STATISTICAL ANALYSIS PLAN

Obesity Treatments to Improve Type 1 Diabetes. The OTID trial

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Principal Investigator

Dr. Ebaa Alozairi

Sponsor

Ulster University

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Abbreviations

ADA - American Diabetes Association

AE - Adverse Events

CKD - Chronic kidney disease

CSII - Continuous subcutaneous insulin infusion

CI – Confidence intervals

FMTC - Familial medullary thyroid carcinoma

GLP1RA - Glucagon-like peptide 1 receptor analogues

HbA1c - Glycated haemoglobin

ITT - Intention-to-treat

MMRM - Mixed model for repeated measures

OTID - Obesity Treatments to Improve Type 1 Diabetes

PP – Per-protocol

RCT - Randomized controlled trial

SAE - Severe Adverse Events

SGLT2i - Sodium-glucose cotransporter-2 inhibitors

T1D - Type 1 diabetes

T2D - Type 2 diabetes

UU - Ulster University

1.0 Study design

This is an open-label, single-center, randomised-pilot study to investigatethe safety and efficacy of combining glucagon-like peptide-1 (GLP-1) analogues with sodium glucose cotransporter 2 inhibitors (SGLT2i) in patients with type 1 diabetes, BMI ≥25 kg/m^2, and early chronic kidney disease. The total duration of participation of follow-up will be 6 months.

Patients will be randomised at a ratio of 1:1:1:1:1 to:

1. Usual care,
2. SGLT2i alone,
3. GLP-1 analogues alone,
4. GLP-1 analogues plus SGLT2i,
5. GLP-1 plus SGLT2i plus lifestyle modification

1.1 Eligibility criteria

1.1.1 Key Inclusion criteria

To be considered eligible to participate in this study, a patient must:

• Be aged between 21-65 years;

• Have a BMI >25kg/m^2;

• Have established diagnosis of T1D (per ADA 2022 definition/criteria) for at least 1 year before screening visit;

• Insulin treatment for T1D may be either via any Food and Drug; Administration approved Continuous subcutaneous insulin infusion pump (CSII) for at least 6 months prior to screening visit or via multiple daily insulin injections. All participants must be stable on insulin doses/ regimen for at least 3 months

• Have established diagnosis of CKD 1-4;

• Able to give informed consent.

1.1.2 Key Exclusion criteria

Participants will be excluded if:

• They have been treated with GLP1RA or SGLT2i within the last 3 months and/or have a history of GLP1RA or SGLT2i intolerance;

• Diagnosis of T2D or any other type of diabetes (other than type 1);

• Treatment with anti-obesity drugs within 12 weeks prior to randomization;

• Significant changes in the lifestyle (Diet or exercise pattern in within 3 months of the screening visit);

• Any self-reported changes (gain or loss) in body weight >5% within 3 months of screening visit;

• eGFR ≤15 mL/min/1.73m^2 ;

• Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using or willing to use adequate contraceptive methods during the study period;

• Experienced diabetic ketoacidosis within 6 months of screening visit;

• Experienced sever hypoglycaemia within 6 months of screening visit;

• Any of the following laboratory values at screening (liver chemistry > 3X upper limit of normal, high triglyceride (> 5.7 mmol/L);

• Have terminal illness or are not primarily responsible for their own care;

• Any other significant disease or disorder which in the opinion of the investigator, may either put the participants at risk or may influence the result of the study or the participant's ability to participate;

• Untreated or uncontrolled hypothyroidism/hyperthyroidism defined as thyroid-stimulating hormone >6 mIU/litre or <0.4 mIU/litre;

• Family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC);

• Personal history of non-familial medullary thyroid carcinoma;

• History of chronic pancreatitis or idiopathic acute pancreatitis;

• Amylase levels three times higher than the upper normal range;

• Obesity induced by other endocrinologic disorders (e.g. Cushing's syndrome);

• Current or history of treatment with medications that may cause significant weight gain, within 12 weeks prior to randomization, including systemic corticosteroids (except for a short course of treatment, i.e. 7−10 days), atypical antipsychotic and mood stabilizers (e.g. clozapine, olanzapine, valproic acid and its derivatives, and lithium);
• Initiation of antidepressants during the last 12 weeks;
• Previous surgical treatment for obesity (excluding liposuction if performed >1 year before trial entry);
• History of other severe psychiatric disorders;
• History of known or suspected abuse of alcohol and/or narcotics;
• History of major depressive episode during the last 2 years;
• Simultaneous participation in other clinical trials of investigational drugs, lifestyle or physical activity interventions. Patients will only be able to take part following participation in a previous clinical trial after a wash-out period of 16 weeks;
• History of dementia or cognitive impairment.

1.2 Sample size

The sample-size calculation assumed at least a 10-percentage-point difference in the mean weight reduction from baseline at 26 weeks for the combination of GLP1RA plus SGLT2i plus lifestyle modification as compared with usual care, a common standard deviation of 10%, and a dropout rate of 17%. Using these parameters, we planned to have 90% power to detect statistically significant differences between the groups at α 0.05. This estimation was based on the available evidence for body weight reduction using liraglutide 3mg daily (13) or semaglutide 1mg weekly (14), dapagliflozin 10mg daily (15) and the weight loss achieved at the Dasman Diabetes Institute when standard care was provided in people with T1D.

2.0 Assignment of intervention

2.1 Sequence generation

Randomization will be carried out by the Sponsor at Ulster University (UU) on the first visit after screening and after confirmation of the participants eligibility is received by the research team at Dasman Diabetes Institute. Randomization will be carried out via www.sealedenvelope.com. Patients

will be randomised at a 1:1:1:1:1 ratio to each of the interventions of the trial. Randomisation is blocked, using random permuted blocks, to ensure that the groups are balanced periodically.

