Oxford University Hospitals NHS
NHS Foundation Trust

Clinical Research Unit

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PARTICIPANT INFORMATION SHEET

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

We would like to invite you to take part in our clinical trial. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read this information, and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please ask us.

What is the purpose of the study?

The purpose of this study is to find out whether two medications, named glibenclamide and dapagliflozin, which are normally used for the management of type 2 diabetes, could help prevent low blood sugar levels in people with type 1 diabetes (T1D).

Type 1 diabetes (T1D) affects around 400,000 people in the UK, and it is caused by almost complete loss of cells that produce insulin, which is needed to balance the changes in blood sugar levels. People with T1D can find it very difficult to manage the variations in their blood sugar levels due to the need to continuously change the amount of insulin they have to take throughout the day. This can lead to episodes of low blood sugar levels, commonly called “hypos”, which is one of the most feared complications of managing diabetes with insulin.

Additionally, we know that in the T1D the balance of other hormones in the body is also affected. This includes the hormone glucagon, which raises blood sugar levels during hypo episodes. A better understanding of how this mechanism works and how it can be controlled could lead to treatments aimed at reducing the risk of hypoglycaemia (low blood sugar levels).

Glibenclamide is a type of anti-diabetic medication commonly used to increase the release of insulin from cells in the pancreas (an organ about the size and shape of a small banana, which is found behind the stomach). Recent laboratory studies have shown that these type of medications can also improve the release of glucagon, when used in very small doses. We previously carried out a small pilot study (LEGEND-A), which suggested that low doses of glibenclamide (0.3mg/day) could alter glucagon release in some people with type 2 diabetes without increasing the risk of hypoglycaemia. In addition, another type of anti-diabetic medication, called dapagliflozin, has also been shown to work on cells in the pancreas responsible for glucagon production.

Therefore, the aim of this follow-up study (LEGEND-D) is to find out whether similar doses of glibenclamide or a single dose of dapagliflozin could restore glucagon release in people with

T1D. We hope that add-on therapies such as these may become a new way of helping people with T1D to prevent hypoglycaemia.

The trial will involve 2 groups of participants:

a) People with T1D, who 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.

b) A control group without diabetes, who will undergo one hypoglycaemia challenge without receiving any medication.

During these challenges, we will gradually drop your blood sugar from a normal level (around 6 mmol/L) to a lower level (around 2.5mmol/L) for 40 minutes. The process is well-established, and you will be constantly monitored by our medical team.

We will use a continuous glucose monitor during the study in participants with T1D. All participants will need to attend the OCDEM Clinical Research Unit at the Churchill Hospital, Oxford for an initial screening visit. This will be followed by 8 study visits over a period of 8-10 weeks (divided into around 2-week blocks) for the people with T1D, and the people without diabetes will have just 1 study visit.

This study is funded by The Leona M. and Harry B. Helmsley Charitable Trust.

Why have I been invited?

You are being invited because:

You have a diagnosis of type 1 diabetes.

Or

You are non-diabetic individual interested in participating in research.

In this follow-up pilot trial, we are aiming to recruit 20 people who have type 1 diabetes, and 10 people who do not have diabetes.

Do I have to take part?

No. This study is voluntary and you are free to decide whether or not you would like to take part.

If you do decide to take part in this study, then in addition to being given this information sheet you will be asked to sign a consent form. Even after signing this form you are free to withdraw at any time without giving a reason. If you decide you don't want to take part or if you withdraw from the study, this will not affect the standard of medical care you will receive in the future.

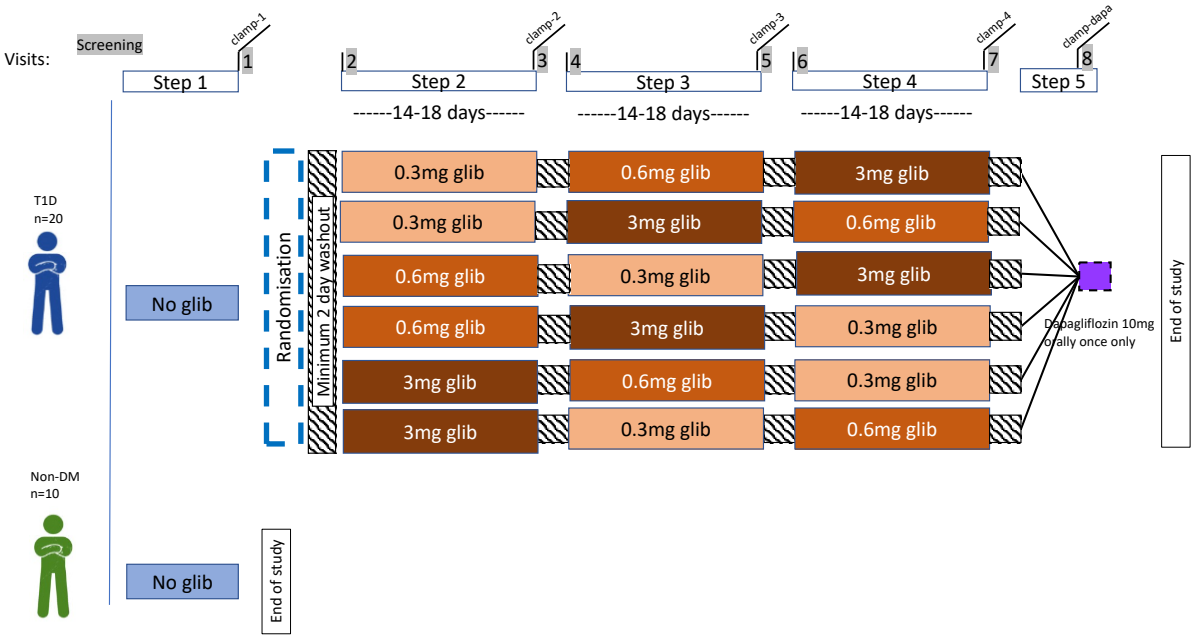
What will happen to me if I decide to take part?

You will be asked to attend the Clinical Research Unit (CRU) in OCDEM, Churchill Hospital, Headington, Oxford for a screening visit (lasting approx. 1 hour), where you will have the opportunity to discuss any questions you might have with a member of the research team. If you are eligible and happy to proceed, you will be asked to sign and date a consent form, a copy of which we will provide to you.

We will note your height, weight, and other aspects of your medical history, and details of your current medications. We will also take some blood samples (approximately 10mL) to ensure it is safe for you to take part in the study, and perform a urine pregnancy test (pre-menopausal females only).

For participants in the T1D group: we will also show you how to apply the Freestyle Libre 2 (flash glucose monitor) and explain to you how to collect regular readings from it via your smartphone or a Libre device monitor that we will provide (if required) for use during the study (see section below).

You will be invited to return to the CRU as follows:



Picture 1 Image showing the timeline and the steps, with associate visits, of the Trial

For participants with T1D

The study will last approximately 8 – 10 weeks, divided into blocks, called “Steps”, and will involve a further 8 visits as described above (picture 1):

Step 1: **Visit 1** – this visit will last approximately 4 hours during which we will measure your blood pressure and heart rate, assess your current health status and perform the first of the hypoglycaemia challenges. No medication will be given on this visit.

Step 2: **Visit 2** – this visit will last about 30 minutes during which we will again measure your blood pressure and heart rate and assess your current health, give you the glibenclamide medication to take home with you and explain how to take the medication and what doses you should take.

You will also receive a leaflet of the medication and we will explain which sections are relevant to you.

Visit 3 – this visit will be 14-18 days after visit 2 and will last around 4 hours during which, alongside assessing the state of your health, the second hypoglycaemia challenge will be performed.

Step 3: **Visit 4** – this visit will again last around 30 minutes and will follow the format of visit 2.

Visit 5 – this visit will again last around 4 hours and will follow the format of visit 3

Step 4: **Visit 6** – this visit will again last around 30 minutes and will follow the format of visit 2.

Visit 7 – this visit will again last around 4 hours and will follow the format of visit 3

Step 5: **Visit 8** - We will ask you to attend a final visit of around 4 hours duration, during which we will again measure your blood pressure and heart rate and assess your current health. You will be given one 10mg dapagliflozin tablet and we will perform the last hypoglycaemia challenge (see picture 1).

The timing of these steps will be flexible and planned around your schedule in order not to interfere with your personal commitments.

Before attending the visits where hypoglycaemia challenges will be involved, we will kindly ask you to fast overnight (i.e. not eat breakfast). If you have T1D, we will kindly ask you not to take your quick acting (meal-time) insulin on the morning of the visit, but you can still take your basal insulin as usual.

Control group (without diabetes)

After completing the hypoglycaemic challenge at study visit 1, you will have reached the end of the study. You will be contacted by phone 4-7 days later to check how you are feeling.

Medication and blood tests:

Participants with T1D

At the beginning of *Step 2*, you will be given a bottle of medication (glibenclamide) in suspension (similar to children's liquid medication) and instructions on how much to take twice daily. The doses will range from 0.3mg daily (about 1/15th the usual starting dose) to 3mg daily (just over half the usual starting dose of 5mg). In terms of volume, this will range from 0.25ml (less than 1/10th of a teaspoon) to 2.5ml (around 1/2 teaspoon). As these are small quantities and it is important to be as accurate as possible, you will also be given a syringe (similar to those used for children's liquid medication) to help with measuring out the glibenclamide.

During each *Step*, the dose of glibenclamide will be different, and the order will be **randomised**. You will take 0.3mg, 0.6mg and 3mg daily in a random order, but you will always know how much medication you are taking.

While you are taking the glibenclamide we will ask you to complete a dosing record to detail each time you take a dose of the medication. These will then be collected at your next visit.

The volume of blood collected during the trial will vary depending on whether you have diabetes or not, and will be approximately:

- T1D group: 180ml (around 10 tablespoons of blood) during each hypoglycaemia

challenge. The total amount of blood taken throughout the trial period will be 900 ml (around 1 ½ pints of blood – compared to 1 pint which is the amount given during normal blood donation)

- Control group without diabetes: 180ml (around 10 tablespoons of blood)

Flash glucose monitoring (Freestyle Libre 2):

Participants with T1D

As part of the study, you will be asked to wear a flash glucose monitor (Picture 1) which will collect and display information about blood glucose variation Freestyle Libre is a cloud-based diabetes management system controlled by Abbot Laboratories .The Libre 2 system, which is CE marked (meaning that the product satisfies the international legislative requirements), consists of a senor with a small plastic tube (called a cannula) placed into the skin of your arm. The sensor wirelessly sends information to a separate monitor device (or compatible mobile phone) every time you scan it. It needs to be scanned at least every 8 hours, and sends information about how your blood sugar has been changing. The sensor can be worn throughout the day, including while showering or sleeping. You will be shown how to attach and remove the sensor, which can be disposed of in a normal rubbish bin, and we will give you the user manual of the device to refer to if needed. You can also visit the manufacturer website (https://www.freestyle.abbott/uk-en/support/tutorialsanddownloads.html) if you wish to see tutorial videos on how to best use this device.

If you are already using a different continuous glucose monitor as part of your normal diabetes management, then we would ask that you use the provided Libre 2 in addition to that.

Picture 1 Flash glucose monitoring system (Freestyle Libre 2)

End of study:

Any left-over liquid medication will be collected at the end of the hypoglycaemia challenge visits. Following the final visit, you will be contacted by phone 4-7 days later to check how you are feeling and if there have been any problems. No additional study information will be collected.

The study medications will not be made available after the end of the study, as we are still investigating them.

What should I consider?

If you have experienced severe hypoglycaemia episodes (involving seizures or a coma) then you will not be able to take part in this study.

In addition, you will not be eligible for this study if you are taking beta-blockers, bosentan medication, or systemic (i.e. other than topical) steroids within 30 days prior to the start or at any time during the trial period. Your regular medications will be reviewed at the screening visit to make sure they would not be influenced by the study medication, and you will be able to take your regular medication throughout the study.

You may not be able to take part in the study if you have:

- significant diabetic retinopathy (eye disease)
- kidney failure
- heart failure or ischaemic heart disease
- previously had a stroke or transient ischaemic attack (TIA)
- certain heart rhythm abnormalities
- a history of blood clots
- Untreated Graves' disease
- Cancer

In addition, if you are pregnant, breastfeeding, or trying to have a baby (i.e. not on an oral contraceptive pill, contraceptive coil/patch/injection or using a barrier method), then you will also not be able to take part in the study. This is because pregnancy can alter the hormones we will be checking.
Please notice that acceptable forms of contraception include the followings: -

- Hormonal contraceptives. This includes the pill, mini-pill, contraceptive injection or implant.
- Placement of an intrauterine device or intrauterine system. These are also known as the copper coil or hormone coil (e.g. Mirena coil).
- Vasectomy (male sterilisation), if this is your only partner.
- Complete abstinence from any sexual relationships in which you may become pregnant. Periodic abstinence and withdrawal methods are not acceptable.

If you become pregnant during the study time, we will stop you from taking part in any study activities including giving you the study medication, and with your permission, we will continue to follow you up for safety reasons only until the baby is born. No other study information will be collected.

