Clinical trial results:
SGLT-2 Inhibitor Empagliflozin Effects on Appetite and Weight Regulation: A randomised double-blind placebo-controlled trial (SEESAW)

Summary

EudraCT number	2015-001594-40
Trial protocol	GB
Global end of trial date	30 July 2019

Results information

Result version number	v1 (current)
This version publication date	27 August 2020
First version publication date	27 August 2020

Trial information

Trial identification

Sponsor protocol code	UNOLE0526

Additional study identifiers

ISRCTN number	ISRCTN82062639
ClinicalTrials.gov id (NCT number)	NCT02798744
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	Research Governance Office, Academic Department, Leicester General Hospital, Leicester, United Kingdom, LE5 4PW
Public contact	Professor Melanie Davies , Leicester Diabetes Centre, +44 01162588973, melanie.davies@uhl-tr.nhs.uk
Scientific contact	Professor Melanie Davies , Leicester Diabetes Centre, +44 01162586481, melanie.davies@uhl-tr.nhs.uk

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	09 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2019
Global end of trial reached?	Yes
Global end of trial date	30 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the cause for the discrepancy in predicted and observed weight loss with empagliflozin by measuring appetite hormone regulation.

Protection of trial subjects:

All study participants were required to read a patient Information Sheet (PIS) about the trial (including trial treatments and any known side-effects) and sign an Informed Consent Form (ICF). Patients were monitored regularly throughout the trial duration.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 2016
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: 68
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	34
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Sponsor Greenlight was issued on 18/11/2016. First Patient First Visit date was 04/01/2017 and Last Patient Last Visit date was 09/07/2017.

Pre-assignment

Screening details:

68 participants (44 men and 24 women) with type 2 diabetes, controlled via lifestyle or stable metformin therapy only, were enrolled into the study.
63 participants completed the study, of which primary outcome data was collected for 61 participants.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Empagliflozin (Jardiance™) and the placebo were formulated and supplied in identical tablet form sealed in identical medication packs by Boehringer Ingelheim and supplied to the third-party company ALMAC. ALMAC organised blinding, packaging and labelling of both Empagliflozin (Jardiance™) and the placebo. The finished stock was sent by ALMAC to the research site. The allocation to placebo or Empagliflozin (Jardiance™) was randomly assigned using an independent online computerised system.

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin (Baseline)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Empagliflozin plus ERD (Baseline)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Placebo (baseline)

Arm description:

The placebo was labelled as '25mg once daily' to match the IMP.

Arm type	Placebo
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as '25mg once daily' to match the IMP.

Arm title	Placebo plus ERD (baseline)

Arm description:

Placebo and energy restriction diet (ERD)

Arm type	Experimental
Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as '25mg once daily' to match the IMP.

Number of subjects in period 1	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)
Started	17	17	17
Completed	17	17	17

Number of subjects in period 1	Placebo plus ERD (baseline)
Started	17
Completed	17

Period 2

Period 2 title	2 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

As before

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin (2 weeks)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Empagliflozin plus ERD (2 weeks)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Placebo (2 weeks)

Arm description:

The placebo was labelled as ‘25mg once daily’ to match the IMP.

Arm type	Placebo
Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as ‘25mg once daily’ to match the IMP.

Arm title	Placebo plus ERD (2 weeks)

Arm description:

Placebo and energy restriction diet (ERD)

Arm type	Experimental

Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as '25mg once daily' to match the IMP.

Number of subjects in period 2	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)
Started	17	17	17
Completed	17	17	17
Not completed	0	0	0
Physician decision	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 2	Placebo plus ERD (2 weeks)
Started	17
Completed	15
Not completed	2
Physician decision	1
Lost to follow-up	1

Period 3

Period 3 title	6 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

As above

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin (6 weeks)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Empagliflozin plus ERD (6 weeks)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Placebo (6 weeks)

Arm description:

The placebo was labelled as ‘25mg once daily’ to match the IMP.

Arm type	Placebo
Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as ‘25mg once daily’ to match the IMP.

Arm title	Placebo plus ERD (6 weeks)

Arm description:

Placebo and energy restriction diet (ERD)

Arm type	Experimental
Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as ‘25mg once daily’ to match the IMP.

Number of subjects in period 3	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)
Started	17	17	17
Completed	17	17	17
Not completed	0	0	0
Voluntary withdrawal	-	-	-

Number of subjects in period 3	Placebo plus ERD (6 weeks)
Started	15
Completed	14
Not completed	1
Voluntary withdrawal	1

Period 4

Period 4 title	12 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

As above

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin (12 weeks)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Empagliflozin plus ERD (12 weeks)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Placebo (12 weeks)

Arm description:

The placebo was labelled as ‘25mg once daily’ to match the IMP.

Arm type	Placebo

Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as '25mg once daily' to match the IMP.

Arm title	Placebo plus ERD (12 weeks)

Arm description:

Placebo and energy restriction diet (ERD)

Arm type	Experimental
Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as '25mg once daily' to match the IMP.

Number of subjects in period 4	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)
Started	17	17	17
Completed	17	17	17

Number of subjects in period 4	Placebo plus ERD (12 weeks)
Started	14
Completed	14

Period 5

Period 5 title	24 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

As above

Arms

Are arms mutually exclusive?	Yes

Arm title	Empagliflozin (24 weeks)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Empagliflozin plus ERD (24 weeks)

Arm description:

Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)

Arm type	Experimental
Investigational medicinal product name	Empagliflozin (Jardiance™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was 25mg once daily for Empagliflozin (Jardiance™), which is the maximum dose licensed for the treatment of Type 2 Diabetes in the UK.

Arm title	Placebo (24 weeks)

Arm description:

The placebo was labelled as ‘25mg once daily’ to match the IMP.

Arm type	Placebo
Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as ‘25mg once daily’ to match the IMP.

Arm title	Placebo plus ERD (24 weeks)

Arm description:

Placebo and energy restriction diet (ERD)

Arm type	Experimental
Investigational medicinal product name	Placebo 25mg once daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo was labelled as ‘25mg once daily’ to match the IMP.

