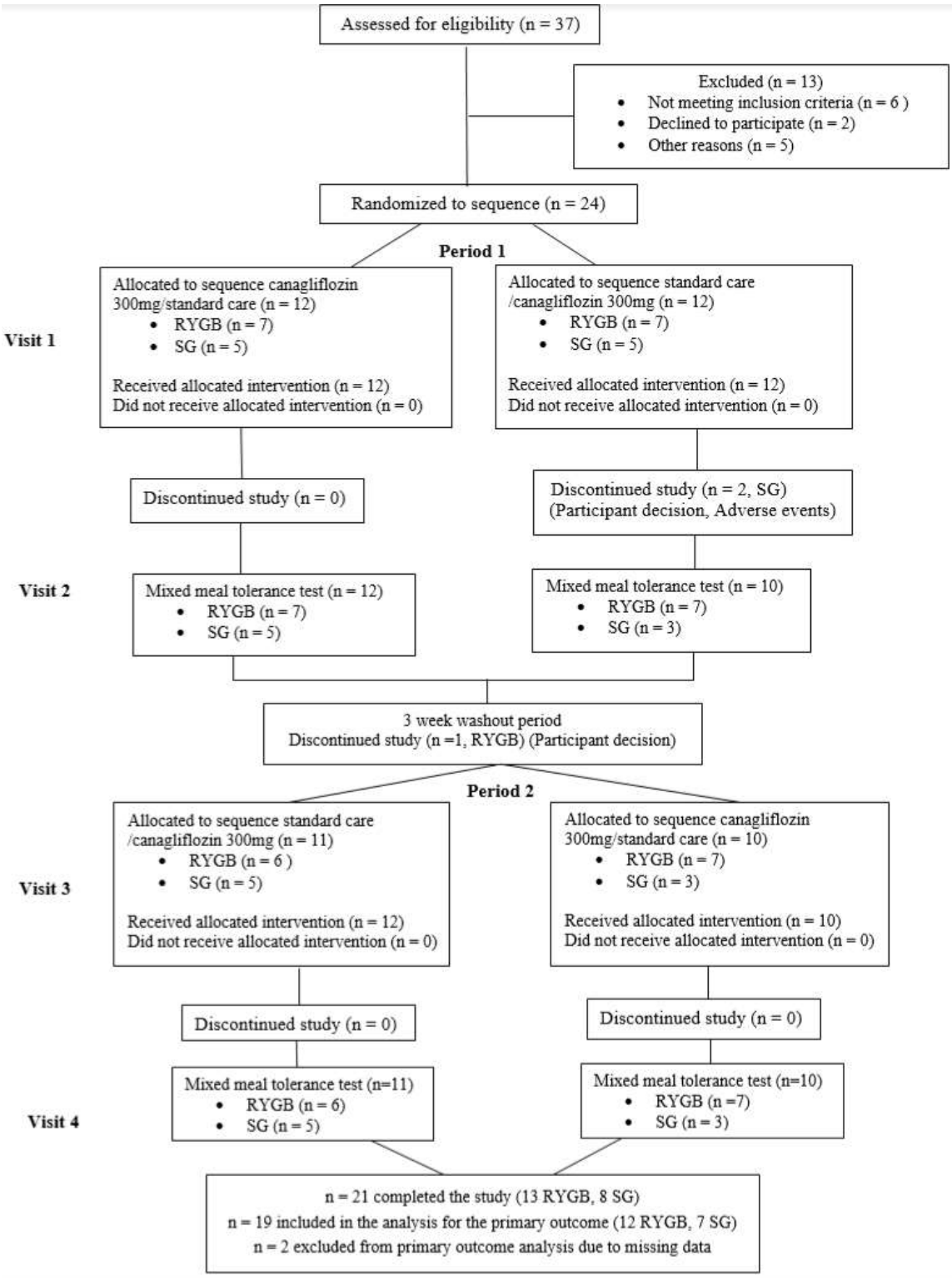
Participant flow



Baseline characteristics

Variable (n, %) or (mean, SD)	Bariatric procedure		
Sex	**RYGB (n=14)**	**SG (n=10)**	**Total (n=24)**
Male	2 (8%)	1 (2%)	3 (10%)
Female	12 (50%)	9 (40%)	21 (90%)
Ethnicity			
White British	12 (50%)	10 (42%)	22 (92%)
Indian	1 (4%)	0 (0%)	1 (4%)
Other African background	1 (4%)	0 (0%)	1 (4%)
Alcohol status			
Current	13 (54%)	8 (33%)	21 (88%)
Ex-drinker	0 (0%)	1 (4%)	1 (4%)
Never drank	1 (4%)	1 (4%)	2 (8%)
Smoking history			
Ex-smoker	5 (21%)	6 (25%)	11 (46%)
Never smoked	9 (38%)	4 (16%)	13 (54%)
Age (years)	55 (11.1)	52 (8.1)	53.8 (9.9)
Height (cm)	165.5 (7.2)	161.1 (7.8)	163.7 (7.6)
Weight (kg)	95.2 (17.7)	98.9 (31.4)	96.8 (23.8)
Body fat percentage (%)	41.6 (10.4)	44.9 (11)	43 (10.5)
Diastolic blood pressure	72.5 (7.4)	78.2 (15.1)	74.9 (11.3)
Systolic blood pressure	120.9 (13.1)	121.3 (20.5)	121 (16.2)
HbA1c (%)	5.4 (0.4)	5.5 (0.5)	5.4 (0.4)
Heart rate (bpm)	70 (8.2)	71.9 (8)	70.8 (8)
BMI (kg/m^2)	34.9 (6.8)	37.6 (10)	36 (8.2)

Outcome measures

1. Glucose

Outcome measure	Mean (SD) or Median (IQR)		Mean/Median (95% CI)	p-value
	Canagliflozin 300mg **(n = 19)**†	No treatment **(n = 19)**†	Treatment effect	
Difference in nadir glucose levels between the two treatment options (canagliflozin 300mg vs no treatment)	3.75 (± 0.7)	3.41 (± 0.78)	-0.35 (0.05, 0.65)	0.03
Difference in glucose tAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment) *	919.88 (± 143.29)	960.23 (± 149.7)	-40.36 (-83.29, 2,58)	0.06
Difference in glucose tAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	177.71 (± 32.61)	204.51 (± 24.75)	-26.8 (-37.95, -15.65)	0.00
Difference in glucose positive iAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment) *	155.53 (± 74.93)	174.61 (± 71.74)	-19.1 (-52.79, 14.64)	0.25
Difference in glucose net iAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment) *	124.50 (± 104.87)	114.23 (± 124.14)	10.27 (-26.43, 46.96)	0.56
Difference in glucose positive iAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	45.87 (± 21.14)	65.39 (± 28.62)	-19.52 (-28.53, -10.51)	0.00
Difference in glucose net iAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	45.87 (± 21.14)	65.25 (± 28.94)	-19.38 (-28.52, -10.24)	0.00
Difference in fasting glucose levels between the two treatment options (canagliflozin 300mg vs no treatment)	4.39 (± 0.46)	4.64 (± 0.45)	-0.25 (-0.37, -0.13)	0.00
Difference in peak glucose levels between the two treatment options (canagliflozin 300mg vs no treatment)	7.25 (± 1.33)	8.26 (± 1.41)	-1.01 (-1.65, -0.37,)	0.00
Difference in peak-nadir glucose levels between the two treatment options (canagliflozin 300mg vs no treatment)	3.49 (± 1.07)	4.85 (± 1.39)	-1.36 (-1.93, -0.79)	0.00
Difference in the max/min ratio of glucose levels between the two treatment options (canagliflozin 300mg vs no treatment)	1.96 (± 0.3)	2.50 (± 0.49)	-0.55 (-0.77, -0.32)	0.00

Difference in glucose negative iAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment)*	116.44 (± 109.84)	98.20 (± 128.10)	18.23 (-17.17, 53.64)	0.29
Difference in glucose negative iAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	45.87 (± 21.14)	65.19 (± 29.09)	-19.32 (-28.52, -10.12)	0.00

† RYGB (n = 12), SG (n = 7)

* n=16, as data for glucose-related outcomes after 60' were not imputed for 3 participants whose MMTT stopped due to hypoglycaemia, RYGB (n = 10), SG (n = 6)

2. Insulin

Outcome measure	**Mean (SD) or Median (IQR)**		**Mean/Median (95% CI)**	**p-value**
	Canagliflozin 300mg **(n = 19)** †	No treatment **(n = 19)** †	Treatment effect	
Difference in insulin tAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment)	5699.72 (± 2984.15)	7086.81 (± 4211.69)	-1387.1 (-2512.97, -261.22)	0.02
Difference in insulin tAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	1753.95 (± 1003.54)	2276.17 (± 1508.77)	-522.22 (-867.69, -176.75)	0.01
Difference in insulin net iAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment)	4410.79 (± 2276.53)	5490.73 (± 3484.68)	-1079.95 (-2243.87, 83.97)	0.07
Difference in insulin net iAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	1416.44 (720.84 to 2093.01)	1515.40 (1298.51 to 2586.68)	-477.81 (-825.30, 99.06)	0.01
Difference in fasting insulin levels between the two treatment options (canagliflozin 300mg vs no treatment) (mIU/ml)	5.83 (4.3 to 8.72)	6.87 (4.46 to 13.06)	-1.18 (-2.56, -0.15)	0.02
Difference in peak insulin levels between the two treatment options (canagliflozin 300mg vs no treatment) (mIU/ml)	102.74 (± 63.62)	123.73 (± 74.86)	-20.99 (-42.73, 0.75,)	0.06
Difference in the ratio AUC insulin/AUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (0-180)*	6.08 (± 3.26)	7.22 (± 4.36)	-1.13 (-2.45, 0.19)	0.09
Difference in the ratio AUC insulin/AUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (0-30)	7.62 (5.27 to 10.53)	8.6 (6.27 to 13.03)	-1.1 (-2.98, -0.94)	0.23

Difference in the ratio iAUC insulin/iAUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (0-180)*	21.33 (13.36 to 57.44)	24.50 (18.64 to 47.04)	-2.11 (-10.57, 197.02)	0.78
Difference in the ratio iAUC insulin/iAUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (0-30)	23.72 (19.14 to 47.77)	21 (15.85 to 38.63)	3.04 (-3.34, 7.96)	0.36
Difference in the ratio AUC insulin/AUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (60-180)*	2.19 (2.07 to 4.67)	2.49 (2.11 to 6.08)	-0.32 (-1.59, 0.04)	0.08
Difference in the ratio iAUC insulin/iAUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (60-180)*	10.52 (2.89 to 26.39)	13.8 (2.11 to 34.73)	6.83 (-1.6,61.05)	0.23

† RYGB (n = 12), SG (n = 7)

* n=16, as data for glucose-related outcomes after 60' were not imputed for 3 participants whose MMTT stopped due to hypoglycaemia, RYGB (n = 10), SG (n = 6)

3. C-peptide

Outcome measure	**Mean (SD) or Median (IQR)**		**Mean/Median (95% CI)**	**p-value**
	Canagliflozin 300mg **(n = 19)** †	No treatment **(n = 19)** †	Treatment effect	
Difference in C-peptide tAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment)	393657.60 (305100.3 to 527728.9)	408722.20 (349033.6 to 578742.8)	-31195.21 (-75875.21, 9387.70)	0.12
Difference in C-peptide tAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	83162.22 (59399.21 to 98316.15)	87094.41 (70364.60 to 135148.88)	-15546.62 (-30245.51, -7091.22)	0.00
Difference in C-peptide net iAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment)	269097 (± 106055.8)	300105.60 (± 137974)	-31008.58 (-76328.72 , 14311.56)	0.17
Difference in C-peptide net iAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	45287.46 (33097.44 to 69817.28)	60668.44 (45645.12 to 105836.15)	-15661.67 (-30537.07, -5086.91)	0.00
Difference in fasting C-peptide levels between the two treatment options (canagliflozin 300mg vs no treatment) (mIU/ml)	798.73 (630.03 to 1109.54)	1044.56 (629.94 to 1261.11)	-61.07 (-171.70, 32.46)	0.16
Difference in peak C-peptide levels between the two treatment options (canagliflozin 300mg vs no treatment) (mIU/ml)	4128.30 (3236.90 to 5296.95)	4278.60 (3554.75 to 7243.80)	-495.9 (-1275.7 , 36.9)	0.07

Difference in the ratio AUC C-peptide/AUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (0-180)*	493.25 (± 169.47)	522.05 (± 207.82)	-28.8 (-87.96, 30.36)	0.32
Difference in the ratio AUC C-peptide/AUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (0-30)	409.49 (357.87 to 580.58)	453.06 (366.33 to 453.06)	-16.88 (-78.5, 24.36)	0.38
Difference in the ratio iAUC C-peptide/iAUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (0-180)*	1644.65 (1037.30 to 2937.94)	1309.24 (1007.74 to 2078.03)	67.82 (-310.75, 10092.43)	0.90
Difference in the ratio iAUC C-peptide/iAUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (0-30)	1147.10 (782.71 to 1718.39)	937.28 (772.38 to 1561.57)	119.49 (-61.98, 280.08)	0.19
Difference in the ratio AUC C-peptide /AUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (60-180)*	392.53 (304.32 to 580.52)	357.78 (323.92 to 531.40)	-1.72 (-63.06, 34.43)	0.86
Difference in the ratio iAUC C-peptide/iAUC glucose during the MMTT between the two treatment options (Canagliflozin 300mg vs no treatment) (60-180)*	698.76 (475.70 to 878.58)	1016.46 (387.63 to 1708.40)	756.17 (-110.82, 3162.20)	0.09

† RYGB (n = 12), SG (n = 7)

* n=16, as data for glucose-related outcomes after 60' were not imputed for 3 participants whose MMTT stopped due to hypoglycaemia, RYGB (n = 10), SG (n = 6)

4. GLP-1

Outcome measure	**Mean (SD) or Median (IQR)**		**Mean/Median (95% CI)**	**p-value**
	Canagliflozin 300mg **(n = 19)** †	No treatment **(n = 19)** †	Treatment effect	
Difference in GLP-1 tAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment)	15312.74 (± 5132.11)	12725.29 (± 3924.41)	2587.45 (1140.67, 4034.229)	0.00
Difference in GLP-1 tAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	3670.62 (± 1533.51)	3483.69 (± 1562.41)	186.93 (-252.73, 626.60)	0.38
Difference GLP-1 net iAUC 0-180 between the two treatment options (canagliflozin 300mg vs no treatment)	8547.46 (± 4988.76)	6845.15 (± 4045.26)	1702.3 (147.70, 3256.91)	0.03
Difference in GLP-1 net iAUC 0-30 between the two treatment options (canagliflozin 300mg vs no treatment)	2543.08 (± 1495.8)	2503.67 (± 1545.62)	39.41 (-425.32, 504.14)	0.86

Difference in fasting GLP-1 levels between the two treatment options (canagliflozin 300mg vs no treatment) (mIU/ml)	37.58 (± 16.32)	32.67 (± 15.91)	4.92 (0.95, 8.88)	0.02
Difference in peak GLP-1 levels between the two treatment options (canagliflozin 300mg vs no treatment) (mIU/ml)	183.06 (± 83.38)	173.56 (± 81.05)	9.49 (-23.356, 42.35)	0.55

† RYGB (n = 12), SG (n = 7)

5. CGM

Outcome measure	**Mean (SD) or Median (IQR)**		**Mean/Median (95% CI)**	**p-value**
	Canagliflozin 300mg **(n = 14)** †	No treatment **(n = 14)** †	Treatment effect	
Difference in nadir glucose during CGM between the two treatment options	3.05 (± 0.68)	2.78 (± 0.65)	0.27 (-0.33, 0.87)	0.35
Difference in % time in interstitial glucose levels in CGM between the two treatment options (Canagliflozin 300mg vs no treatment), for the following glucose level ranges: < 3.9mmol/l	0.81 (0.14 to 2.64)	0.69 (0.30 to 1.16)	0.39 (-0.82, 3.62)	0.78
Difference in % time in interstitial glucose levels in CGM between the two treatment options (Canagliflozin 300mg vs no treatment), for the following glucose level ranges: between 3.0 – 10 mmol/l	98.62 (96.88 to 99.20)	97.34 (96.66 to 98.50)	0.95 (-0.22, 2.90)	0.14
Difference in % time in interstitial glucose levels in CGM between the two treatment options (Canagliflozin 300mg vs no treatment), for the following glucose level ranges: between 3.9 – 10 mmol/l	96.31 (95.21 to 98.36)	96.63 (94.92 to 98.21)	0.46 (-2.74, 2.27)	0.62
Difference in % time in interstitial glucose levels in CGM between the two treatment options (Canagliflozin 300mg vs no treatment), for the following glucose level ranges: above 7.8 mmol/l	9.46 (± 4.96)	13.01 (± 6.79)	-3.55 (-7.72, 0.62)	0.09
Difference in % time in interstitial glucose levels in CGM between the two treatment options (Canagliflozin 300mg vs no treatment), for the following glucose level ranges: above 10 mmol/l	0.89 (0.53 to 2.52)	2.42 (1.15 to 3.05)	-0.92 (-3.02, 0.26)	0.12
Difference in % time in hypoglycaemia (defined as interstitial glucose levels ≤3.0 mmol/l) in CGM between the two treatment options (Canagliflozin 300mg vs no treatment)	0.00 (0.00 to 0.55)	0.11 (0.00 to 0.28)	-0.07 (-0.6, 0.58)	0.82

Difference in % time in range (defined as 3.9 – 7.8 mmol/l) in CGM between the two treatment options (Canagliflozin 300mg vs no treatment)	88.23 (± 4.15)	85.78 (± 6.28)	2.44 (-1.12, 6.00)	0.16
Difference in the mean interstitial glucose in CGM between the two treatment options (Canagliflozin 300mg vs no treatment)	6.03 (± 0.57)	6.40 (± 0.58)	-0.37 (-0.79, 0.05)	0.08
Difference in the standard deviation (SD) of the mean interstitial glucose between the two treatment options (Canagliflozin 300mg vs no treatment)	1.25 (± 0.20)	1.36 (± 0.32)	-0.11 (-0.30, 0.07)	0.21
Difference in the coefficient of variation (CV) between the two treatment options (Canagliflozin 300mg vs no treatment)	0.21 (± 0.03)	0.21 (± 0.04)	0 (-0.03, 0.02)	0.79
Difference in mean amplitude glucose excursion (MAGE) in CGM between the two treatment options (Canagliflozin 300mg vs no treatment)	3.45 (± 0.53)	3.84 (± 0.88)	-0.39 (-0.84, 0.05)	0.08

† RYGB (n = 8), SG (n = 6)

Adverse events and serious adverse events

	Canagliflozin 300mg		**Standard care**	
	Patients (n=24)	**Events**	**Patients (n=24)**	**Events**
Serious Adverse Events	0 (0%)	0	0 (0%)	0
Any AEs	8 (33%)	8	18 (71%)	22
Nervous system disorders	1 (4%)	1	1 (4%)	1
General disorders and administration site conditions	1 (4%)	1	2 (8%)	2
Ear and labyrinth disorders	1 (4%)	1	2 (8%)	2

Gastrointestinal disorders	2 (8%)	2	2 (8%)	4
Respiratory, thoracic and mediastinal disorders	0 (0%)	0	1 (4%)	1
Infections and infestations	0 (0%)	0	2 (8%)	2
Musculoskeletal and connective tissue disorders	0 (0%)	0	2 (8%)	2
Renal and urinary disorders	0 (0%)	0	1 (4%)	1
Psychiatric disorders	1 (4%)	1	0 (0%)	0
Skin and subcutaneous tissue disorders	0 (0%)	0	1 (4%)	2
Endocrine disorders	1 (4%)	1	4 (17%)	5
Metabolism and nutrition disorders	1 (4%)	1	0 (0%)	0