LEGEND-D Protocol Lay Summary

Type 1 diabetes (T1D) affects around 400,000 people in the UK and is caused by nearly complete loss of insulin-producing cells in the pancreas. It is often challenging to achieve good control of blood glucose throughout the day in T1D, in part because of fluctuations associated with giving insulin. Severe episodes of low blood sugar levels, commonly called “hypos”, are one of the most feared complications of managing diabetes with insulin.

The impaired release of other hormones, such as glucagon which raises blood sugar, during hypo episodes is also part of type 1 diabetes. A better understanding of this mechanism could lead to treatments aimed at reducing the risk of hypoglycaemia.

Glibenclamide is a type of anti-diabetic medication (sulfonylurea) which is commonly used to increase the amount of insulin released by the pancreatic beta-cells. Recent pre-clinical 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. We have previously conducted a 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 pancreatic alpha-cells.

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) 20 people with T1D, who will be given a liquid form of glibenclamide for a maximum of 54 days (at 3 different doses, in 3 blocks of 14-18 days), followed by a single dose of dapagliflozin, and undergo five controlled hypoglycaemia challenges.

b) A control group of 10 people without diabetes, who will undergo one hypoglycaemia challenge without receiving any medication.

During these challenges, we will gradually drop the participants’ blood sugar from a normal level (around 6 mmol/L) to a lower level (around 2.5mmol/L) for 40 minutes. While this is a well-established procedure, this change in blood sugar can be stressful and participants without diabetes will probably not have experienced the symptoms before. We will screen all participants for high risk conditions, and monitor them closely during the entire procedure.

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.

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