Number of subjects in period 5	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)
Started	17	17	17
Completed	16	17	16
Not completed	1	0	1
Adverse event, non-fatal	-	-	1
Voluntary withdrawal	1	-	-

Number of subjects in period 5	Placebo plus ERD (24 weeks)
Started	14
Completed	14
Not completed	0
Adverse event, non-fatal	-
Voluntary withdrawal	-

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	68	68	
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)	34	34	
From 65-84 years	34	34	
85 years and over	0	0	
Age continuous			
The median age of the combined study population was 63 years			
Units: years			
median	63		
full range (min-max)	39 to 74	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	44	44	
Ethnicity Units: Subjects			
White	49	49	
South Asian	13	13	
Other	6	6	
Smoking Status Units: Subjects			
Ex-smoker	32	32	
Current smoker	6	6	
Never smoker	30	30	
Alcohol drinking status Units: Subjects			
Ex-drinker	3	3	
Current drinker	51	51	
Never drinker	14	14	
Family History - Diabetes in Mother Units: Subjects			
No diabetes	42	42	
Type 1 Diabetes	2	2	

Type 2 Diabetes	17	17	
Diabetes - type unknown	3	3	
Not Reported	4	4	
Family History - Diabetes in Father Units: Subjects			
No Diabetes	45	45	
Type 1 Diabetes	2	2	
Type 2 Diabetes	11	11	
Diabetes - Type Unknown	0	0	
Not reported	10	10	
Family History - Diabetes in Siblings Units: Subjects			
No Diabetes	38	38	
1 Sibling Diabetes	13	13	
2 or more Siblings with Diabetes	4	4	
Not reported	13	13	
Family History - Diabetes in First Degree Relatives Units: Subjects			
No Diabetes	40	40	
At least 1 Relative with Diabetes	16	16	
Not Reported	12	12	
Family History - Cardiovascular Disease Units: Subjects			
No	23	23	
Yes	43	43	
Unknown	2	2	
Family History - Stroke Units: Subjects			
No	39	39	
Yes	24	24	
Unknown	5	5	
Family History - High Blood Pressure Units: Subjects			
No	16	16	
Yes	36	36	
Unknown	16	16	
Family History - High Cholesterol Units: Subjects			
No	17	17	
Yes	23	23	
Unknown	28	28	
Family History - Gestational Diabetes Units: Subjects			
No	42	42	
Yes	0	0	
Unknown	26	26	
Concomitant Medication Units: Subjects			
Yes	56	56	
No	12	12	

Medical History - Myocardial Infarction Units: Subjects			
No	60	60	
Yes	7	7	
Unknown	1	1	
Medical History - Heart Valve Disease Units: Subjects			
No	64	64	
Yes	3	3	
Unknown	1	1	
Medical History - Heart Failure Units: Subjects			
No	67	67	
Yes	0	0	
Unknown	1	1	
Medical History - Atrial Fibrillation Units: Subjects			
No	64	64	
Yes	3	3	
Unknown	1	1	
Medical History - Angina Units: Subjects			
No	65	65	
Yes	2	2	
Unknown	1	1	
Medical History - Stroke Units: Subjects			
No	66	66	
Yes	1	1	
Unknown	1	1	
Medical History - Angioplasty Units: Subjects			
No	64	64	
Yes	3	3	
Unknown	1	1	
Medical History - Leg Angioplasty Units: Subjects			
No	67	67	
Yes	0	0	
Unknown	1	1	
Medical History - Peripheral Vascular Disease Units: Subjects			
No	67	67	
Yes	0	0	
Unknown	1	1	
Medical History - High Blood Pressure Units: Subjects			
No	26	26	
Yes	40	40	
Unknown	2	2	

Medical History - High Cholesterol Units: Subjects			
No	21	21	
Yes	46	46	
Unknown	1	1	
Medical History - Gestational Diabetes Units: Subjects			
N/A	44	44	
No	21	21	
Yes	2	2	
Unknown	1	1	
Medical History - Polycystic Ovaries Units: Subjects			
N/A	44	44	
No	21	21	
Yes	2	2	
Unknown	1	1	
Medical History - Thyroid Disorder Units: Subjects			
No	63	63	
Yes	4	4	
Unknown	1	1	
Duration of Diabetes Units: Years			
median	6		
full range (min-max)	0.58 to 15	-	
Average Systolic Blood Pressure Units: mmHg			
median	127		
full range (min-max)	101 to 177	-	
Average Diastolic Blood Pressure Units: mmHg			
median	77.5		
full range (min-max)	57 to 117.5	-	
Average Heart Rate Units: bpm			
median	68.25		
full range (min-max)	43.5 to 96	-	
Weight Units: Kg			
median	91		
full range (min-max)	59.5 to 146.6	-	
Body Mass Index Units: Kg^m2			
median	31.8		
full range (min-max)	25 to 44.8	-	
Hip Circumference Units: cm			
median	111.5		
full range (min-max)	93 to 147	-	
Waist Circumference			

Units: cm			
median	110.9		
full range (min-max)	84 to 140	-	
Sodium			
Units: mmol/L			
median	140		
full range (min-max)	136 to 144	-	
Potassium			
Units: mmol/L			
median	4.3		
full range (min-max)	3.3 to 5.3	-	
Urea			
Units: mmol/L			
median	5.8		
full range (min-max)	2.8 to 9.8	-	
Creatinine			
Units: umol/L			
median	70.5		
full range (min-max)	49 to 102	-	
eGFR			
Units: ml/min/1.73m2			
median	89		
full range (min-max)	67 to 90	-	
Albumin			
Units: g/L			
median	45		
full range (min-max)	38 to 50	-	
Alkaline Phosphatase			
Units: iu/L			
median	80		
full range (min-max)	35 to 126	-	
Alanine Transaminase			
Units: iu/L			
median	25.5		
full range (min-max)	10 to 85	-	
Bilirubin			
Units: mg/dL			
median	9		
full range (min-max)	4 to 23	-	
Total Cholesterol			
Units: mmol/L			
median	4.1		
full range (min-max)	2.2 to 7	-	
Triglycerides			
Units: mmol/L			
least squares mean	1.67		
full range (min-max)	0.51 to 3.54	-	
HDL Cholesterol			
Units: mmol/L			
median	1.2		
full range (min-max)	0.7 to 2.2	-	
Total cholesterol:HDL ratio			

Units: none			
median	3.4		
full range (min-max)	1.9 to 6.4	-	
LDL Cholesterol (calculated)			
Units: None			
median	2		
full range (min-max)	0.8 to 4.8	-	
HbA1c			
Units: percentage			
median	6.8		
full range (min-max)	6 to 8.2	-	
HbA1c			
Units: mmol/mol			
median	51		
full range (min-max)	42 to 67	-	

End points

End points reporting groups

Reporting group title	Empagliflozin (Baseline)
Reporting group description: Empagliflozin (Jardiance™) 25mg once daily	
Reporting group title	Empagliflozin plus ERD (Baseline)
Reporting group description: Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)	
Reporting group title	Placebo (baseline)
Reporting group description: The placebo was labelled as ‘25mg once daily’ to match the IMP.	
Reporting group title	Placebo plus ERD (baseline)
Reporting group description: Placebo and energy restriction diet (ERD)	

Reporting group title	Empagliflozin (2 weeks)
Reporting group description: Empagliflozin (Jardiance™) 25mg once daily	
Reporting group title	Empagliflozin plus ERD (2 weeks)
Reporting group description: Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)	
Reporting group title	Placebo (2 weeks)
Reporting group description: The placebo was labelled as ‘25mg once daily’ to match the IMP.	
Reporting group title	Placebo plus ERD (2 weeks)
Reporting group description: Placebo and energy restriction diet (ERD)	

Reporting group title	Empagliflozin (6 weeks)
Reporting group description: Empagliflozin (Jardiance™) 25mg once daily	
Reporting group title	Empagliflozin plus ERD (6 weeks)
Reporting group description: Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)	
Reporting group title	Placebo (6 weeks)
Reporting group description: The placebo was labelled as ‘25mg once daily’ to match the IMP.	
Reporting group title	Placebo plus ERD (6 weeks)
Reporting group description: Placebo and energy restriction diet (ERD)	

Reporting group title	Empagliflozin (12 weeks)
Reporting group description: Empagliflozin (Jardiance™) 25mg once daily	
Reporting group title	Empagliflozin plus ERD (12 weeks)
Reporting group description: Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)	
Reporting group title	Placebo (12 weeks)
Reporting group description: The placebo was labelled as ‘25mg once daily’ to match the IMP.	

Reporting group title	Placebo plus ERD (12 weeks)
Reporting group description:	
Placebo and energy restriction diet (ERD)	

Reporting group title	Empagliflozin (24 weeks)
Reporting group description:	
Empagliflozin (Jardiance™) 25mg once daily	
Reporting group title	Empagliflozin plus ERD (24 weeks)
Reporting group description:	
Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)	
Reporting group title	Placebo (24 weeks)
Reporting group description:	
The placebo was labelled as '25mg once daily' to match the IMP.	
Reporting group title	Placebo plus ERD (24 weeks)
Reporting group description:	
Placebo and energy restriction diet (ERD)	

Primary: Total PYY AUC

End point title	Total PYY AUC
End point description:	
Change in total PYY AUC during mixed meal tolerance test	
End point type	Primary
End point timeframe:	
0, 2, 6, 12 and 24 weeks	

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[1]	17	15[2]	14[3]
Units: pg/mL				
arithmetic mean (standard deviation)	146.2 (± 49.2)	134.4 (± 46.8)	143.5 (± 67.0)	157.4 (± 57.6)

Notes:

[1] - Complete case analysis: 1 x withdrawn, 1 x data not available

[2] - Complete case analysis: 1 x withdrawn, 1 x data not available

[3] - Complete case analysis: 3 x withdrawn

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[4]	17	16[5]	14[6]
Units: pg/mL				
arithmetic mean (standard deviation)	153.6 (± 55.2)	141.3 (± 51.2)	143.9 (± 44.2)	159.7 (± 39.9)

Notes:

[4] - Complete case analysis: 1 x withdrawn, 1 x data not available

[5] - Complete case analysis: 1 x data not available

[6] - Complete case analysis: 3 x withdrawn

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[7]	16[8]	16[9]	13[10]
Units: pg/mL				
arithmetic mean (standard deviation)	159.3 (± 57.2)	140.2 (± 43.4)	150.2 (± 66.1)	154.2 (± 29.5)

Notes:

[7] - Complete case analysis: 1 x data not available

[8] - 1 x did not attend

[9] - Complete case analysis: 1 x data not available

[10] - Complete case analysis: 3 x withdrawn, 1 x data not available

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[11]	16[12]	16[13]	14[14]
Units: pg/mL				
arithmetic mean (standard deviation)	176.2 (± 60.6)	143.6 (± 55.6)	136.1 (± 63.7)	149.5 (± 43.3)

Notes:

[11] - Complete case analysis: 2 x data not available

[12] - 1 x data not available

[13] - Complete case analysis: 1 x data not available

[14] - Complete case analysis: 3 x withdrawn

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[15]	17	15[16]	14[17]
Units: pg/mL				
arithmetic mean (standard deviation)	165.8 (± 56.2)	141.2 (± 39.4)	146.4 (± 69.7)	149.6 (± 36.3)

Notes:

[15] - Complete case analysis: 1 x withdrawn, 1 x data not available

[16] - Complete case analysis: 1 x withdrawn, 1 x data not available

[17] - Complete case analysis: 3 x withdrawn

Statistical analyses

Statistical analysis title	GLM - placebo plus ERD vs placebo @24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4 [18]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-8.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.58
upper limit	11.4

Notes:

[18] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.179 [19]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	13.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.13
upper limit	32.97

Notes:

[19] - Not significant

Statistical analysis title	GLM - empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92 [20]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.01
upper limit	19.95

Notes:

[20] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.772 [21]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	3.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	26.94

Notes:

[21] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [22]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	34.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.38
upper limit	57.29

Notes:
[22] - Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.177 [23]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	15.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.04
upper limit	38.19

Notes:
[23] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.521 [24]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-6.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.17
upper limit	14.27

Notes:
[24] - Not Significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential

Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.498 [25]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	6.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.02
upper limit	26.8

Notes:

[25] - Not Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.738 [26]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	3.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.65
upper limit	23.51

Notes:

[26] - Not Significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.511 [27]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	7.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.97
upper limit	30.09

Notes:

[27] - Not Significant

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.406 [28]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	9.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.67
upper limit	31.32

Notes:

[28] - Not Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.711 [29]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	4.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.35
upper limit	25.42

Notes:
[29] - Not Significant

Secondary: Acylated ghrelin AUC

End point title	Acylated ghrelin AUC

End point description:
Change in acylated ghrelin AUC during mixed meal tolerance test

End point type	Secondary

End point timeframe:
0, 2, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	14
Units: pg/mL				
arithmetic mean (standard deviation)	43.2 (± 39.0)	53 (± 56.1)	35.4 (± 33.8)	41.2 (± 80.3)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	17	16	14
Units: pg/mL				
arithmetic mean (standard deviation)	42.6 (± 39.9)	52.3 (± 58.1)	33.4 (± 28.4)	83.8 (± 214.2)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	13
Units: pg/mL				
arithmetic mean (standard deviation)	42.6 (± 39.5)	47.3 (± 46.9)	28.8 (± 21.6)	98.8 (± 261.1)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	16	14
Units: pg/mL				
arithmetic mean (standard deviation)	61.3 (± 71.0)	64.3 (± 59.1)	38.4 (± 38.5)	79.3 (± 202.9)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	15	14
Units: pg/mL				
arithmetic mean (standard deviation)	42.3 (± 50.7)	57.4 (± 49.4)	50.6 (± 51.0)	58.9 (± 126.3)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.765 [30]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	3.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.69
upper limit	24.06

Notes:

[30] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.187 [31]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-13.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.26
upper limit	6.68

Notes:

[31] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.185 [32]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-13.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.47
upper limit	6.47

Notes:

[32] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049 [33]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	32.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	64.92

Notes:

[33] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81 [34]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.88
upper limit	35.67

Notes:

[34] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.538 [35]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-9.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.35
upper limit	21.58

Notes:

[35] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [36]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	61.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.67
upper limit	112.79

Notes:

[36] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.965 [37]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.68
upper limit	47.52

Notes:

[37] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.775 [38]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-7.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.92
upper limit	41.69

Notes:

[38] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037 [39]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	42.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.65
upper limit	83.12

Notes:

[39] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.874 [40]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-3.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.4
upper limit	36.89

Notes:

[40] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.586 [41]
Method	Generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-10.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.12
upper limit	27.75

Notes:

[41] - Not significant

Secondary: GLP-1 AUC

End point title	GLP-1 AUC

End point description:

Change in GLP-1 AUC during mixed meal tolerance test

End point type	Secondary

End point timeframe:

0, 2, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	14
Units: pmol/L				
arithmetic mean (standard deviation)	47.9 (± 15.1)	43.1 (± 11.5)	45.5 (± 10.6)	46.3 (± 12.4)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	16	14
Units: pmol/L				
arithmetic mean (standard deviation)	52.7 (± 13.7)	48.3 (± 18.1)	44.0 (± 9.1)	47.5 (± 12.3)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	13
Units: pmol/L				
arithmetic mean (standard deviation)	50.8 (± 14.1)	45.6 (± 14.8)	44.3 (± 13.1)	45.8 (± 13.5)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	16	14
Units: pmol/L				
arithmetic mean (standard deviation)	54.0 (± 17.6)	47.0 (± 17.4)	44.2 (± 10.6)	44.0 (± 14.5)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	15	14
Units: pmol/L				
arithmetic mean (standard deviation)	49.9 (± 10.9)	43.8 (± 13.3)	46.1 (± 11.9)	47.0 (± 13.7)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.657 [42]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.14
upper limit	6.56

Notes:

[42] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [43]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	3.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	8.32

Notes:

[43] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.896 [44]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.77
upper limit	5.45

Notes:

[44] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.976 [45]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.61
upper limit	7.38

Notes:

[45] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055 [46]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	7.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	14.57

Notes:

[46] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.163 [47]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	5.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.09
upper limit	12.38

Notes:

[47] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.922 [48]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.12
upper limit	5.66

Notes:

[48] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential

Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.093 [49]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	4.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	9.42

Notes:

[49] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.257 [50]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	2.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.14
upper limit	8.01

Notes:

[50] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28 [51]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	3.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	9.43

Notes:

[51] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049 [52]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	6.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	11.99

Notes:

[52] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028 [53]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	6.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	12.28

Notes:

[53] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Secondary: Hunger - VAS

End point title	Hunger - VAS

End point description:

Change in Hunger AUC (measured using visual analogue scale - (VAS)) during mixed meal tolerance test

End point type	Secondary

End point timeframe:

0, 2, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mm				
arithmetic mean (standard deviation)	36.5 (± 19.8)	29.0 (± 18.8)	29.3 (± 21.5)	24.0 (± 16.3)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	16	15
Units: mm				
arithmetic mean (standard deviation)	38.1 (± 18.3)	29.6 (± 20.9)	27.3 (± 17.6)	24.6 (± 17.9)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	17	14
Units: mm				
arithmetic mean (standard deviation)	35.3 (± 23.1)	32.5 (± 19.7)	32.3 (± 21.2)	23.8 (± 20.2)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	17	14
Units: mm				
arithmetic mean (standard deviation)	30.7 (± 20.2)	29.8 (± 23.9)	28.2 (± 18.3)	33.3 (± 23.2)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	17	16	14
Units: mm				
arithmetic mean (standard deviation)	41.6 (± 19.4)	36.0 (± 24.9)	31.2 (± 18.4)	26.5 (± 18.7)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.645 [54]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.12
upper limit	8.13

Notes:

[54] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.199 [55]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	6.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.67
upper limit	17.58

Notes:

[55] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.495 [56]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	3.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.53
upper limit	13.51

Notes:

[56] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.225 [57]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	8.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.08
upper limit	21.57

Notes:

[57] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.898 [58]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.87
upper limit	12.17

Notes:

[58] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.793 [59]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.81
upper limit	14.15

Notes:

[59] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42 [60]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-5.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.74
upper limit	7.39

Notes:

[60] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.999 [61]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.07
upper limit	12.06

Notes:

[61] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.913 [62]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.63
upper limit	11.3

Notes:

[62] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.937 [63]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.46
upper limit	10.26

Notes:

[63] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266 [64]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	5.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.27
upper limit	15.47

Notes:

[64] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.745 [65]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.86
upper limit	10.99

Notes:

[65] - Not significant

Secondary: Fullness - VAS

End point title	Fullness - VAS

End point description:

Change in Fullness AUC (measured using visual analogue scale - (VAS)) during mixed meal tolerance test

End point type	Secondary

End point timeframe:

0, 2, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mm				
arithmetic mean (standard deviation)	50.6 (± 22.7)	54.1 (± 22.3)	50.5 (± 24.1)	59.3 (± 20.1)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	15
Units: mm				
arithmetic mean (standard deviation)	56.3 (± 17.2)	53.8 (± 19.5)	50.9 (± 27.8)	59.8 (± 23.4)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	16	17	14
Units: mm				
arithmetic mean (standard deviation)	61.7 (± 21.4)	54.0 (± 21.3)	52.0 (± 25.0)	54.2 (± 28.9)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	17	14
Units: mm				
arithmetic mean (standard deviation)	56.7 (± 23.0)	49.4 (± 28.8)	56.4 (± 24.3)	59.0 (± 25.0)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	16	14
Units: mm				
arithmetic mean (standard deviation)	53.4 (± 18.0)	51.8 (± 22.8)	53.9 (± 22.2)	61.7 (± 24.0)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.479 [66]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	4.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.09
upper limit	17.24

Notes:

[66] - not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86 [67]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	11.19

Notes:

[67] - not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.608 [68]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-3.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.05
upper limit	8.8

Notes:

[68] - not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.903 [69]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.91
upper limit	15.81

Notes:

[69] - not significant

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.971 [70]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.73
upper limit	16.33

Notes:

[70] - not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.292 [71]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-8.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.33
upper limit	7.32

Notes:

[71] - not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768 [72]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.41
upper limit	13.59

Notes:

[72] - not significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential

Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.205 [73]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	9.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.26
upper limit	24.55

Notes:

[73] - not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.882 [74]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.03
upper limit	16.33

Notes:

[74] - not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769 [75]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.52
upper limit	15.59

Notes:

[75] - not significant

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.356 [76]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	6.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.88
upper limit	19.13

Notes:

[76] - not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.972 [77]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.65
upper limit	13.11

Notes:

[77] - not significant

Secondary: Satisfaction - VAS

End point title	Satisfaction - VAS

End point description:

Change in Satisfaction AUC (measured using visual analogue scale - (VAS)) during mixed meal tolerance test

End point type	Secondary

End point timeframe:

0, 2, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mm				
arithmetic mean (standard deviation)	48.6 (± 20.0)	55.6 (± 16.7)	54.0 (± 21.8)	59.1 (± 20.0)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	15
Units: mm				
arithmetic mean (standard deviation)	58.8 (± 16.6)	52.6 (± 21.0)	51.7 (± 22.1)	62.3 (± 23.0)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	16	17	14

Units: mm				
arithmetic mean (standard deviation)	62.4 (± 21.2)	50.6 (± 25.2)	53.3 (± 23.6)	53.7 (± 27.2)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	17	14
Units: mm				
arithmetic mean (standard deviation)	65.5 (± 18.8)	51.1 (± 27.7)	57.0 (± 23.8)	61.2 (± 23.0)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	16	14
Units: mm				
arithmetic mean (standard deviation)	54.5 (± 16.1)	50.8 (± 24.0)	56.6 (± 21.0)	63.4 (± 24.1)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.369 [78]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	5.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	18.86

Notes:

[78] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using

models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.903 [79]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.89
upper limit	13.46

Notes:

[79] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.383 [80]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-5.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.69
upper limit	6.79

Notes:

[80] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79 [81]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.54
upper limit	17.8

Notes:

[81] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134 [82]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	11.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.56
upper limit	26.64

Notes:

[82] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.387 [83]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-6.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.31
upper limit	8.25

Notes:

[83] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.772 [84]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.56
upper limit	13.79

Notes:

[84] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132 [85]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.54
upper limit	26.93

Notes:

[85] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.757 [86]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.86
upper limit	12.99

Notes:

[86] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306 [87]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	6.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	18.82

Notes:

[87] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075 [88]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	10.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	23.07

Notes:

[88] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.986 [89]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.75
upper limit	11.96

Notes:

[89] - Not significant

Secondary: PFC - VAS

End point title	PFC - VAS

End point description:

Change in Prospective Food Consumption (PFC) AUC (measured using visual analogue scale - (VAS)) during mixed meal tolerance test

End point type	Secondary

End point timeframe:
0, 2, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mm				
arithmetic mean (standard deviation)	46.9 (± 20.9)	35.5 (± 21.0)	41.9 (± 21.5)	28.7 (± 17.7)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	15
Units: mm				
arithmetic mean (standard deviation)	41.1 (± 19.6)	36.0 (± 18.9)	38.0 (± 23.3)	29.0 (± 18.2)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	16	17	14
Units: mm				
arithmetic mean (standard deviation)	40.4 (± 23.5)	36.3 (± 20.8)	40.8 (± 24.9)	33.7 (± 23.3)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	17	14
Units: mm				
arithmetic mean (standard deviation)	36.8 (± 24.9)	35.5 (± 25.8)	32.8 (± 20.6)	34.9 (± 21.8)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	17	16	14
Units: mm				

arithmetic mean (standard deviation)	44.3 (± 19.1)	39.0 (± 24.8)	39.1 (± 18.5)	31.2 (± 20.6)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.976
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.66
upper limit	10.34

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.652
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.71
upper limit	12.31

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.513
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.49
upper limit	12.99

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.222
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	9.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.62
upper limit	24.21

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.924
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.28
upper limit	14.63

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.368
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	6.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.45
upper limit	20.1

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.911
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.82
upper limit	14.11

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.679
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.6
upper limit	10.82

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.732
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-2.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.41
upper limit	11.53

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.745
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.23
upper limit	9.47

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.607
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-2.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.78
upper limit	8.06

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.34
upper limit	11.02

Secondary: Body weight	
End point title	Body weight
End point description:	
Change in body weight	
End point type	Secondary
End point timeframe:	
0, 2, 6, 12 and 24 weeks	

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: kg				
arithmetic mean (standard deviation)	89.1 (± 18.9)	90.2 (± 16.2)	96.5 (± 17.9)	95.8 (± 21.1)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	15
Units: kg				
arithmetic mean (standard deviation)	88.3 (± 18.7)	88.6 (± 16.1)	96.4 (± 17.6)	92.4 (± 20.9)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	16	17	14
Units: kg				
arithmetic mean (standard deviation)	87.9 (± 18.5)	88.5 (± 15.2)	96.5 (± 17.7)	90.7 (± 20.7)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	17	14
Units: kg				
arithmetic mean (standard deviation)	87.0 (± 19.0)	85.8 (± 16.1)	96.4 (± 17.1)	90.0 (± 23.0)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	14
Units: kg				
arithmetic mean (standard deviation)	86.3 (± 18.2)	84.5 (± 16.5)	95.6 (± 17.8)	92.4 (± 19.7)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.191 [90]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.79
upper limit	0.76

Notes:

[90] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049 [91]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-2.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.45
upper limit	-0.01

Notes:

[91] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [92]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-5.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.79
upper limit	-3.44

Notes:

[92] - Significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048 [93]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-4.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	-0.04

Notes:

[93] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.333 [94]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.34
upper limit	2.14

Notes:

[94] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029 [95]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-4.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.74
upper limit	-0.48

Notes:

[95] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042 [96]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.34
upper limit	-0.04

Notes:

[96] - Significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 [97]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	-0.34

Notes:

[97] - Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [98]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-3.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.39
upper limit	-2.17

Notes:

[98] - Significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.135 [99]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	0.17

Notes:

[99] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031 [100]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	-0.07

Notes:

[100] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [101]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	-0.83

Notes:

[101] - Significant

Secondary: Fat mass - DEXA

End point title	Fat mass - DEXA

End point description:

Change in fat mass (measured using DEXA)

End point type	Secondary

End point timeframe:

0 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: kg				
arithmetic mean (standard deviation)	34.8 (± 8.3)	35.0 (± 10.5)	37.4 (± 10.5)	36.4 (± 10.2)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	14
Units: kg				
arithmetic mean (standard deviation)	33.9 (± 8.3)	30.6 (± 9.5)	36.9 (± 10.2)	32.8 (± 9.1)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033 [102]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.72
upper limit	-0.16

Notes:

[102] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential

Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.264 [103]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	0.74

Notes:

[103] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [104]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-4.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.76
upper limit	-2.36

Notes:

[104] - Significant

Secondary: Lean mass - DEXA

End point title	Lean mass - DEXA

End point description:

Change in lean mass (measured using DEXA)

End point type	Secondary

End point timeframe:

0 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: kg				
arithmetic mean (standard deviation)	51.1 (± 13.0)	52.2 (± 11.1)	55.6 (± 9.9)	55.7 (± 11.5)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	14
Units: kg				
arithmetic mean (standard deviation)	49.5 (± 12.4)	51.1 (± 10.8)	55.5 (± 9.8)	56.2 (± 11.3)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo plus ERD (24 weeks) v Placebo (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.428 [105]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.18

Notes:

[105] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [106]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	-0.6

Notes:

[106] - Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [107]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.8

Notes:

[107] - Significant

Secondary: REE

End point title	REE

End point description:

Change in resting energy expenditure (REE) (measured using indirect calorimetry)

End point type	Secondary

End point timeframe:

0, 2, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: kcal/day				
arithmetic mean (standard deviation)	1469.9 (± 375.1)	1391.8 (± 408.4)	1500.5 (± 399.0)	1605.0 (± 423.5)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	16	15
Units: kcal/day				
arithmetic mean (standard deviation)	1461.8 (± 399.5)	1443.8 (± 269.5)	1528.8 (± 381.6)	1570.6 (± 431.5)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	14
Units: kcal/day				
arithmetic mean (standard deviation)	1484.5 (± 400.2)	1338.0 (± 429.9)	1611.9 (± 477.4)	1599.2 (± 430.4)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	16	14
Units: kcal/day				
arithmetic mean (standard deviation)	1467.6 (± 364.9)	1402.0 (± 377.6)	1537.1 (± 393.1)	1547.5 (± 359.9)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	15	13
Units: kcal/day				
arithmetic mean (standard deviation)	1446.5 (± 385.9)	1397.7 (± 362.5)	1606.6 (± 335.4)	1667.2 (± 402.8)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.545 [108]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-58.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-249.44
upper limit	131.71

Notes:

[108] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.143 [109]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-133.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-311.28
upper limit	44.84

Notes:

[109] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [110]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-176.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-351.85
upper limit	-0.21

Notes:

[110] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.361 [111]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-72.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-228.17
upper limit	83.09

Notes:

[111] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.534 [112]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-46.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-193.31
upper limit	100.21

Notes:

[112] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.493 [113]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-51.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-199.06
upper limit	95.81

Notes:

[113] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.633 [114]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-62.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-317.62
upper limit	193.15

Notes:

[114] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.385 [115]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-108.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-353.86
upper limit	136.47

Notes:

[115] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045 [116]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-250.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	-495.64
upper limit	-5.79

Notes:

[116] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.958 [117]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-5.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-199.79
upper limit	189.33

Notes:

[117] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62 [118]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-47.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-235.22
upper limit	140.15

Notes:
[118] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.875 [119]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-15.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-203.6
upper limit	173.46

Notes:
[119] - Not significant

Secondary: Physical activity - Daily steps	
End point title	Physical activity - Daily steps

End point description:

Change in daily steps (measured using wrist-worn accelerometer)

End point type	Secondary

End point timeframe:

0, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: steps/day				
arithmetic mean (standard deviation)	5952.1 (± 2283.8)	5819.0 (± 2402.0)	5347.6 (± 2213.9)	5155.7 (± 2335.8)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	15	17	10

Units: steps/day				
arithmetic mean (standard deviation)	5255.4 (± 1614.2)	6503.8 (± 2563.1)	6384.0 (± 3188.4)	6064.4 (± 2992.8)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	17	13
Units: steps/day				
arithmetic mean (standard deviation)	5838.1 (± 1708.3)	6261.3 (± 2500.5)	5549.0 (± 2251.1)	6435.5 (± 3159.9)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	13
Units: steps/day				
arithmetic mean (standard deviation)	5234.2 (± 1650.0)	6722.4 (± 2924.9)	5822.4 (± 2312.4)	6355.1 (± 2239.4)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.363 [120]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	604.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-697.64
upper limit	1905.9

Notes:

[120] - Not significant

	GLM - empa vs placebo @ 24wks

Statistical analysis title	

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.209 [121]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-799.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2046.99
upper limit	447.07

Notes:

[121] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.375 [122]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	573.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-694.97
upper limit	1842.79

Notes:

[122] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.339 [123]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	507.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-531.65
upper limit	1546.02

Notes:

[123] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.737 [124]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-167.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1144.49
upper limit	809.94

Notes:

[124] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.919 [125]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	50.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-922.41
upper limit	1022.73

Notes:

[125] - Not significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.628 [126]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-318.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1607.36
upper limit	970.59

Notes:

[126] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [127]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1410.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2580.31
upper limit	-241.24

Notes:

[127] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.454 [128]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-436.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1580.43
upper limit	707.03

Notes:

[128] - Not significant

Secondary: HbA1c

End point title	HbA1c

End point description:

Change in HbA1c

End point type	Secondary

End point timeframe:

0, 2, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: percent				
arithmetic mean (standard deviation)	6.9 (± 0.8)	6.8 (± 0.5)	7.1 (± 0.6)	6.9 (± 0.5)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	17	17	13
Units: percent				

arithmetic mean (standard deviation)	6.8 (± 0.7)	6.7 (± 0.5)	7.0 (± 0.5)	6.8 (± 0.4)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	16	13
Units: percent				
arithmetic mean (standard deviation)	6.6 (± 0.5)	6.5 (± 0.4)	6.9 (± 0.6)	6.5 (± 0.5)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	14
Units: percent				
arithmetic mean (standard deviation)	6.4 (± 0.4)	6.3 (± 0.4)	6.9 (± 0.6)	6.5 (± 0.8)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	14
Units: percent				
arithmetic mean (standard deviation)	6.6 (± 0.4)	6.5 (± 0.5)	7.1 (± 0.7)	6.8 (± 0.9)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Placebo plus ERD (24 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.626 [129]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.28

Notes:

[129] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041 [130]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	-0.02

Notes:

[130] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [131]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	-0.06

Notes:

[131] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06 [132]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.01

Notes:

[132] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [133]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.12

Notes:

[133] - Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [134]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	-0.14

Notes:

[134] - Significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 [135]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.05

Notes:

[135] - Significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [136]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.07

Notes:

[136] - Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [137]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	-0.12

Notes:

[137] - Significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 [138]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	-0.01

Notes:

[138] - Not significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.221 [139]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.04

Notes:

[139] - Not significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058 [140]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0

Notes:

[140] - Not significant

Secondary: Fasting plasma glucose

End point title	Fasting plasma glucose

End point description:

Change in fasting plasma glucose

End point type	Secondary

End point timeframe:

0, 2, 6, 12 and 24 weeks

End point values	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)	Placebo plus ERD (baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mmol/L				
arithmetic mean (standard deviation)	6.4 (± 1.1)	6.6 (± 1.1)	7.3 (± 1.4)	6.8 (± 1.3)

End point values	Empagliflozin (2 weeks)	Empagliflozin plus ERD (2 weeks)	Placebo (2 weeks)	Placebo plus ERD (2 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	17	14
Units: mmol/L				
arithmetic mean (standard deviation)	5.9 (± 1.0)	5.6 (± 0.8)	6.9 (± 1.3)	6.4 (± 1.0)

End point values	Empagliflozin (6 weeks)	Empagliflozin plus ERD (6 weeks)	Placebo (6 weeks)	Placebo plus ERD (6 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	17	12
Units: mmol/L				
arithmetic mean (standard deviation)	5.6 (± 1.1)	5.4 (± 0.5)	6.9 (± 1.2)	6.5 (± 1.1)

End point values	Empagliflozin (12 weeks)	Empagliflozin plus ERD (12 weeks)	Placebo (12 weeks)	Placebo plus ERD (12 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	17	13
Units: mmol/L				
arithmetic mean (standard deviation)	5.6 (± 0.8)	5.5 (± 0.6)	7.0 (± 1.0)	6.7 (± 1.1)

End point values	Empagliflozin (24 weeks)	Empagliflozin plus ERD (24 weeks)	Placebo (24 weeks)	Placebo plus ERD (24 weeks)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	13
Units: mmol/L				
arithmetic mean (standard deviation)	5.6 (± 0.8)	5.3 (± 0.6)	6.9 (± 1.4)	6.5 (± 1.2)

Statistical analyses

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo plus ERD (24 weeks) v Placebo (24 weeks)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.872 [141]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.53

Notes:

[141] - Not significant

Statistical analysis title	GLM - empa vs placebo @ 24wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 24 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin (24 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [142]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	-0.31

Notes:

[142] - Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 24wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 24 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (24 weeks) v Empagliflozin plus ERD (24 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [143]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	-0.69

Notes:

[143] - Significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Placebo plus ERD (12 weeks)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.923 [144]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.55

Notes:

[144] - Not Significant

Statistical analysis title	GLM - empa vs placebo @ 12wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 12 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin (12 weeks)

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [145]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	-0.42

Notes:

[145] - Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 12wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 12 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (12 weeks) v Empagliflozin plus ERD (12 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [146]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-0.69

Notes:

[146] - Significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Placebo plus ERD (6 weeks)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.305 [147]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.23

Notes:

[147] - Not Significant

Statistical analysis title	GLM - empa vs placebo @ 6wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 6 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin (6 weeks)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [148]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	-0.32

Notes:

[148] - Significant

Statistical analysis title	GLM – empa plus ERD vs placebo @ 6wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 6 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (6 weeks) v Empagliflozin plus ERD (6 weeks)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [149]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	-0.59

Notes:

[149] - Significant

Statistical analysis title	GLM – placebo plus ERD vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of placebo plus diet vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Placebo plus ERD (2 weeks)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.503 [150]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.26

Notes:

[150] - Not Significant

Statistical analysis title	GLM - empa vs placebo @ 2wks

Statistical analysis description:

Complete case generalized linear model analyses of empagliflozin 25mg vs placebo at 2 weeks; using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin (2 weeks)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [151]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	-0.05

Notes:

[151] - Not Significant (note application of Holm's Sequential Bonferroni procedure to adjust for multiple comparisons)

Statistical analysis title	GLM – empa plus ERD vs placebo @ 2wks

Statistical analysis description:

Generalized linear model analyses of empagliflozin 25mg plus ERD vs placebo at 2 weeks, using models with normal distribution, identity link and adjusted for randomization stratification factors (sex and BMI) and baseline value of outcome. Statistical significance was determined using Holm's Sequential Bonferroni procedure.

Comparison groups	Placebo (2 weeks) v Empagliflozin plus ERD (2 weeks)

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [152]
Method	generalised linear model
Parameter estimate	adjusted beta co-efficient
Point estimate	-0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	-0.35

Notes:

[152] - Significant

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Randomisation to 5 days post last dose (up to 25 weeks).	
Adverse event reporting additional description:	
At each visit the study Investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the study Investigator was recorded, irrespective if the relation to study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Empagliflozin (Baseline)
Reporting group description:	
Empagliflozin (Jardiance™) 25mg once daily	
Reporting group title	Empagliflozin plus ERD (Baseline)
Reporting group description:	
Empagliflozin (Jardiance™) 25mg once daily and energy restriction diet (ERD)	
Reporting group title	Placebo (baseline)
Reporting group description:	
The placebo was labelled as '25mg once daily' to match the IMP.	
Reporting group title	Placebo plus ERD (baseline)
Reporting group description:	
Placebo and energy restriction diet (ERD)	

Serious adverse events	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia	Additional description: Participant reported two hospital admissions for the investigation and treatment of pyrexia. Minimal information provided to the study team.		
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Exacerbation of Asthma			

subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo plus ERD (baseline)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Pyrexia	Additional description: Participant reported two hospital admissions for the investigation and treatment of pyrexia. Minimal information provided to the study team.		
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Exacerbation of Asthma			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Empagliflozin (Baseline)	Empagliflozin plus ERD (Baseline)	Placebo (baseline)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 17 (35.29%)	7 / 17 (41.18%)	8 / 17 (47.06%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	0
Thirst			

subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Fall (Mechanical)			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	0
Head injury			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0

Muscle strain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Splinter			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Thermal burn			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dizziness postural			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	1 / 17 (5.88%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Normocytic anaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Eye disorders			

Eye swelling			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Lacrimination increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 17 (11.76%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Dry skin			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Rash			

subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Micturition urgency			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Plantar fasciitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Cystitis			

subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	2 / 17 (11.76%)	0 / 17 (0.00%)	2 / 17 (11.76%)
occurrences (all)	2	0	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 17 (17.65%)	2 / 17 (11.76%)	1 / 17 (5.88%)
occurrences (all)	3	2	1
Viral infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Placebo plus ERD (baseline)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 17 (47.06%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		

Thirst			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Fall (Mechanical)			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Head injury			

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Muscle strain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Splinter subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Thermal burn subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Dizziness postural subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Presyncope subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Blood and lymphatic system disorders			
Normocytic anaemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Ear and labyrinth disorders			

Vertigo positional			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Lacrimination increased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Visual impairment			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Dysuria			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Micturition urgency			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Joint swelling			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Plantar fasciitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Cellulitis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Cystitis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Viral infection subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gout subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Iron deficiency subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2016	Protocol Amendment:- Amendment to the stratification criteria to remove 'sex'. Update to safety reporting procedures following the receipt of a Direct Healthcare Professional Communication report (dated 21st March 2016) regarding diabetic ketoacidosis and the use of Empagliflozin. Exclusion criteria updated to reflect safety information and diabetic ketoacidosis included as an Adverse Events of Special Interest.
29 June 2016	Protocol Amendment:- Inclusion and exclusion criteria amended to widen HbA1c range and increase upper age limit. Change to breakfast standardisation; standardised breakfast meal to represent 33.3% of daily energy requirement as opposed to 30%. Clarification provided regarding the timing of samples collected at visits 1-5; 1 fasting sample and 6 samples after the standardised breakfast meal. Change to wording in section 8.5 (investigations) which references the timing of indirect calorimetry assessment; assessment performed at visit 1 not visit 0. Change to the timing of provision of baseline activity monitors to participants; monitors to be given at visit 0 not visit 1. Study measures added to table 1 (scheduled of assessments) for clarity. Clarification providing regarding the visit window between visit 0 and visit 1. Boehringer Ingelheim added to the reporting procedure for SAE. Additional recruitment activity in primary care added to recruitment strategy section. Minor amendment to randomisation and code breaking section to change description of placebo/IMP from 'capsules' to 'tablets'.
29 September 2016	Protocol Amendment:- Removal of study contact details from the front cover of the protocol. Change of name from Project Management Committee to Trial Management Group. Trial Summary updated to more accurately reflect visit length. Exclusion criteria updated to allow any future emerging safety concerns to be addressed without compromising participant safety. Treatment Management section updated to include information on acute kidney injury. Amendment to the number and timing of blood samples collected during study visits 1-5. Addition of information regarding storage of blood samples for future research.

08 February 2017	Protocol Amendment:- Exclusion criteria amended to exclude rotating day/night shift workers, as well as to allow investigators to use clinical judgement in assessing excessive alcohol consumption. Addition of increased Lower Limb Amputation to the section on Adverse Events of Special Interest (AESI). Addition of a follow-up telephone call within 1 week (+/-3days) of medication completion to capture any potential Adverse Events during the drug wash-out period. Amendment to recruitment strategy allowing for more strategies to be adopted. Amendment to the visit window in which screening bloods results can be used from 6 to 3 months prior to study visit. Clarification of the use of indirect calorimeter for determining participants' daily energy requirement. Amendment to the time required for inclinometer wear from 8 to 9 days.
20 March 2018	Protocol Amendment:- Visit window for visits 1-5 and end of study telephone call amended (widened to +/-5 days) to allow flexibility with appointment booking and reduce protocol deviations. Amendment to the wording within the 24 hour Meal Standardisation section to reflect current practice; all participants will consume a standardised evening meal provided to them at least 10 hours before their visit. Amendment to the physical activity section to allow for flexibility with provision of monitors. The study team chose to avoid these holiday periods, as it is not habitual behaviour.

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.

None

Notes: