Clinical trial results:
The effect of Canagliflozin 300mg, in subjects without diabetes after bariatric surgery, on glucose homeostasis (The CONTROL Study): A proof-of-concept, randomised, open-label, two period crossover study.

Summary

EudraCT number	2019-004041-32
Trial protocol	GB
Global end of trial date	31 December 2023

Results information

Result version number	v2 (current)
This version publication date	01 May 2026
First version publication date	05 January 2025
Version creation reason	• Correction of full data set Correction required post MHRA inspection

Trial information

Trial identification

Sponsor protocol code	0701

Additional study identifiers

ISRCTN number	ISRCTN11342830
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	University Road, Leicester, United Kingdom, LE1 7RH
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2023
Global end of trial reached?	Yes
Global end of trial date	31 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of canagliflozin 300 mg (CANA300) on glucose levels, insulin and gut hormones after a meal in people without diabetes after weight-loss surgery.

This was a randomised, open-label, two period, cross-over study comparing CANA300 with standard care in people after weight loss surgery.

Protection of trial subjects:

In UK, more than 25% of the population is living with obesity and approximately 10% suffers from severe and complex obesity (defined as BMI≥35 kg/m2 with obesity related comorbidities). Bariatric surgery (BS) is currently the most effective method to achieve substantial weight loss and maintenance in people with severe and complex obesity.
Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) account for more than 90% of bariatric procedures worldwide. Despite the successful weight loss and weight maintenance, some long-term complications can develop after both RYGB and SG, such as nutritional and vitamin deficiencies, early dumping syndrome and postprandial hyperinsulinaemic hypoglycaemia (PHH).

PHH is a condition characterised by hypoglycaemic symptoms occurring 1-3 hours after a meal accompanied by a low glucose value, typically preceded by a high rise in both glucose and insulin concentration due to rapid gastric emptying and changes in glucose absorption post operatively. PHH has been described since 1940s as complication of gastric resection in people suffering from peptic ulcers and was named “late dumping”. The condition has recently warranted further attention due to the increased number of bariatric procedures worldwide. It is of note that recurrent PHH after BS is associated with reduced quality of life, high degree of functional disability (inability to work, drive, care for others) and weight regain. In addition, an increased rate of accidental deaths, syncopal episodes and seizures among people who have undergone BS has been reported, and it is speculated that this could be partially due to neuroglycopenic symptoms as result of severe PHH.

In this study, all participants were people without known history of PHH and without frequent symptoms suggestive of hypoglycaemia in daily life.

Background therapy:

People allocated to standard care treatment sequence were asked to continue their usual daily life without changing their diet and daily life habits.

Evidence for comparator:

Treatment options for PHH after BS are limited, and people experiencing PHH are most commonly encouraged to follow dietary modifications consisting of small, frequent and low in carbohydrates meals. Medical treatments for PHH after BS include mainly acarbose but effectiveness can be limited, while the gastrointestinal side effects limits further its use.
Canagliflozin is a Sodium-glucose co-transporter-2 (SGLT-2) inhibitor that is used worldwide for type 2 diabetes management. However, CANA300 once daily - the highest licensed dose - has a transient inhibitory effect on SGLT-1, on top of the relatively strong inhibition of SGLT-2. Mild to moderate pharmacological inhibition of SGLT-1 in the small intestine reduces postprandial excursion of glucose without causing severe diarrhoea or malabsorption.
Indeed, CANA300 reduces the postprandial glucose excursions and insulin secretion and increases the postprandial glucose nadir in healthy individuals – this effect appears stronger with CANA300 compared to other available SGLT-2 inhibitors. So, if this effect on glucose homeostasis is also observed after BS then CANA300 could potentially be a treatment option for PHH after BS. Indeed, there are case reports and small observational studies where CANA300 has been successfully used to treat cases of PHH after

BS. In addition, SGLT-2 inhibitors may increase glucagon secretion in normal healthy people, which could also play a role in preventing hypoglycaemic episodes in people on SGLT-2 inhibitors. Taking into account that CANA300 has also known cardiometabolic benefits (including weight loss), it could become an attractive option for PHH treatment after BS.

Actual start date of recruitment	10 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 24
Worldwide total number of subjects	24
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	20
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from the University Hospitals of Leicester NHS Trust, UK
Recruitment open: 21/05/2021
First recruit: 10/08/2021
Last recruit: 13/04/2023
Recruitment closed: 13/04/2023

Pre-assignment

Screening details:

Participants were screened for eligibility by their age, ability to understand English and give consent, lack of diabetes diagnosis and whether they were at least one year after RYGB or SG surgery. We screened a total of 36 participants.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	CANA 300mg

Arm description:

Pooled data from visits 2 and 4, were used to analyse the treatment effect of canagliflozin 300mg, based on the two randomisation groups:

Group A = canagliflozin 300mg and then standard care

Group B = standard care and then canagliflozin 300 mg

Arm type	Experimental
Investigational medicinal product name	Canagliflozin 300mg
Investigational medicinal product code	
Other name	Invokana
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

one tablet of canagliflozin 300mg daily for 5 days

Arm title	Standard care

Arm description:

Pooled data from visits 2 and 4, were used to analyse the treatment effect of standard care, based on the two randomisation groups:

Group A = canagliflozin 300 mg and then standard care

Group B = standard care and then canagliflozin 300 mg

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	CANA 300mg	Standard care
Started	24	24
Visit 1-randomisation/baseline	24	24
Visit 2 -mixed meal tolerance test	22	22
Washout period of 3 weeks	22	22
Visit 3-switching groups	21	21
Visit 4-mixed meal tolerance test	21	21
Completed	21	21
Not completed	3	3
Consent withdrawn by subject	2	2
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall period
Reporting group description:	
24 participants attended the baseline visit, 14 of which had undergone Roux-en-Y Gastric Bypass (RYGB) and 10 who had undergone Sleeve gastrectomy (SG) bariatric surgery. Depending on the amount of missing data, less participants were included in the analysis of primary and secondary outcomes.	

Reporting group values	Overall period	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	53.8		
standard deviation	± 9.9	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	3	3	
Ethnicity Units: Subjects			
White British	22	22	
Indian	1	1	
Other African background	1	1	
Alcohol Status Units: Subjects			
Current	21	21	
Ex-drinker	1	1	
Never drank	2	2	
Smoking history Units: Subjects			
Ex-smoker	11	11	
Never smoked	13	13	
Height Units: centimetre			
arithmetic mean	163.7		

standard deviation	± 7.6	-	
Weight			
Units: kilogram(s)			
arithmetic mean	96.8		
standard deviation	± 23.8	-	
Body fat			
Units: percent			
arithmetic mean	43		
standard deviation	± 10.5	-	
Systolic blood pressure			
Units: mm Hg			
arithmetic mean	121		
standard deviation	± 16.2	-	
Diastolic blood pressure			
Units: mm Hg			
arithmetic mean	74.9		
standard deviation	± 11.3	-	
HbA1c			
Units: percent			
arithmetic mean	5.4		
standard deviation	± 0.4	-	
Heart rate			
Units: bpm			
arithmetic mean	70.8		
standard deviation	± 8	-	
BMI			
Units: kilogram(s)/square metre			
arithmetic mean	36		
standard deviation	± 8.2	-	

End points

End points reporting groups

Reporting group title	CANA 300mg

Reporting group description:

Pooled data from visits 2 and 4, were used to analyse the treatment effect of canagliflozin 300mg, based on the two randomisation groups:

Group A = canagliflozin 300mg and then standard care

Group B = standard care and then canagliflozin 300 mg

Reporting group title	Standard care

Reporting group description:

Pooled data from visits 2 and 4, were used to analyse the treatment effect of standard care, based on the two randomisation groups:

Group A = canagliflozin 300 mg and then standard care

Group B = standard care and then canagliflozin 300 mg

Primary: The difference in nadir glucose levels between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in nadir glucose levels between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

The lowest plasma glucose value detected during visits 2,4 for CANA300 mg and standard care groups

End point type	Primary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	3.75 (± 0.7)	3.41 (± 0.78)		

Statistical analyses

Statistical analysis title	Paired t-test

Statistical analysis description:

Paired t-test to compare the mean difference in nadir glucose values between the CANA300 mg and standard care groups.
The analysis subjects were 19 in total, given the paired nature of the crossover study. 12 subjects had undergone RYGB and 7 had undergone SG bariatric surgery.

For all secondary outcomes with 19 participants reported, the number of participants having undergone

RYGB and SG bariatric surgery, remains the same.

Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.65
Variability estimate	Standard error of the mean

Secondary: Difference in fasting glucose levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	Difference in fasting glucose levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	4.39 (± 0.46)	4.64 (± 0.45)		

Statistical analyses

Statistical analysis title	Paired t-test

Statistical analysis description:

Paired t-test to compare the mean difference in fasting glucose values between the CANA300 mg and standard care
The analysis subjects in are 19 in total, given the paired nature of the crossover study

Comparison groups	CANA 300mg v Standard care

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.13
Variability estimate	Standard error of the mean

Secondary: Difference in peak glucose levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	Difference in peak glucose levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	7.25 (± 1.33)	8.26 (± 1.41)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	Standard care v CANA 300mg
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	-0.37
Variability estimate	Standard error of the mean

Secondary: Difference in peak-nadir glucose levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	Difference in peak-nadir glucose levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	3.49 (± 1.07)	4.85 (± 1.39)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.93
upper limit	-0.79
Variability estimate	Standard error of the mean

Secondary: Difference in the max/min ratio of glucose levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	Difference in the max/min ratio of glucose levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: standardised ratio				
arithmetic mean (standard deviation)	1.96 (± 0.3)	2.50 (± 0.49)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.32
Variability estimate	Standard error of the mean

Secondary: The difference in glucose tAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in glucose tAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:
Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: minutes × mmol/L				
arithmetic mean (standard deviation)	919.88 (± 143.29)	960.23 (± 149.7)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.06
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-40.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.29
upper limit	2.58
Variability estimate	Standard error of the mean

Notes:

[1] - For the secondary outcomes regarding AUC of 0-180,60-180 glucose calculations only, it was decided not to impute missing data, as 3 participants had to stop the MMTT due to hypoglycaemia. Therefore, the total number of participants was 16.

Secondary: The difference in glucose tAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in glucose tAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:
Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × mmol/L				
arithmetic mean (standard deviation)	177.71 (± 32.61)	204.51 (± 24.75)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-26.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.95
upper limit	-15.65
Variability estimate	Standard error of the mean

Secondary: The difference in glucose positive iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in glucose positive iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: minutes × mmol/L				
arithmetic mean (standard deviation)	155.53 (± 74.93)	174.61 (± 71.74)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.79
upper limit	14.64
Variability estimate	Standard error of the mean

Secondary: The difference in glucose net iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in glucose net iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: minutes × mmol/L				
arithmetic mean (standard deviation)	124.50 (± 104.87)	114.23 (± 124.14)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	10.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.43
upper limit	46.96
Variability estimate	Standard error of the mean

Secondary: The difference in glucose positive iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in glucose positive iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × mmol/L				
arithmetic mean (standard deviation)	45.87 (± 21.14)	65.39 (± 28.62)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-19.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.53
upper limit	-10.51
Variability estimate	Standard error of the mean

Secondary: The difference in glucose net iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in glucose net iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × mmol/L				
arithmetic mean (standard deviation)	45.87 (± 21.14)	65.25 (± 28.94)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-19.38

Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.52
upper limit	-10.24
Variability estimate	Standard error of the mean

Secondary: The difference in glucose negative iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in glucose negative iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test
End point description:	
End point type	Secondary
End point timeframe: Visits 2,4	

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: minutes × mmol/L				
arithmetic mean (standard deviation)	116.44 (± 109.84)	98.20 (± 128.10)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	18.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.17
upper limit	53.64
Variability estimate	Standard error of the mean

Secondary: The difference in glucose negative iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in glucose negative iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × mmol/L				
arithmetic mean (standard deviation)	45.87 (± 21.14)	65.19 (± 29.09)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-19.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.52
upper limit	-10.12
Variability estimate	Standard error of the mean

Secondary: Difference in fasting insulin levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	Difference in fasting insulin levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal

	tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: mIU/L				
median (inter-quartile range (Q1-Q3))	5.83 (4.3 to 8.72)	6.87 (4.46 to 13.06)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	-0.15

Secondary: The difference in peak insulin levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in peak insulin levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: mIU/L				
arithmetic mean (standard deviation)	102.74 (± 63.62)	123.73 (± 74.86)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-20.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.73
upper limit	0.75
Variability estimate	Standard error of the mean

Secondary: The difference in insulin tAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in insulin tAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × mIU/L				
arithmetic mean (standard deviation)	5699.72 (± 2984.15)	7086.81 (± 4211.69)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1387.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2512.97
upper limit	-261.22
Variability estimate	Standard error of the mean

Secondary: The difference in insulin tAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in insulin tAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × mIU/L				
arithmetic mean (standard deviation)	1753.95 (± 1003.54)	2276.17 (± 1508.77)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-522.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-867.69
upper limit	-176.75
Variability estimate	Standard error of the mean

Secondary: The difference in insulin net iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in insulin net iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test
End point description:	
End point type	Secondary
End point timeframe:	
Visits 2,4	

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × mIU/L				
arithmetic mean (standard deviation)	4410.79 (± 2276.53)	5490.73 (± 3484.68)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1079.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2243.87
upper limit	83.97
Variability estimate	Standard error of the mean

Secondary: The difference in insulin net iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in insulin net iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test
End point description:	
End point type	Secondary
End point timeframe:	
Visits 2,4	

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × mIU/L				
median (inter-quartile range (Q1-Q3))	1416.44 (720.84 to 2093.01)	1515.40 (1298.51 to 2586.68)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-477.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-825.3
upper limit	99.06

Secondary: The difference in the ratio AUC insulin(0-180)/AUC glucose(0-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio AUC insulin(0-180)/AUC glucose(0-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test
End point description:	
End point type	Secondary
End point timeframe:	
Visits 2,4	

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mIU/mmol				
arithmetic mean (standard deviation)	6.08 (± 3.26)	7.22 (± 4.36)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.45
upper limit	0.19
Variability estimate	Standard error of the mean

Secondary: The difference in the ratio AUC insulin(0-30)/AUC glucose(0-30) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio AUC insulin(0-30)/AUC glucose(0-30) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test
End point description:	
End point type	Secondary
End point timeframe:	
Visits 2,4	

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: mIU/mmol				
median (inter-quartile range (Q1-Q3))	7.62 (5.27 to 10.53)	8.6 (6.27 to 13.03)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	-0.94

Secondary: The difference in the ratio net iAUC insulin(0-180)/iAUC glucose(0-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio net iAUC insulin(0-180)/iAUC glucose(0-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mIU/mmol				
median (inter-quartile range (Q1-Q3))	21.33 (13.36 to 57.44)	24.50 (18.64 to 47.04)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.57
upper limit	197.02

Secondary: The difference in the ratio net iAUC insulin(0-30)/iAUC glucose(0-30) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio net iAUC insulin(0-30)/iAUC glucose(0-30) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: mIU/mmol				
median (inter-quartile range (Q1-Q3))	23.72 (19.14 to 47.77)	21 (15.85 to 38.63)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.34
upper limit	7.96

Secondary: The difference in the ratio AUC insulin(60-180)/AUC glucose(60-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio AUC insulin(60-180)/AUC glucose(60-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mIU/mmol				
median (inter-quartile range (Q1-Q3))	2.19 (2.07 to 4.67)	2.49 (2.11 to 6.08)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	0.04

Secondary: The difference in the ratio net iAUC insulin(60-180)/iAUC glucose(60-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio net iAUC insulin(60-180)/iAUC glucose(60-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mIU/mmol				
median (inter-quartile range (Q1-Q3))	10.52 (2.89 to 26.39)	13.8 (2.11 to 34.73)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	3.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	61.05

Secondary: The difference in fasting C-peptide levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in fasting C-peptide levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: picogram(s)/millilitre				
median (inter-quartile range (Q1-Q3))	798.73 (630.03 to 1109.54)	1044.56 (629.94 to 1261.11)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-61.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-171.7
upper limit	32.46

Secondary: The difference in peak C-peptide levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in peak C-peptide levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: picogram(s)/millilitre				
median (inter-quartile range (Q1-Q3))	4128.30 (3236.90 to 5296.95)	4278.60 (3554.75 to 7243.80)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-495.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1275.7
upper limit	36.9

Secondary: The difference in C-peptide tAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in C-peptide tAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × pg/mL				
median (inter-quartile range (Q1-Q3))	393657.60 (305100.3 to 527728.9)	408722.20 (349033.6 to 578742.8)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	Standard care v CANA 300mg

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-31195.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-75875.21
upper limit	9387.7

Secondary: The difference in C-peptide tAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in C-peptide tAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test
End point description:	
End point type	Secondary
End point timeframe:	
Visits 2,4	

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × pg/mL				
median (inter-quartile range (Q1-Q3))	83162.22 (59399.21 to 98316.15)	87094.41 (70364.60 to 135148.88)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-15546.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-30245.51
upper limit	-7091.22

Secondary: The difference in C-peptide net iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in C-peptide net iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test
End point description:	
End point type	Secondary
End point timeframe: Visits 2,4	

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × pg/mL				
arithmetic mean (standard deviation)	269097 (± 106055.8)	300105.60 (± 137974)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-31008.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-76328.72
upper limit	14311.56
Variability estimate	Standard error of the mean

Secondary: The difference in C-peptide net iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in C-peptide net iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × pg/mL				
median (inter-quartile range (Q1-Q3))	45287.46 (33097.44 to 69817.28)	60668.44 (45645.12 to 105836.15)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	Standard care v CANA 300mg
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-15661.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30537.07
upper limit	-5086.91

Secondary: The difference in the ratio AUC C-peptide(0-180)/AUC glucose(0-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio AUC C-peptide(0-180)/AUC glucose(0-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:
Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: (pg × L) / (mL × mmol)				
arithmetic mean (standard deviation)	493.25 (± 169.47)	522.05 (± 207.82)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-28.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-87.96
upper limit	30.36
Variability estimate	Standard error of the mean

Secondary: The difference in the ratio AUC C-peptide(0-30)/AUC glucose(0-30) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio AUC C-peptide(0-30)/AUC glucose(0-30) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:
Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: (pg × L) / (mL × mmol)				
median (inter-quartile range (Q1-Q3))	409.49 (357.87 to 580.58)	453.06 (366.33 to 453.06)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.38
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-16.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-78.5
upper limit	24.36

Secondary: The difference in the ratio iAUC C-peptide(0-180)/iAUC glucose(0-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio iAUC C-peptide(0-180)/iAUC glucose(0-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: (pg × L) / (mL × mmol)				
median (inter-quartile range (Q1-Q3))	1644.65 (1037.30 to 2937.94)	1309.24 (1007.74 to 2078.03)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	Standard care v CANA 300mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	67.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-310.75
upper limit	10092.43

Secondary: The difference in the ratio iAUC C-peptide(0-30)/iAUC glucose(0-30) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio iAUC C-peptide(0-30)/iAUC glucose(0-30) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: (pg × L) / (mL × mmol)				
median (inter-quartile range (Q1-Q3))	1147.10 (782.71 to 1718.39)	937.28 (772.38 to 1561.57)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	119.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.98
upper limit	280.08

Secondary: The difference in the ratio AUC C-peptide(60-180)/AUC glucose(60-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio AUC C-peptide(60-180)/AUC glucose(60-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: (pg × L) / (mL × mmol)				
median (inter-quartile range (Q1-Q3))	392.53 (304.32 to 580.52)	357.78 (323.92 to 531.40)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.06
upper limit	34.43

Secondary: The difference in the ratio iAUC C-peptide(60-180)/iAUC glucose(60-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in the ratio iAUC C-peptide(60-180)/iAUC glucose(60-180) between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: (pg × L) / (mL × mmol)				
median (inter-quartile range (Q1-Q3))	698.76 (475.70 to 878.58)	1016.46 (387.63 to 1708.40)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	756.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-110.82
upper limit	3162.2

Secondary: The difference in fasting GLP-1 levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in fasting GLP-1 levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test
End point description:	
End point type	Secondary
End point timeframe:	
Visits 2,4	

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: pmol/L				
arithmetic mean (standard deviation)	37.58 (± 16.32)	32.67 (± 15.91)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	4.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	8.88
Variability estimate	Standard error of the mean

Secondary: The difference in peak GLP-1 levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point title	The difference in peak GLP-1 levels between the two treatment options (CANA300 mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: pmol/L				
arithmetic mean (standard deviation)	183.06 (± 83.38)	173.56 (± 81.05)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	9.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.36
upper limit	42.35
Variability estimate	Standard error of the mean

Secondary: The difference in GLP-1 tAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in GLP-1 tAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:
Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × pmol/L				
arithmetic mean (standard deviation)	15312.74 (± 5132.11)	12725.29 (± 3924.41)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2587.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1140.67
upper limit	4034.229
Variability estimate	Standard error of the mean

Secondary: The difference in GLP-1 tAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in GLP-1 tAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:
Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × pmol/L				
arithmetic mean (standard deviation)	3670.62 (± 1533.51)	3483.69 (± 1562.41)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	Standard care v CANA 300mg
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	186.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-252.73
upper limit	626.6
Variability estimate	Standard error of the mean

Secondary: The difference in GLP-1 net iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in GLP-1 net iAUC(0-180) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × pmol/L				
arithmetic mean (standard deviation)	8547.46 (± 4988.76)	6845.15 (± 4045.26)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1702.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	147.7
upper limit	3256.91
Variability estimate	Standard error of the mean

Secondary: The difference in GLP-1 net iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point title	The difference in GLP-1 net iAUC(0-30) between the two treatment options (CANA300mg vs standard care) after the mixed meal tolerance test

End point description:

End point type	Secondary

End point timeframe:

Visits 2,4

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: minutes × pmol/L				
arithmetic mean (standard deviation)	2543.08 (± 1495.8)	2503.67 (± 1545.62)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	39.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-425.32
upper limit	504.14
Variability estimate	Standard error of the mean

Secondary: Difference in nadir glucose during CGM between the two treatment options (CANA 300mg vs standard care)

End point title	Difference in nadir glucose during CGM between the two treatment options (CANA 300mg vs standard care)
End point description:	
End point type	Secondary
End point timeframe:	
5 days after Visit 1 and 5 days after Visit 3	

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	3.05 (± 0.68)	2.78 (± 0.65)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.87
Variability estimate	Standard error of the mean

Secondary: Difference in % time in interstitial glucose levels in CGM spent in< 3.9 mmol/l between the two treatment options (CANA 300mg vs standard care)

End point title	Difference in % time in interstitial glucose levels in CGM spent in< 3.9 mmol/l between the two treatment options (CANA 300mg vs standard care)

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: percent				
median (inter-quartile range (Q1-Q3))	0.81 (0.14 to 2.64)	0.69 (0.30 to 1.16)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test

Statistical analysis description:

Out of 14 participants with available CGM data, 8 had undergone RYGB and 6 SG bariatric surgery.

Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	3.62

Secondary: Difference in % time in interstitial glucose levels in CGM spent between (3.9-10.0 mmol/l) between the two treatment options (CANA 300mg vs standard care)

End point title	Difference in % time in interstitial glucose levels in CGM spent between (3.9-10.0 mmol/l) between the two treatment options (CANA 300mg vs standard care)

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: percent				
median (inter-quartile range (Q1-Q3))	96.31 (95.21 to 98.36)	96.63 (94.92 to 98.21)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	Standard care v CANA 300mg
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	2.27

Secondary: Difference in % time in interstitial glucose levels in CGM spent between (3.0-10.0) mmol/l between the two treatment options (CANA 300mg vs standard care

End point title	Difference in % time in interstitial glucose levels in CGM spent between (3.0-10.0) mmol/l between the two treatment options (CANA 300mg vs standard care

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: percent				
median (inter-quartile range (Q1-Q3))	98.62 (96.88 to 99.20)	97.34 (96.66 to 98.50)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	2.9

Secondary: Difference in % time in interstitial glucose levels in CGM spent above 7.8 mmol/l between the two treatment options (CANA 300mg vs standard care)

End point title	Difference in % time in interstitial glucose levels in CGM spent above 7.8 mmol/l between the two treatment options (CANA 300mg vs standard care)

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: percent				
arithmetic mean (standard deviation)	9.46 (± 4.96)	13.01 (± 6.79)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.72
upper limit	0.62
Variability estimate	Standard error of the mean

Secondary: Difference in % time in interstitial glucose levels in CGM spent above 10.0 mmol/l between the two treatment options (CANA 300mg vs standard care)

End point title	Difference in % time in interstitial glucose levels in CGM spent above 10.0 mmol/l between the two treatment options (CANA 300mg vs standard care)

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: percent				
median (inter-quartile range (Q1-Q3))	0.89 (0.53 to 2.52)	2.42 (1.15 to 3.05)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.02
upper limit	0.26

Secondary: Difference in % time in interstitial glucose levels in CGM spent in hypoglycemia (<= 3 .0 mmol/l) between the two treatment options (CANA 300mg vs standard care)

End point title	Difference in % time in interstitial glucose levels in CGM spent in hypoglycemia (<= 3 .0 mmol/l) between the two treatment options (CANA 300mg vs standard care)

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: percent				
median (inter-quartile range (Q1-Q3))	0.00 (0.00 to 0.55)	0.11 (0.00 to 0.28)		

Statistical analyses

Statistical analysis title	Wilcox signed rank test
Comparison groups	CANA 300mg v Standard care

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.58

Secondary: Difference in % time in interstitial glucose levels in CGM spent between (3.9-7.8) mmol/l between the two treatment options (CANA 300mg vs standard care)

End point title	Difference in % time in interstitial glucose levels in CGM spent between (3.9-7.8) mmol/l between the two treatment options (CANA 300mg vs standard care)

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: percent				
arithmetic mean (standard deviation)	88.23 (± 4.15)	85.78 (± 6.28)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	6
Variability estimate	Standard error of the mean

Secondary: Difference in mean interstitial glucose in CGM between the two treatment options (CANA300 mg vs standard care)

End point title	Difference in mean interstitial glucose in CGM between the two treatment options (CANA300 mg vs standard care)

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	6.03 (± 0.57)	6.40 (± 0.58)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.05
Variability estimate	Standard error of the mean

Secondary: Difference in standard deviation (SD) of the mean interstitial glucose in CGM between the two treatment options (CANA300 mg vs standard care

End point title	Difference in standard deviation (SD) of the mean interstitial glucose in CGM between the two treatment options (CANA300 mg vs standard care

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	1.25 (± 0.20)	1.36 (± 0.32)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	Standard care v CANA 300mg
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.07
Variability estimate	Standard error of the mean

Secondary: Difference in the coefficient of variation (CV) of the mean interstitial glucose in CGM between the two treatment options (CANA300 mg vs standard care)

End point title	Difference in the coefficient of variation (CV) of the mean interstitial glucose in CGM between the two treatment options (CANA300 mg vs standard care)

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: index				
arithmetic mean (standard deviation)	0.21 (± 0.03)	0.21 (± 0.04)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	CANA 300mg v Standard care
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.02
Variability estimate	Standard error of the mean

Secondary: Difference in mean amplitude glucose excursion (MAGE) in CGM between the two treatment options (CANA300 mg vs standard care)

End point title	Difference in mean amplitude glucose excursion (MAGE) in CGM between the two treatment options (CANA300 mg vs standard care)

End point description:

End point type	Secondary

End point timeframe:

5 days after Visit 1 and 5 days after Visit 3

End point values	CANA 300mg	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: index				
arithmetic mean (standard deviation)	3.45 (± 0.53)	3.84 (± 0.88)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	Standard care v CANA 300mg
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	0.05
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Between visits 2-6	
Assessment type	Systematic
Dictionary used	
Dictionary name	no dictionary used
Dictionary version	NA
Reporting groups	
Reporting group title	All participants randomised

Reporting group description: -

Serious adverse events	All participants randomised		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All participants randomised		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 24 (66.67%)		
Nervous system disorders			
Stabbing sensation in head			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Bells' Palsy			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Brain Fog			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
General disorders and administration site conditions			
Discomforting left axilla			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Feeling hot			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Gastrointestinal disorders			
Stomach Cramps			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Dumping syndrome symptoms			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Bloating			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Chest tightness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Sore Throat			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Hepatobiliary disorders			
Right upper quadrant ache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash at tourniquet site			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Itchy lesions R leg			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Rash on stomach at CGM site			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Psychiatric disorders			
Worsening of depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Infections and infestations			
Ear Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

UTI			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Increased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hypoglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	6		
Hypoglycaemia symptoms			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2021	SA01 Within this amendment we have updated the current recruitment strategy outlined within the study protocol to include additional ways to promote and advertise the study using research registry databases (such as UHL research registry) and relevant charities (such as Obesity UK) to target a wider population which will support recruitment to time and target projections. A Patient Information Leaflet (PIL) has been produced and will be used as a study advertising material but will also support study mail outs to reduce printing costs/overburden of information on patients via 'cold call' mailings. We have updated the patient reply slip due to the addition of the Patient Information Leaflet. Change made within the current study Consent form to revise Participant ID to Participant Screening ID. We will also take this opportunity to inform the MHRA of changes made within the protocol around pregnancy reporting as per REC comments on Protocol v2.0 (original study submission). Details of the changes made within the protocol include the process of reporting pregnancies to sponsor and the responsibility of the study team to follow up participants according to sponsor SOP and guidelines.
12 October 2021	SA02 Within this amendment, we have updated the current exclusion criteria outlined within the study protocol around the use of oral steroids and intolerance to the Mixed Meal Tolerance Test. This proposed amendment was discussed at the recent Data Safety Monitoring Committee and all DSMC Members agree with the PI that these statements should be amended. The current statement around the use of steroids excludes patients on any form of steroids therefore we are updating this to exclude patients on oral or injectable steroids only (topical or inhaled corticosteriods are allowed). We are also excluding those patients with a severe lactose intolerance - severity will be assessed by a clinician during screening visit to determine if a patient should be excluded or not.
23 August 2023	SA03 With this amendment we have updated the main statistical analysis primary and secondary outcomes. We have also updated the description of subgroup analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although REC and HRA approvals were in place, the start of the trial was delayed because of COVID-19. The study had 5 core study visits in which participants were required to attend on site and these visits could not be adapted to virtual visits.

Notes: