Objective: The objective of this study is to find out whether adults with type 1 diabetes can reach better levels of blood glucose on a triple therapy combination (dapagliflozin, semaglutide, and insulin) than on either a dual therapy combination (semaglutide and insulin) or insulin only (standard) treatment. As well as blood glucose, we will check the effects of the triple and dual therapy combinations on blood pressure, weight, quality of life, side effects, and a number of hormones.

Background/Rationale: Most people with type 1 diabetes struggle to reach and then keep their blood sugar close to target with an HbA1c level of less than 7.0%. High and low blood sugars lead in time to serious complications including eye, kidney, and nerve damage, as well as premature heart attacks and strokes. Life expectancy is shortened by around 12 years, so there is clearly an urgent need for better treatments. Our recent studies have shown that two different new medicines approved for type 2 diabetes can, separately, improve blood sugar control when used as dual therapy combinations with insulin in type 1 diabetes. These are dapagliflozin (an SGLT-2 inhibitor taken by mouth once daily) and liraglutide (a GLP-1 receptor agonist taken by injection once daily). Very recently a once weekly and more powerful GLP-1 receptor agonist, semaglutide, has become available. We now want to find out whether adults with type 1 diabetes can reach better levels of blood glucose on a triple therapy combination with dapagliflozin, semaglutide, and insulin than when they use a dual therapy combination (semaglutide and insulin) or insulin only (standard) treatment.

Description of the Project: Most people with type 1 diabetes struggle to reach and then keep their blood sugar close to target with an HbA1c level of less than 7.0%. High and low blood sugars lead in time to serious complications including eye, kidney, and nerve damage as well as premature heart attacks and strokes. Life expectancy is shortened by around 12 years, so there is clearly an urgent need for better treatments. Recent studies have shown that two different new medicines approved for type 2 diabetes can, separately, improve blood sugar control when used in type 1 diabetes. These are dapagliflozin (an SGLT-2 inhibitor taken by mouth once daily) and liraglutide (a GLP-1 receptor agonist taken by injection once daily). We have conducted a pilot study asking people with type 1 diabetes to add both these medicines in with their insulin treatment. With the “triple therapy” combination, there were improvements in blood sugar control (HbA1c fell by another 0.66%), body weight, and blood pressure. We now need to test whether adding dapagliflozin and semaglutide (a once weekly GLP-1 receptor agonist), to insulin treatment in these individuals can improve blood sugar control, help achieve HbA1c levels of less than 7.0%, and improve blood pressure, body weight, and quality of life. The study will be conducted in two centers (one in the U.S. and one in Glasgow, UK) over one year for each participant and will compare three different combination of therapies. One hundred and fourteen people with type 1 diabetes aged 18-65 years and with current HbA1c >8.0 % despite regular fingerstick testing and carbohydrate counting will be invited to take part. During the first six months, those who agree will either continue on their usual insulin treatment or start semaglutide 1mg once weekly along with their usual insulin. During the second six months, those who were taking semaglutide in the first six months will continue to take it along with either active dapagliflozin medication (10mg daily) or a matching inactive (placebo), masked until the study has finished. The group taking usual insulin treatment in the first six months will continue as before, and all participants will have the same number of study visits and assessments. We will check how the different treatments are working by measuring average blood sugar over a period of three months (HbA1c), rates of low blood glucose (“hypos”), time spent in an acceptable range of blood sugar, sugar, and other hormone levels following a meal, as well as change in insulin dose, blood pressure, and body
weight. Side effects, including any rise in urine ketones, will be carefully monitored and managed with regular telephone and in-person contact. We will store blood, urine, fat, and other cells so that we can later do laboratory experiments to understand how these medicines act in type 1 diabetes. Overall, the study will show whether and how the triple therapy combination can improve blood sugar, weight, and blood pressure control, and quality of life. If so, it could be a useful strategy to help people with type 1 diabetes avoid long term complications and enjoy a better life expectancy.

**Anticipated Outcome:** If the study shows that the triple therapy combination (semaglutide, dapagliflozin, and insulin) is safe and more effective than a dual therapy combination (semaglutide and insulin) or insulin only, it will be more widely adopted by adults with type 1 diabetes who are struggling to keep their blood sugar close to target despite multiple daily fingerstick tests and careful carbohydrate counting. If our early findings are confirmed, this will lead to better quality of life and a lower risk of long-term complications of diabetes for these individuals.

**Relevance to Type 1 Diabetes:** Currently, people with type 1 diabetes have limited options to manage their blood sugar levels. The scientific community as well as the patient community is eagerly waiting for ground-breaking, comprehensive, and lasting treatment for this disease, such as effective and durable islet or pancreatic transplants or efficient and user-friendly artificial pancreas/pumps. In the meantime, other alternatives should be tested to support, improve, and augment current treatment with insulin. The suggested new adjunct therapies currently approved for type 2 diabetes may just provide such practical and simple additional options. Not only we predict that these additional therapies will contribute to significant improvements in blood sugar control, but they might also have additional benefits such as weight loss and blood pressure reduction. These combined effects should provide additional protection from known complications of type 1 diabetes.