SGLT2 inhibitors to target prediabetes in adults: a randomised, double-blind, placebo-controlled, parallel-group, proof-of-concept study.

Background

Clinical trials on the prevention of progression from prediabetes (impaired glucose tolerance or impaired fasting glucose) to diabetes provide evidence that beta-cell function can be improved in adults by pharmacologic therapies including metformin, insulin, and GLP1 receptor agonists (Ras).

In adults at risk for diabetes, a reduced risk of progression to type 2 diabetes was observed after metformin use in The Diabetes Prevention Program (DPP) and Indian Diabetes Prevention Program (Knowler, N Engl J Med 2002; Ramachandran, Diabetologia 2009) and after long-acting insulin glargine use in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) study (ORIGIN Trial Investigator, N Engl J Med 2012).

The SCALE Obesity and Prediabetes trial showed the effect of liraglutide in reducing the risk of type 2 diabetes in patients with pre-existing prediabetes over a three-year follow-up (Pi-Sunyer, N Engl J Med 2015).

Preliminary data have been published on the protective effects of SGLT2 inhibitors on beta-cells in mice (Kimura, Diabetes Obes Metab 2018), but it is not yet know whether they could delay the onset of type 2 diabetes in humans. Remarkably, these diabetes drugs are effective also in euglycaemic subjects. Compared with placebo, canagliflozin significantly reduced body weight in overweight and obese subjects without diabetes mellitus (Bays, Obesity 2014).

Hypothesis

SGLT2 inhibitors might be able to contrast the progressive decline in beta-cell function observed in prediabetes, through several mechanisms of action.

Objectives

To evaluate preservation or improvement in beta-cell function in prediabetes under SGLT2 inhibitor treatment and persistent benefits after withdrawal of therapy.

Primary outcome is intravenous glucose tolerance test (IVGTT)-derived glucose-stimulated C-peptide secretion; measurements are made at baseline, after 12 months of treatment, and 3 months after treatment withdrawal.

Secondary outcomes:

- Oral glucose tolerance test (OGTT)-derived measures of beta-cell function (measurements are made at baseline, after 6 and 12 months of treatment, and 3 and 6 months after treatment withdrawal);
- HbA1c (measured at baseline, after 6 and 12 months on treatment, and 3 and 6 months after treatment withdrawal);
- Body weight and composition (measured by dual-energy X-ray absorptiometry at baseline and after 12 months on treatment);
- Lipid panel, including FFA (at baseline, after 6 and 12 months of treatment, and 3 to 6 months after treatment withdrawal).

Main inclusion criteria

Adults (male or females) with impaired fasting glucose or impaired glucose tolerance; age 20-65 years; BMI 25-40 kg/m^2; glucose-lowering medication–naïve.

Safety Surveillance

For the unlikely events of hypoglycaemia or euglycaemic DKA, participants will be given glucometer and ketone meter. Subjects will be instructed not to fast, nor follow low-carb diets.

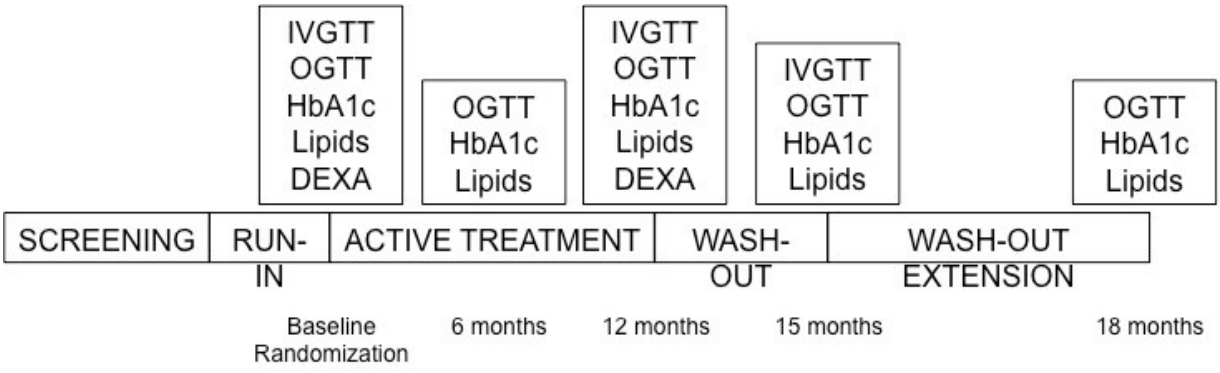
Sample size

A sample size of 56 per arm (112 total) at the end of the washout was estimated to provide 80% power to detect a minimum effect size of 0.60 SD units favouring SGLT2 inhibitors.

DESIGN:

Experimental, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial. Eligible subjects will be randomized to 12 months of SGLT2 inhibitor or placebo in a 1:1 ratio. The complete wash-out period lasts 6 months. A 3-week run-in period is required prior to randomization. The duration for recruitment is 24 months.

Analysis will be conducted according to the ITT principle.



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Planned publication Target

Diabetes Care / Diabetes

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