2.2 Concealment mechanism

Randomization will be carried out via www.sealedenvelope.com. The investigator will text the participant's code to the website and receive the randomisation back directly from the website in order to maintain the integrity of the concealment mechanism. The allocation will be announced to the patient at the same visit.

2.3 Implementation

Randomization will be carried out via www.sealedenvelope.com, a central randomisation system. The investigator will text the participant's code to the website and receive the randomisation back directly from the website in order to maintain the integrity of the concealment mechanism. The allocation will be announced to the patient at the same visit.

3.0 Study objectives and endpoints

3.1 Study objective

The study objective is to perform a randomised clinical trial (RCT) investigating the clinical effectiveness of patients receiving either: the usual care, or glucagon-like peptide-1 (GLP-1) analogue alone, or sodium glucose cotransporter 2 inhibitors (SGLT2i) alone, or combining GLP1RA and SGLT2i, or combining GLP1RA and SGLT2i and lifestyle modification in patients with type 1 diabetes, BMI ≥25 kg/m2, and early chronic kidney disease

The primary objective is to compare the clinical effectiveness of patients receiving either: the usual care, or glucagon-like peptide-1 (GLP-1) analogue alone, or sodium glucose cotransporter 2 inhibitors (SGLT2i) alone, or combining GLP1RA and SGLT2i, or combining GLP1RA and SGLT2i and lifestyle modification in patients with type 1 diabetes, BMI >25 kg/m^2, and early chronic kidney disease

3.2 Study endpoints

Primary endpoint

The primary outcome will be the percentage change in total body weight at 6 months.

Secondary endpoints

Secondary outcomes at 6 months will be:

Change in waist circumference

Percentage of participants losing ≥5, ≥10 and ≥15% of their body weight

Change in albumin creatinine ratio

Change in renal function

Change in HbA1c

Change in glycemic endpoints measured by continuous glucose monitoring (glucose time above range, glucose time below range, glucose coefficient of variation)

Change in mean 24 hour systolic blood pressure

Change mean 24 hour diastolic blood pressure

Change in lipid profile

Change in liver function

4.0 Analysis population

4.1 Intention-to-treat population

We will recruit 60 participants, with each group comprising twelve participants randomised at a 1:1:1:1:1 ratio. The intention-to-treat (ITT) population will include all patients who were initially assigned to either group, regardless of any deviations from the trial protocol or the actual treatment they received. The analysis of this population will be based on their original assignment group.

4.2 Per-protocol population

Per-protocol (PP) population included all randomised participant who completed the trial at 6 months without major deviation from the study protocol.

5.0 Statistical analysis

We will use SPSS (version 27, IL, USA) for all analyses. Two-sided P-values < 0.05 will be considered statistically significant. Summary statistics for continuous measures will include sample size, mean, SD, median, interquartile range. Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Summary statistics for discrete count measures will include sample size, mean, and standard deviation, median, minimum, and maximum. The Fisher's exact test will be used to examine the treatment difference in categorical outcomes.

5.2 Efficacy analysis

The primary outcome is % total body weight loss at 6 months. The primary analysis of the primary outcome will employ a hierarchical model. Secondary analysis of the primary and all secondary outcomes will utilize a mixed model for repeated measures. Primary and secondary analyses will be conducted on the ITT and PP populations.

5.2.1 Hierarchical model

The primary outcome will be analysed following the hierarchical model to compare the effectiveness of different treatment groups in a stepwise manner, employing parametric tests based on the established normality of the data distribution, as follows:

(i) Difference in % total body weight loss between the combination of GLP1RA plus SGLT2i plus lifestyle modification group vs. the usual care group. If statistically significant the following comparison will be made;

(ii) Difference in % total body weight loss between the combination of GLP1RA plus SGLT2i plus lifestyle modification group vs. the SGLT2i alone group. If statistically significant the following comparison will be made;

(iii) Difference in % total body weight loss between the combination of GLP1RA plus SGLT2i plus lifestyle modification group vs. the GLP1RA S alone group. If statistically significant the following comparison will be made;
(iv) Difference in % total body weight loss between the combination of GLP1RA plus SGLT2i plus lifestyle modification group vs. the combination of GLP1RA plus SGLT2i group.

5.2.2 Mixed model for repeated measures (MMRM)

In MMRM analysis, fixed-effects terms will include group (1= usual care group, 2= GLP1RA alone, 3= SGLT2i alone, 4=GLP1RA+ SGLT2i, 5= GLP1RA+ SGLT2i+ lifestyle modification) and visit (baseline and 6-month), and group-by-visit interaction. MMRM inherently accounts for missing data, assuming that data are missing at random. Continuous secondary outcomes will be presented as means with corresponding 95% confidence intervals. Pairwise comparisons between the combination GLP1RA plus SGLT2i plus lifestyle modification group compared to the other groups at 6 months will be presented as mean difference and 95% CI. Post-hoc tests will be corrected for multiple comparison using the SIDAK method.

5.3 Interim analysis

No interim analyses planned.

6.0 Demographic and other baseline characteristics

6.1 Demographics

Demographics will be summarised by randomised treatment groups. There will be no formal statistical comparisons between treatment groups on demographic variables. We will present variables with a normal distribution as mean (standard deviation). Variables with a skewed distribution will be summarised as median (interquartile range). Categorical variables will be presented as numbers (percentages).

6.2 Baseline laboratory measurements

A table presenting descriptive statistics (sample size, mean, standard deviation, median, min and max) of laboratory variables by treatment group at baseline will be provided for the ITT analysis set. If the baseline value is missing for a given variable and patient, the screening value will be used before calculating the descriptive statistics.

6.0 Safety analysis

6.1 Primary and secondary safety outcome

The primary safety outcome will be the incidence risk of treatment-emergent serious adverse events (SAEs) and adverse events (AE) through the 6-month follow-up period. Treatment-emergent adverse events will be summarized as number of patients and percentages for each treatment group.

RESULTS

Primary outcome

When participants were analysed according to the ITT allocation and using the hierarchical model, there was a significant difference in percentage body weight loss between the GLP-1 plus SGLT2i plus lifestyle modification group and the usual care group at 6 months [mean difference -9.6%, 95% CI (-14.4, -4.9), p<0.001], and between the GLP-1 plus SGLT2i plus lifestyle modification group versus the SGLT2i group [mean difference -8.0 (-12.6 , -3.4), p=0.002] **(Table 3)**. There was a trend for a significant difference in weight loss between the GLP-1 plus SGLT2i plus lifestyle modification and the GLP-1 only group [mean difference -4.5, 95% CI (-9.7 , 0.6), p=0.08]. In the PP analysis, the weight loss achieved in in the GLP-1 plus SGLT2i plus lifestyle modification group was significantly higher compared to the usual care, SGLT2i and GLP-1, but not the GLP-1 plus SGLT2i groups **(Table 4)**.

Using the mixed model, there was a significantly greater weight loss in the GLP-1 plus SGLT2i plus lifestyle modification group compared to the usual care group [mean difference -9.6%, 95% CI (-16.2, -3.1), p<0.001] and the SGLT2i group [mean difference -8.0%, 95% CI (-14.5, -1.4), p=0.008]. This reduction was not significantly different when compared to the GLP-1 group [mean difference -4.5%, 95% CI (-11.1, 2.0), p=0.39] and GLP-1 plus SGLT2i group [mean difference -6.4%, 95% CI (-13.0, 0.1), p=0.06] **(Table 2)**.

Participants in the combination group had significantly higher rates of patients achieving specific weight loss cut-offs compared to the other groups as evidenced by 91.7% achieving at least a 5% weight loss (p=0.001), 58.3% reaching at least a 10% weight loss (p=0.021), and 41.7% attaining at least a 15% weight loss (p=0.002).

Secondary outcomes

There was no significant difference between the groups in terms of HbA1c and markers of glycaemic variability in either the ITT or PP analysis at 6 months **(Table 2 and Table 4)**. There was no difference in the 24-hour mean systolic or diastolic blood pressure, lipid, liver and renal profile outcomes between the groups at 6 months in the ITT or PP analyses **(Table 2 and Table 4).** There was no significant difference between the groups in uACR and eGFR at 6 months in the ITT analysis **(Table 2)**. Similar results were seen in the PP population **(Table 4).** Only the GLP-1 plus SGLT2i plus lifestyle modification group showed a difference in uACR between baseline and 26 weeks (784.9, 95% CI (500.7, 1069.1) to 287.6, 95% CI (-1.6, 576.8) mg/g; p<0.001).

Adverse events

The incidence of treatment-emergent adverse events was numerically higher with combinations of GLP-1 analogues and SGLT2i groups (both treatments pooled; n=13/24, 54%) compared with the usual care group (n=6/12, 50%; table 3). Gastrointestinal disorders were the most common

treatment-emergent adverse events, occurring in 46% (n=11/24) of participants receiving combinations of GLP-1 analogues and SGLT2i and 16.7% (n=2/12) of participants in the usual care group. Serious drug-related adverse events were reported by one participant receiving GLP-1 analogue alone (hospital admission for ketoacidosis one day after taking medicine). The medication was stopped and the patients continued to receive usual care without any further episodes of ketoacidosis. No other unexpected tolerability concerns were identified in the rest of the cohorts.

Adverse events led to treatment discontinuation or change in treatment in 21% of participants receiving combinations of GLP-1 analogues and SGLT2i (n= 6/24) and 8.3% of participants receiving SGLT2i alone (n=1/12). These AEs were most commonly gastrointestinal disorders (35% [n=17/48] of participants receiving GLP-1 analogues.

Table 2: Analysis of the primary outcome using a hierarchical model in the ITT population

		Mean difference 95% (CI)	**P value**
%weight change in GLP-1+ SGLT2i+ lifestyle	vs. usual care	-9.6 (-14.4 , -4.9)	<0.001
	vs.SGLT2i	-8.0 (-12.6 , -3.4)	0.002
	vs. GLP1R	-4.5 (-9.7 , 0.6)	0.08
	vs. GLP1R+SGLT2i	-6.4 (-11.3 , -1.5)	Not applicable

The intention-to-treat analysis includes all randomized participants.

Table 3 Mixed model for repeated measures estimates for the primary and secondary endpoints from baseline to Week 26 in the ITT population

	Usual care N=12	**GLP1R alone N=12**	**SGLT2i alone N=12**	**GLP12+SGLT2i N=12**	**GLP1R+SGLT2i+lifestyle N=12**	**P value**
Weight change (%)	-1.3 (-4.5 , 1.9)	-6.4 (-9.6 , -3.2)	-3.0 (-6.1 , 0.2)	-4.5 (-7.7 , -1.3)	-10.9 (-14.1 , -7.8)	
Mean difference ‡	-9.6 (-16.2 , -3.1)*	-4.5 (-11.1 , 2.0)	-8.0 (-14.5 , -1.4)*	-6.4 (-13.0 , 0.1)	-	<0.001
% weight loss categories§						
≥5%	16. 7	58.3	25.0	33.3	91. 7	0.001
≥10%	8.3	25.0	8.3	16. 7	58.3	0.021
≥15%	0	0	0	8.3	41. 7	0.002
Weight change (kg)	-1.3 (-4.2 , 1.7)	-5.2 (-8.1 , -2.2)	-3.1 (-6.0 , -0.1)	-4.1 (-7.0 , -1.2)	-9.8 (-12.8 , -6.9)	
Mean difference ‡	-8.6 (-14.6 , -2.6)*	-4.7 (-10.7 , 1.3)	-6.8 (-12.8 , -0.8)*	-5.7 (-11.7 , 0.3)*	-	0.002
Waist circumference (cm)						
Baseline	92.3 (84.9 , 99.6)	96.7 (89.3 , 104)	98.1 (90.8 , 105.4)	98.5 (90.9 , 106.1)	106.8 (99.5 , 114.2)	
6-months	91.3 (84 , 98.7)	91.5 (84.2 , 98.8)#	97 (89.7 , 104.3)	93.9 (86.3 , 101.5)#	99.1 (91.8 , 106.5)#	
Mean difference ‡	7.8 (-2.6 , 18.2)	7.6 (-2.7 , 18)	2.1 (-8.2 , 12.5)	5.2 (-5.4 , 15.8)	-	0.03
Glycated haemoglobin (mmol/mol)						
Baseline	8.2 (7.5 , 9)	8.6 (7.8 , 9.3)	9.0 (8.2 , 9.7)	8.3 (7.5 , 9.1)	8.8 (8 , 9.5)	0.80
6-months	7.9 (7.1 , 8.6)	7.9 (7.2 , 8.7)	8.7 (7.9 , 9.4)	7.5 (6.7 , 8.3)	8.0 (7.3 , 8.8)	
Mean difference ‡	0.2 (-1.4 , 1.7)	0.1 (-1.5 , 1.7)	-0.7 (-2.2 , 0.9)	0.5 (-1.1 , 2.1)	-	0.80
Glucose time above range (≥ 10 mmol/l)						
Baseline	35.3 (28.8 , 41.9)	32.7 (25.9 , 39.6)	29.6 (22.7 , 36.4)	35.9 (29.2 , 42.6)	27.6 (21.0 , 34.2)	
6-months	31.4 (24.8 , 38)	26.2 (19 , 33.3)	32.7 (26.1 , 39.2)	30.7 (24 , 37.3)	20.8 (14.3 , 27.4)	
Mean difference ‡	-10.6 (-24 , 2.8)	-5.3 (-19.4 , 8.7)	-11.8 (-25.2 , 1.6)	-9.8 (-23.3 , 3.7)	-	0.44
Glucose time in range						
Baseline	45.6 (35.7 , 55.5)	42.8 (32.5 , 53.2)	48.4 (38.1 , 58.6)	45.9 (35.7 , 56.1)	48.2 (38.3 , 58.1)	
6-months	53.9 (44 , 63.8)	53.1 (42.4 , 63.8)	43.2 (33.3 , 53.1)	50.1 (40 , 60.3)	57.4 (47.5 , 67.3)	
Mean difference ‡	3.5 (-16.8 , 23.8)	4.3 (-16.8 , 25.4)	14.3 (-6 , 34.5)	7.3 (-13.3 , 27.8)	-	0.19

Glucose time below range (≤ 3.9 mmol/l)						
Baseline	3.1 (1.1 , 5.0)	2.4 (0.3 , 4.4)	3.2 (1.2 , 5.3)	4.2 (2.2 , 6.2)	4.3 (2.3 , 6.2)	
6-months	1.7 (-0.3 , 3.6)	3.1 (0.9 , 5.2)	1.8 (-0.1 , 3.8)	4.1 (2.1 , 6.1)	3.9 (2.0 , 5.9)	
Mean difference ‡	2.3 (-1.7 , 6.2)	0.9 (-3.3 , 5.0)	2.1 (-1.9 , 6.1)	-0.2 (-4.2 , 3.9)		0.52
Glucose coefficient of variation						
Baseline	38.2 (33.5 , 42.8)	37.7 (32.8 , 42.6)	35.5 (30.7 , 40.4)	37.8 (32.5 , 43.1)	39.8 (35.2 , 44.4)	
6-months	37.1 (32.3 , 42)	39.7 (34.8 , 44.6)	35.2 (30.6 , 39.8)	41.3 (35.9 , 46.7)	39.3 (34.6 , 44)	
Mean difference ‡	2.1 (-7.6 , 11.9)	-0.4 (-10.3 , 9.4)	4.1 (-5.5 , 13.6)	-2.0 (-12.4 , 8.4)	-	0.41
Urine Albumin Creatinine Ratio (mg/g)						
Baseline	97.8 (-186.4 , 382)	565.7 (281.5 , 849.9)	179.3 (-104.9 , 463.5)	86.3 (-208.4 , 380.9)	784.9 (500.7 , 1069.1)	
6-months	91.5 (-192.7 , 375.7)	488.3 (204.1 , 772.5)	80.8 (-203.4 , 365)	80.4 (-214.2 , 375.1)	287.6 (-1.6 , 576.8) #	
Mean difference ‡	196.1 (-209.4 , 601.6)	-200.7 (-606.2 , 204.8)	206.9 (-198.6 , 612.3)	207.2 (-205.7 , 620.1)	-	0.005
eGFR						
Baseline	103.7 (88 , 119.4)	107.6 (91.9 , 123.3)	105.9 (90.2 , 121.6)	111.7 (95.4 , 128)	86.2 (70.5 , 101.9)	
6-months	98.6 (82.9 , 114.3)	110.3 (94.6 , 126)	101.8 (86.1 , 117.4)	110.5 (94.2 , 126.8)	86.8 (71.1 , 102.4)	
Mean difference ‡	-11.8 (-44 , 20.3)	-23.6 (-55.7 , 8.6)	-15 (-47.2 , 17.2)	-23.7 (-56.5 , 9.1)	-	0.72
24 hour average systolic Blood pressure (mmHg)						
Baseline	129.8 (120.8 , 138.7)	137.1 (130.2 , 144.1)	127.7 (120.6 , 134.9)	129 (121.5 , 136.5)	132.8 (125.2 , 140.4)	
6-months	128.7 (119.8 , 137.7)	137.2 (128 , 146.3)	128.2 (120.8 , 135.6)	131.2 (118.8 , 143.7)	128 (118.8 , 137.3)	
Mean difference ‡	-0.7 (-19.3 , 18.0)	-9.1 (-28 , 9.7)	-0.2 (-17.4 , 17.0)	-3.2 (-25.7 , 19.3)	-	0.89
24 hour average diastolic Blood pressure (mmHg)						
Baseline	78.1 (72.2 , 84)	81.3 (76.7 , 86)	76.8 (72 , 81.5)	77.6 (72.6 , 82.7)	78.5 (73.4 , 83.6)	
6-months	75.5 (69.5 , 81.4)	82.2 (76.2 , 88.2)	77.4 (72.4 , 82.3)	73.3 (65.2 , 81.4)	76.8 (70.7 , 82.9)	
Mean difference ‡	1.4 (-11 , 13.7)	-5.4 (-17.8 , 7)	-0.6 (-11.9 , 10.8)	3.5 (-11.2 , 18.3)	-	0.74
Total cholesterol (mmol/L)						
Baseline	5.1 (4.5 , 5.7)	4.6 (4 , 5.2)	4.5 (3.9 , 5.1)	4.6 (4 , 5.2)	5.3 (4.7 , 5.9)	
6-months	4.5 (3.9 , 5.1) #	4.7 (4.1 , 5.2)	4.0 (3.5 , 4.6)	4.3 (3.7 , 4.9)	4.5 (3.9 , 5) #	
Mean difference ‡	-0.1 (-1.2 , 1.1)	-0.2 (-1.4 , 1.0)	0.4 (-0.8 , 1.6)	0.1 (-1.1 , 1.3)	-	0.24
High-density lipoprotein cholesterol (mmol/L)						

Baseline	1.5 (1.3 , 1.8)	1.6 (1.3 , 1.8)	1.5 (1.3 , 1.8)	1.5 (1.3 , 1.8)	1.3 (1.1 , 1.6)	
6-months	1.5 (1.2 , 1.7)	1.5 (1.2 , 1.7)	1.4 (1.2 , 1.6)	1.5 (1.2 , 1.7)	1.3 (1.0 , 1.5)	
Mean difference ‡	-0.2 (-0.7 , 0.3)	-0.2 (-0.7 , 0.3)	-0.1 (-0.6 , 0.4)	-0.2 (-0.7 , 0.3)	-	0.95
Low-density lipoprotein cholesterol (mmol/L)						
Baseline	3.1 (2.6 , 3.7)	2.5 (1.9 , 3.0)	2.5 (1.9 , 3.0)	2.7 (2.2 , 3.3)	3.4 (2.9 , 4.0)	
6-months	2.7 (2.1 , 3.2)	2.7 (2.1 , 3.3)	2.2 (1.7 , 2.8)	2.5 (1.9 , 3.0)	2.8 (2.2 , 3.3) #	
Mean difference ‡	0.1 (-1.0 , 1.2)	0.1 (-1.1 , 1.2)	0.5 (-0.6 , 1.7)	0.3 (-0.8 , 1.4)	-	0.31
Alkaline phosphatase (U/L)						
Baseline	33.6 (22 , 45.2)	34.9 (23.3 , 46.5)	34.4 (22.8 , 46)	32.7 (20.7 , 44.8)	34.2 (22.5 , 45.8)	
6-months	35.0 (23.4 , 46.6)	27.9 (16.3 , 39.5)	33.0 (21.4 , 44.6)	29.7 (17.6 , 41.7)	30.1 (18.5 , 41.7)	
Mean difference ‡	-4.9 (-28.7 , 18.9)	2.2 (-21.6 , 25.9)	-2.9 (-26.7 , 20.9)	0.4 (-23.8 , 24.6)	-	0.73
Alanine transaminase (U/L)						
Baseline	21.7 (14.4 , 29)	21.9 (14.6 , 29.2)	27.7 (20.4 , 35)	19.2 (11.8 , 26.7)	18.7 (11.4 , 26)	
6-months	20.9 (13.6 , 28.2)	20.7 (13.4 , 28)	25.4 (18.1 , 32.7)	18.0 (10.5 , 25.5)	19.2 (11.9 , 26.5)	
Mean difference ‡	-1.8 (-16.6 , 13.1)	-1.5 (-16.4 , 13.4)	-6.3 (-21.1 , 8.6)	1.2 (-13.9 , 16.3)	-	0.99
Gamma-glutamyl transferase (U/L)						
Baseline	38.0 (17.9 , 58.1)	47.3 (27.2 , 67.4)	41.3 (21.2 , 61.4)	23.2 (2.2 , 44.1)	36.6 (16.5 , 56.7)	
6-months	33.4 (13.3 , 53.5)	50.0 (29.9 , 70.1)	40.4 (20.3 , 60.5)	22.3 (1.4 , 43.3)	31.7 (11.6 , 51.8)	
Mean difference ‡	-1.8 (-43.0 , 39.5)	-18.3 (-59.6 , 22.9)	-8.8 (-50 , 32.5)	9.3 (-32.8 , 51.4)	-	0.81

The intention-to-treat analysis includes all randomized participants. The primary and continuous secondary endpoints were assessed with the use of mixed-model repeated measures analysis, with treatment group (usual care, GLP1R alone, SGLT2i alone, GLP1R + SGLT2i, GLP1R + SGLT2i+excercise) and visit (baseline and 6-month) and their interaction. Missing data were handled under the assumption of missing at random. SIDAK correction was applied in pairwise comparisons between the combination GLP1RA + SGLT2i + lifestyle group compared to the other groups at 6 months are presented as mean difference and 95% CI. P value column includes the overall interaction p values of the between group comparisons at 6-months.

§ Proportion of participants who achieved 5, or 10, or 15% of weight loss at 6 months. Differences between groups were compared using the Chi-square test

‡ The mean difference of the combination GLP1RA + SGLT2i + lifestyle group was computed from a mixed-model (group*visit) interaction.

* The mean difference between the combination GLP1RA + SGLT2i + lifestyle group and other groups was significant at $p<0.05$ in the mixed model

Within-group significant change at 6-month compared to baseline at $p<0.05$

Table 4: Analysis of the primary outcome using a hierarchical model in the per protocol population

		Mean difference 95% (CI)	**P value**
%weight change in GLP-1+ SGLT2i + lifestyle	vs. usual care	-12.8 (-16.9 , -8.7)	<0.001
	vs.SGLT2i	-9.4 (-13.1 , -5.7)	<0.001
	vs. GLP1R	-4.9 (-9.5 , -0.4)	0.04
	vs. GLP1R+SGLT2i	-5.0 (-9.9 , 0.02)	0.05

Per-protocol analysis includes all randomized participants who completed the trial without major deviation from the protocol. The mean difference in weight changes percentages at 6 months between the combination group GLP-1+ SGLTT2i+ lifestyle and the other treatment groups, with confidence intervals and P values indicating statistical significance

Table 5: Mixed model for repeated measures estimates for the primary and secondary endpoints from baseline to Week 26 in the per-protocol population

	Usual care n=15	GLP1R alone n=11	SGLT2i alone n=16	GLP12+SGLT2i n=8	GLP1R+SGLT2i+lifestyle n=10	P value
Weight change (%)	0.3 (-2.1 , 2.7)	-7.6 (-10.3 , -4.8)	-3.1 (-5.4 , -0.8)	-7.5 (-10.8 , -4.3)	-12.5 (-15.4 , -9.6)	<0.001
Mean difference ‡	-12.8 (-18.3 , -7.3) *	-4.9 (-10.8 , 0.9)	-9.4 (-14.8 , -4) *	-5.0 (-11.3 , 1.4)	-	
Weight loss categories (%)§						
>=5%	6.7	63.6	18.8	75.0	100.0	<0.001
>10%	6.7	27.3	6.3	25.0	70.0	0.002
>=15%	0.0	0.0	0.0	12.5	50.0	<0.001
Weight change (kg)	0.2 (-2.0 , 2.4)	-6.2 (-8.7 , -3.6)	-3.0 (-5.1 , -0.9)	-7.1 (-10.1 , -4.1)	-11.2 (-13.9 , -8.5)	<0.001
Mean difference ‡	-11.5 (-16.5 , -6.4) *	-5.0 (-10.4 , 0.4)	-8.2 (-13.2 , -3.2) *	-4.2 (-10 , 1.7)		
Waist circumference (cm)						
Baseline	93 (86.5 , 99.5)	95.5 (87.8 , 103.1)	98.5 (92.8 , 104.3)	105.1 (98.1 , 112.1)	104.9 (96.9 , 112.9)	
6-months	92.2 (85.6 , 98.7)	89.3 (81.6 , 96.9)#	96.2 (90.4 , 101.9)	101.0 (94.0 , 108.0)#	96.7 (88.7 , 104.7) #	
Mean difference ‡	4.5 (-10.5 , 19.6)	7.4 (-8.6 , 23.5)	0.5 (-13.8 , 14.8)	-4.3 (-19.7 , 11.1)	-	0.17
Glycated haemoglobin (mmol/mol)						
Baseline	8.5 (7.8 , 9.2)	8.5 (7.7 , 9.3)	8.5 (7.8 , 9.1)	8.6 (7.7 , 9.5)	9.0 (8.1 , 9.8)	0.23
6-months	8.3 (7.6 , 9.0)	7.7 (6.9 , 8.6)	8.2 (7.5 , 8.8)	7.4 (6.5 , 8.3)	8.1 (7.2 , 8.9)	
Mean difference ‡	-0.2 (-1.8 , 1.4)	0.3 (-1.4 , 2)	-0.1 (-1.7 , 1.4)	0.6 (-1.1 , 2.4)	-	
Glucose time above range (≥ 10 mmol/l)						
Baseline	36.1 (30.2 , 41.9)	31 (23.8 , 38.2)	33.1 (27.3 , 39)	29.5 (21.6 , 37.5)	28.6 (21.4 , 35.8)	0.26
6-months	29.1 (23.3 , 35)	24.4 (16.9 , 32)	33 (27.4 , 38.7)	32.8 (24.8 , 40.8)	20.1 (12.9 , 27.3)	
Mean difference ‡	-9.0 (-22.4 , 4.4)	-4.3 (-19.3 , 10.7)	-12.9 (-26.1 , 0.3)	-12.7 (-28.2 , 2.8)	-	
Glucose time in range						
Baseline	38.1 (29.5 , 46.8)	45.6 (35 , 56.2)	49.3 (41 , 57.7)	55.6 (44.3 , 67)	46.8 (36.2 , 57.4)	0.09
6-months	45.2 (36.6 , 53.8)	57.9 (46.9 , 68.8)	45.5 (37.3 , 53.6)	59.8 (48.4 , 71.1)	58.5 (47.9 , 69.1)	
Mean difference ‡	13.3 (-6.4 , 33)	0.6 (-21.3 , 22.6)	13 (-6.3 , 32.3)	-1.3 (-23.6 , 21.1)	-	
Glucose time below range (≤ 3.9 mmol/l)						
Baseline	3.3 (1.5 , 5.1)	2.6 (0.4 , 4.8)	3.5 (1.8 , 5.2)	4.1 (1.8 , 6.4)	3.7 (1.5 , 5.9)	0.41
6-months	2.2 (0.4 , 4)	3.4 (1.1 , 5.7)	3.1 (1.4 , 4.8)	2.1 (-0.2 , 4.4)	3.8 (1.6 , 6)	

Mean difference ‡	1.6 (-2.5 , 5.7)	0.4 (-4.2 , 5)	0.7 (-3.3 , 4.7)	1.7 (-2.9 , 6.3)		
Glucose coefficient of variation						
Baseline	36 (31.9 , 40.2)	39.2 (34 , 44.4)	36.7 (32.7 , 40.7)	38.6 (32.7 , 44.4)	40.2 (35.1 , 45.3)	0.86
6-months	36.1 (31.8 , 40.4)	41.6 (36.4 , 46.8)	37.1 (33.2 , 41)	40.1 (34 , 46.2)	39.7 (34.6 , 44.7)	
Mean difference ‡	3.6 (-6.0 , 13.2)	-1.9 (-12.4 , 8.6)	2.6 (-6.7 , 11.8)	-0.4 (-11.8 , 11)	-	
Urine Albumin Creatinine Ratio (mg/g)						
Baseline	236.6 (-23.4 , 496.7)	607.9 (304.3 , 911.6)	137.7 (-101.4 , 376.9)	114.2 (-202.7 , 431.1)	722.8 (404.2 , 1041.3)	0.026
6-months	186.7 (-73.3 , 446.8)	514.4 (210.7 , 818)	61.2 (-177.9 , 300.3)	81.2 (-235.8 , 398.1)	225.9 (-99.6 , 551.4)[#]	
Mean difference ‡	39.2 (-563.8 , 642.2)	-288.4 (-932.7 , 355.9)	164.7 (-419.3 , 748.8)	144.8 (-510.9 , 800.4)	-	
eGFR						
Baseline	106.1 (89.4 , 122.9)	107.5 (88 , 127.1)	86.1 (72.1 , 100.1)	146.3 (130.6 , 161.9)	86.3 (65.8 , 106.8)	
6-months	102.6 (85.9 , 119.3)	110.8 (91.3 , 130.3)	83.1 (69.1 , 97.1)	144.6 (129 , 160.3)	85.5 (65 , 106)	
Mean difference ‡	-17.1 (-55.6 , 21.4)	-25.3 (-66.5 , 15.9)	2.4 (-33.7 , 38.5)	-59.1 (-96.5 , -21.8)	-	0.35
24 hour average systolic Blood pressure (mmHg)						
Baseline	128.6 (121.4 , 135.9)	137 (129.7 , 144.4)	132.1 (125.7 , 138.4)	125.8 (116.8 , 134.8)	131.4 (122.8 , 140.1)	0.95
6-months	128.6 (120.4 , 136.8)	135 (125.1 , 144.9)	132.5 (125.5 , 139.5)	124.8 (112.1 , 137.5)	127.2 (116.9 , 137.4)	
Mean difference ‡	-1.4 (-20.4 , 17.6)	-7.8 (-28.5 , 12.8)	-5.3 (-23.3 , 12.7)	2.3 (-21.3 , 26)	-	
24 hour average diastolic Blood pressure (mmHg)						
Baseline	77.7 (72.8 , 82.6)	81 (76.1 , 86)	78.9 (74.7 , 83.2)	75.1 (69.1 , 81)	78.5 (72.7 , 84.4)	0.89
6-months	76.1 (70.7 , 81.5)	80.5 (74 , 87)	79.3 (74.6 , 83.9)	70.9 (62.7 , 79.2)	77.2 (70.4 , 84.0)	
Mean difference ‡	1.1 (-11.5 , 13.6)	-3.3 (-16.9 , 10.3)	-2.1 (-14 , 9.8)	6.2 (-9.3 , 21.7)	-	
Total cholesterol (mmol/L)						
Baseline	5.0 (4.4 , 5.5)	4.7 (4.1 , 5.3)	4.5 (4 , 5)	4.5 (3.9 , 5.2)	5.5 (4.8 , 6.1)	
6-months	4.6 (4.1 , 5.1)	4.8 (4.2 , 5.4)	4.1 (3.6 , 4.6)	4.1 (3.4 , 4.8)	4.4 (3.7 , 5)	
Mean difference ‡	-0.2 (-1.4 , 0.9)	-0.4 (-1.7 , 0.8)	0.2 (-0.9 , 1.4)	0.3 (-1.1 , 1.6)	-	0.11
High-density lipoprotein cholesterol (mmol/L)						
Baseline	1.6 (1.4 , 1.8)	1.6 (1.4 , 1.8)	1.4 (1.2 , 1.6)	1.5 (1.3 , 1.8)	1.3 (1.1 , 1.6)	
6-months	1.5 (1.3 , 1.7)	1.5 (1.2 , 1.7)	1.4 (1.2 , 1.6)	1.4 (1.2 , 1.7)	1.2 (1.0 , 1.5)	
Mean difference ‡	-0.3 (-0.8 , 0.2)	-0.2 (-0.8 , 0.3)	-0.1 (-0.6 , 0.3)	-0.2 (-0.7 , 0.4)	-	>0.99

Low-density lipoprotein cholesterol (mmol/L)						
Baseline	3.0 (2.5 , 3.5)	2.6 (2 , 3.2)	2.6 (2.1 , 3)	2.6 (2 , 3.3)	3.5 (2.9 , 4.1)	
6-months	2.7 (2.2 , 3.2)	2.8 (2.2 , 3.4)	2.4 (1.9 , 2.8)	2.3 (1.6 , 3)#	2.7 (2.1 , 3.3)	
Mean difference ‡	0 (-1.1 , 1.1)	-0.1 (-1.3 , 1.1)	0.3 (-0.8 , 1.4)	0.4 (-0.9 , 1.7)	-	0.21
Alkaline phosphatase (U/L)						
Baseline	26.3 (16.1 , 36.5)	35.8 (23.9 , 47.7)	34.9 (25.5 , 44.4)	41.9 (29.3 , 54.5)	35.9 (23.4 , 48.4)	
6-months	29.1 (18.9 , 39.3)	27.7 (15.8 , 39.7)	36.4 (26.9 , 45.8)	28.6 (16 , 41.3)	32.0 (19.5 , 44.5)	
Mean difference ‡	2.9 (-20.4 , 26.3)	4.3 (-20.8 , 29.3)	-4.4 (-27.0 , 18.3)#	3.4 (-22.3 , 29)	-	0.07
Alanine transaminase (U/L)						
Baseline	16.9 (10.4 , 23.4)	22.6 (15 , 30.2)	25.4 (19.2 , 31.6)	26.3 (17.6 , 34.9)	19.5 (11.5 , 27.5)	
6-months	18.3 (11.8 , 24.8)	21 (13.4 , 28.6)	24.7 (18.4 , 30.9)	18.4 (9.8 , 27.1)	20.6 (12.6 , 28.6)	
Mean difference ‡	2.3 (-12.6 , 17.1)	-0.4 (-16.3 , 15.5)	-4.1 (-18.6 , 10.5)	2.2 (-14.8 , 19.1)	-	0.55
Gamma-glutamyl transferase (U/L)						
Baseline	34.1 (15.8 , 52.4)	45.9 (24.5 , 67.2)	34.8 (18.7 , 50.9)	39.2 (19.3 , 59)	36.1 (13.7 , 58.5)	
6-months	38.7 (20.4 , 57)	44.5 (23.2 , 65.9)	35.3 (19.2 , 51.4)	24.7 (4.8 , 44.5)	31.1 (8.7 , 53.5)	
Mean difference ‡	-7.6 (-49.6 , 34.3)	-13.4 (-58.4 , 31.5)	-4.2 (-44.2 , 35.8)	6.4 (-36.8 , 49.7)	-	0.12

The per-protocol analysis includes participants who completed the trial without major deviation from the protocol. The primary and continuous secondary endpoints were assessed with the use of mixed-model repeated measures analysis, with treatment group (usual care, GLP1R alone, SGLT2i alone, GLP1R + SGLT2i, GLP1R + SGLT2i+excercise) and visit (baseline and 6-month) and their interaction. Missing data were handled under the assumption of missing at random. SIDAK correction was applied in pairwise comparisons between the combination GLP1RA + SGLT2i + lifestyle group compared to the other groups at 6 months will be presented as mean difference and 95% CI. P value column includes the overall interaction p values of the between group comparisons at 6-month

§ Proportion of participants who achieved 5, or 10, or 15% of weight loss at 6 months. Differences between groups were compared using the Chi-square test

‡ The mean difference of the combination GLP1RA + SGLT2i + lifestyle group was computed from a mixed-model (group*visit) interaction.

* The mean difference between the combination GLP1RA + SGLT2i + lifestyle group and other groups is significant at $p<0.05$ in the mixed model

Within-group significant change at 6-month compared to baseline at $p<0.05$

Table 6 Summary of treatment emergent adverse event

TEAE, n (%)	Treatment groups				
	Usual care (n=12)	**GLP-1 alone (n=12)**	**SGLT2i alone (n=12)**	**GLP-1 + SGLT2i (n=12)**	**GLP-1 + SGLT2i + lifestyle modification (n=12)**
Any TEAE	6 (50.0)	7 (58.3)	4 (33.3)	8 (66.7)	5 (41.7)
Nausea	0	4(33.3)	0	6 (50.0)	3 (25.0)
Vomiting	0	3 (25.0)	0	3 (25.0)	2 (16.7)
Diarrhoea	0	0	0	2 (16.7)	0
Constipation	2 (16.7)	1 (8.3)	1 (8.3)	0	1 (8.3)
Stomach pain	0	1 (8.3)	0	1 (8.3)	0
UTI	0	1 (8.3)	1 (8.3)	0	1 (8.3)
Headache	4 (33.3)	1 (8.3)	0	4 (33.3)	1 (8.3)
DKA	1 (8.3)	0	0	1 (8.3)	0
Weakness	3 (25.0)	0	0	1 (8.3)	1 (8.3)
Eye problems	1 (8.3)	0	1 (8.3)	1 (8.3)	1 (8.3)
Leading to treatment discontinuation	0	0	1 (8.3)	6 (50.0)	1 (8.3)
Serious	0	0	0	0	0
Investigator defined; drug related	0	0	0	0	0
Serious, investigator defined, drug related	0	0	0	0	0

TEAE: treatment-emergent adverse event. Safety was analysed in the treated set, comprising all randomised participants who received at least one dose of trial treatment, and based on planned treatment