Finally, we appreciate that you might have been involved in other research projects, and as long as you haven't had any other study medications in the previous 3 months you would still be eligible for the study.

Are there any possible disadvantages or risks from taking part?

Glibenclamide itself has been used in the treatment of type 2 diabetes for nearly 50 years, and so we are very familiar with its safety profile. The suspension uses ingredients commonly used in other liquid medications.

The main risk with **glibenclamide** is that it can cause low blood glucose (hypoglycaemia) if taken in excess. It is not, however, 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.

We will give each participant details of the symptoms and management of hypoglycaemia, but these are also summarised below:

> *Symptoms of hypoglycaemia vary from person to person but can include: feeling shaky, sweating, hunger, tiredness, blurred vision, lack of concentration, headaches, irritability and going pale. These 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 (again 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 **hypoglycaemia challenge (hypoglycaemic clamp)** will involve gradually dropping your blood sugar from normal levels (around 6mmol/L) to low levels (2.5mmol/L) for a period of 40min. While this is a well-established procedure, this change in blood sugar can be stressful and people without diabetes will probably not have experienced the symptoms before. All participants will be screened for high risk conditions, and they will be monitored closely during the entire procedure.

Although only a small amount of blood is taken during each visit and as such you shouldn't feel any significant after-effects, however some people feel dizzy or faint during and after the blood sample is taken. We will always use appropriate sterile techniques to minimise the risk of any infection or bruising, as we would normally do during our usual clinical practice.

Some individuals may be sensitive to the adhesive that keeps the FreeStyle Libre Sensor attached to the skin. If you notice significant skin irritation or discomfort around or under your Sensor, remove the Sensor, stop using the FreeStyle Libre system and contact the study team who will inform you on what to do next

During all study visits we will be adhering to the latest **local and national guidelines regarding COVID-19, or any other infections**.

What are the possible benefits of taking part?

As this is a new method of using glibenclamide and dapagliflozin, we are still not sure whether it will make a difference to blood sugar levels. For participants with T1D, we can provide you with a print-out of your Libre 2 report at the end of each Step. This will display your blood sugar levels day and night throughout the 2 weeks, and may be of interest to you.

This study will at present not change the way diabetes is managed. It will however help us better understand the mechanisms underlying hypoglycaemia in type 1 diabetes and whether these commonly used medications might have a new role in the helping people with T1D prevent hypoglycaemia episodes.

Will my General Practitioner/family doctor (GP) be informed of my participation?

Yes, your GP will be informed that you are taking part in this clinical trial, as it may affect your clinical care (for example, if you need to start extra medication). In addition, the results of some of your blood tests will be made available to your GP.

Will my taking part in the study kept confidential?

Yes, all information in this study is confidential. You will be assigned a study ID number which will be used on all study documents instead of your name. All documents will be stored securely and only accessible by study staff and authorised personnel.

Results of blood samples taken for baseline tests will be made available to your GP as part of the hospital laboratory's sample processing procedure. Information identifying these blood results will include your name, date of birth, study ID and NHS number, but will only be seen by the CRU and laboratory personnel (in addition to your GP). We will bring to the attention of your GP any abnormal blood results.

Blood samples analysed within the University of Oxford will be labelled with the Study ID only to ensure that you will not be identified.

Responsible members of the University of Oxford, regulatory authorities and the OUH NHS Trust(s) may be given access to your data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

Will I be reimbursed for taking part?

Participants with T1D will be reimbursed at the level of £625 upon completing the trial, to account for loss of earnings and inconvenience. We will reimburse participants who do not fully complete the trial pro rata based on the number of completed hypoglycaemia challenges.

The participants without diabetes will be reimbursed at a level of £125 upon completion of the trial.

We will reimburse reasonable travel expenses for any visits additional to normal care.

What will happen to the samples I give?

Blood samples collected during the study will be analysed for levels of blood sugar, C-peptide, glucagon and somatostatin (another hormone).

We will process and store these blood samples in OCDEM at the Churchill Hospital, Oxford, for one year after the end of the study, in order to verify any results. Screening blood tests will be performed at the OUH NHS Foundation Trust clinical laboratories. Once all analysis has taken place and the results verified, we will destroy the samples.

For female participants who are not post-menopausal, we will collect a urine sample for pregnancy testing (the rest of the sample will be discarded according to the local procedure). We will do this initially at the screening visit and repeat it at Visits 1, 2, 4, 6 & 8. If deemed necessary by our research clinicians, this test can also be done on the other visits of the

study.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the sponsor for this study. It is the data controller, and is responsible for looking after your information and using it properly.

We will be using information from you and your medical notes in order to undertake this study and will use the minimum personally-identifiable information possible.

We will store any research documents with personal information, such as consent forms, securely for 5 years after the end of the study, as part of the research record.

We will store the pseudo-anonymised research data in the Oxford Research Archive (http://ora.ox.ac.uk/) at the University of Oxford and stored securely for 5 years after the end of the study. This will provide a link between the results presented in publications and the underlying data.

The research team will use your name, NHS number and contact details as well as contact details for your GP to make sure that relevant information about the study is recorded for your care.

All research documents with participants' personal information, such as ICFs will be stored at the research site and archived in line with university departmental procedures. If you are a patient, a copy of the consent form from this study will be kept in your medical records for as long as those records are retained according to local NHS policy and procedure.

The information collected by the continuous glucose monitor will be stored securely in the Abbott Laboratories (manufacturer) cloud based system in an anonymised manner with no links to you for 90 days, after which your de-identified data will be integrated to other data within their system. This further ensures that you are not traceable. This glucose monitor system has been assessed and deemed safe to collect your information by the University of Oxford information security team.

An electronic Trial Master File (eTMF) will also be adopted for data keeping and filing. The eTMF server is located in an access restricted area and will be used to archive your data for a maximum of 25 years. The anonymised database will be kept indefinitely. Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights

You can find out more about how we use your information by contacting the study chief investigator at the following email address: ioannis.spiliotis@ocdem.ox.ac.uk

What will happen if I don't want to carry on with the study?

You are free to withdraw from this study at any time without giving any reason. We will ask whether we may keep in contact with you to find out your progress. We will also ask whether you are happy for us to use the information and/or blood samples collected from you up to that point. If you are unhappy with this, any stored samples, identified as yours, will be destroyed.

What will happen to the results of this study?

The aim of this study is to further our knowledge of diabetes and its management. The results of this study will be presented at regional, national and international meetings, and published in medical journals. All results and information will be de-identified. If you wish to know the outcome of the study, please contact us and we can direct you to where the results are published in a scientific journal or to the website. If you wish to keep up to date with the study progress, please visit the following webpage: https://www.rdm.ox.ac.uk/about/our-clinical-facilities-and-mrc-units/DTU/current-trials/legend-d

What if you find something unexpected?

If we identify clinically relevant abnormal blood results during the baseline screening tests then we will notify your GP.

What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided and any compensation will be paid on a “no fault” basis.

If you wish to complain about any aspect of the way in which you have been approached or treated or how your information is handled during the course of this study, you should contact Dr. Ioannis Spiliotis on 01865-857284 (email: ioannis.spiliotis@ocdem.ox.ac.uk) or you may contact University of Oxford Research Governance, Ethics & Assurance (RGEA) on 01865 616480, or the director of RGEA at rgea.complaints@admin.ox.ac.uk

How have patients and the public been involved in this study?

We used a Patient Involvement Project to help design the previous trial (LEGEND-A): we consulted 68 patients with type 2 diabetes (who had previous given their consent to be contacted about future research) on the clinical trial protocol. Their contributions were very much appreciated and directly influenced the design of the dosing record in both the LEGEND-A and LEGEND-D studies.

In addition, we presented our proposal for the current study to the Oxford Diabetes Patient Panel. Their feedback helped us include the onset of hypoglycaemic symptoms as part of our investigations.

Who is organising and funding the study?

This study has been designed and is being coordinated by the Oxford Centre for Diabetes, Endocrinology and Metabolism. It is sponsored by the University of Oxford and funding for the study is provided by a grant from The Leona M. and Harry B. Helmsley Charitable Trust.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by South West - Central Bristol Research Ethics Committee.

Participation in future research

We will contact you for future studies happening in our department that we think might be of your interest. In order to do this, we will retain your contact details. These details would be held securely, separately from this study on a password protected computer at the Oxford Centre for Diabetes Endocrinology and Metabolism. Your contact will only be accessible by the chief investigator and research nurses, part of our research team. Agreeing to be contacted does not oblige you to take part in future research. If you wish for us not to contact you in future, please notify one our team members at any time so that we can remove you from our contact list.

Further information and contact details:

Dr. Ioannis Spiliotis
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Thank you for considering taking part.