haemoglobin <125 g/L
2. History of seizure or coma
3. Pregnancy, breast feeding or women of childbearing potential without adequate contraception
4. Renal impairment (eGFR ≤50 ml/min) at screening
5. ALT >2.5×upper limit of the assay normal range or known liver disease, specifically bilirubin >30 µmol/L that is associated with other evidence of liver failure.
6. Uncontrolled hypertension (>180 mmHg systolic or > 100 mmHg diastolic)
7. History of ischaemic heart disease (unless has had successful reperfusion), stroke/transient ischaemic attack, ventricular rhythm disturbances or thromboembolic disease
8. On beta-blocker medication
9. A history of heart failure (New York Heart Association Class 3 or 4)
10. Untreated Grave's disease
11. History of ECG or stress test findings indicating active ischaemia or a condition that would compromise the participant's safety
12. Known history of porphyria
13. Concomitant use of bosentan
14. Known or suspected allergy to the trial product or related products
15. Have received any investigational drug within 3 months prior to screening
16. Systemic (i.e. other than topical) corticosteroid treatment within 30 days prior to the start or at any time during the trial period
17. Major psychiatric disease including eating disorders, history of drug and alcohol abuse
18. Known malignancy or any other condition or circumstance which, in the opinion of the investigator, would affect the participant's ability to participate in the protocol

Date of first enrolment
26/02/2024

Date of final enrolment
31/05/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM)
Oxford University Hospitals NHS Foundation Trust
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Leona M. and Harry B. Helmsley Charitable Trust

Alternative Name(s)
Helmsley Charitable Trust, The Leona M. and Harry B. Helmsley Charitable Trust, Leona M. & Harry B. Helmsley Charitable Trust, The Helmsley Charitable Trust, The Leona M and Harry B Helmsley Charitable Trust, Helmsley

Funding Body Type
Private sector organisation

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

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

IPD sharing plan summary
Available on request, Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 4.0	19/02/2025	20/03/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes